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Influence of hydration state and homologue composition of magnesium stearate on the physical chemical properties of liquid paraffin lipogels

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ABSTRACT

Lipogels were prepared by dispersing mixed (60:40 C_{16}–C_{18}) and pure (C_{18}) homologue magnesium stearate (MgSt) in liquid paraffin, using three methods of preparation, *i.e.* addition of water at 95 °C during cooling cycle (method 1), homogenisation upon cooling (method 2) or cooling without addition of water or homogenisation (method 3). The systems were characterised by physical inspection, polarised, hot stage and scanning electron microscopy (SEM), differential scanning calorimetry (DSC), rheology, and X-ray diffraction (XRD). Systems formed stable semisolid lipogels (no syneresis), unstable solids showing syneresis or structured fluids, depending on the type of magnesium stearate used and the preparation technique. The stable semisolid lipogels containing mixed homologue MgSt (commercial-as received, anhydrous or dihydrate) prepared by methods 1 (~1–2% water) and 2 contained α-crystalline lamellar structure. These were not present in the unstable solids formed with method 3 or in systems prepared from pure homologue MgSt which were generally structured fluids rather than semisolids. In addition, semisolid lipogels of pure homologue trihydrate MgSt prepared by method 3 showed plate-like crystals, implying pressure sensitivity. There is significantly more amorphous MgSt in the unstable solids compared to the stable semisolid lipogels, which are mainly crystalline (confirmed by XRD).

1. Introduction

Drugs and excipients may show polymorphism. Transformation from one polymorphic form to another during processing can affect the physical chemical properties of the dosage form (Miller and York, 1985; Ertel and Carstensen, 1988; Rajala and Laine, 1995). Magnesium stearate (MgSt) exists as polymorphs and may be composed of either pure or mixed homologues. The commonly used stearic acid (component of MgSt) is not pure but a "triple pressed" homologue mixture of ~60% palmitic acid and 40% stearic acid with traces of other saturated and unsaturated fatty acids (Eccleston, 1997). It has been reported that pure stearic acid in liquid paraffin produces unstable solid gel systems (Bozic et al., 1980). Commercial MgSt is available as a mixture of monohydrate and dihydrate and its moisture treatment produces different pseudopolymorphic form affecting its physical chemical properties (Swaminathan and Kildsig, 2001; Bracconi et al., 2005; Okoye and Wu, 2007). Milling of magnesium stearate has also shown to affect its particle size and surface area causing changes in the lubrication properties which may be related to the polymorphic modifications in MgSt (Leinonen et al., 1992). It is reported that aqueous semisolid systems containing stearic acid are markedly affected by processing variables such as mixing, producing metastable polymorphic form (Garti et al., 1982; Lin et al., 1994; Eccleston, 1997). Swelling of aqueous stearate creams has been attributed to the existence of α-crystalline lamellar structure (Eccleston, 1997; Savic et al., 2009). However, swollen lamellar structures appeared to be metastable and under pressure broken down to non-swollen plate like crystalline structures, producing mobile lotions. The aim of this work was to investigate the influence of the crystal state and the homologue composition of MgSt on the physical chemical properties of lipogels prepared from them using three different methods of preparation, *i.e.* addition of water or homogenisation during cooling cycle or cooling without addition of water or homogenisation.

2. Material and methods

2.1. Materials

Liquid paraffin BP was purchased from JM Loveridge Plc, Southampton, England. Mixed homologue magnesium stearate (60:40 C_{16}–C_{18}), batch no. 41505-7 was purchased from Sigma–Aldrich (Dorset, UK). Stearic acid (~97% C_{18}), magnesium

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oxide and potassium sulfate (K_2SO_4) were obtained from Merck (Germany). Nitrogen and oxygen gas used for DSC were purchased from MOX Gas, Sdn. Bhd. Malaysia. Aluminium crucibles for DSC (40 μL capacity) and TGA (70 μL capacity) were purchased from Mettler Toledo, Switzerland. Double distilled de-ionised water was used.

2.2. Preparation of lipogels

Five forms of MgSt were used to prepare the lipogels. Pure anhydrous magnesium stearate obtained by heating magnesium oxide in pure stearic acid (~97% C_{18}) (S1) on hydration formed the trihydrate (S2). Commercial mixed homologue MgSt was used as received (S3) and dried to form a mixed homologue anhydrate (S4), which was rehydrated to yield dihydrate (S5).

Thirty (30) lipogels were prepared from these samples. Approximately 12.5% magnesium stearate (S1–S5) was dispersed in liquid paraffin, heated to 110 °C at a rate of 10 °C/min, held at 110 °C for 1 h and upon cooling (~0.1–0.2 °C/min) either added ~1–4% water at 90 °C (method 1), homogenised at room temperature (method 2) or cooled to room temperature without addition of water or homogenisation (method 3).

2.3. Visual inspection

The lipogels were visually inspected for changes in appearance during heating and cooling cycles. In addition, lipogels were investigated for separation of oil (syneresis) on storage.

2.4. Polarised microscopy

Reichert-Jung Polyvar (Ansberg, Germany) compound microscope was used to study the microstructure of the lipogels prepared from magnesium stearate (S1–S5). A small amount of each sample was placed on clean microscope slides (76 × 26 mm) using a clean, wooden stick. Slides were placed between cross polars and studied at various magnifications (×5, ×10, ×20 and ×40) and photomicrographs taken using a manual SLR film camera.

2.5. Hot stage microscopy

A TMS 91 hot stage (Linkam Scientific Instruments, UK) attached to the Polyvar microscope was used to investigate phase transition temperatures in the lipogels. A thin smear of sample was sandwiched between two 16 mm circular glass cover-slips. All samples were analysed by a standard method of 25 °C to 140 °C at a rate of 5 °C/min and the phase transition temperature range was recorded as the temperature between which the sample started to flow and the temperature at which the structure completely disappeared.

2.6. Scanning electron microscopy (SEM)

A Leo 1450VP electron microscope (Oxford Instruments, UK) was used to study structure of the selected lipogels containing MgSt (S3) prepared by methods 1–3. The lipogels were studied directly without gold coating, by placing a small sample on the stub using cold plate under low vacuum. Each sample was studied at powers between ×15 and ×5000, and photographed at appropriate magnifications.

2.7. Differential scanning calorimetry (DSC)

A DSC 822^e (Mettler Toledo, Leicester, UK) was used for the analysis of stearic acid and magnesium stearate in addition to the lipogels using a standard heating cycle of 25–150 °C at a rate of 10 °C/min to observe thermal changes in the samples. The results were plotted together after normalisation to eliminate the weight bias due to the weight differences of the samples.

2.8. Rheology

A cone and plate Physica MCR 301, air-bearing Pelletier rheometer (Anton Paar, Germany) with parallel plates (5 cm diameter) and zero gap (1 mm) was used to investigate the rheology of selected lipogels prepared by methods 1–3 using four samples (S1–S3) of magnesium stearate. The lipogels were characterised by flow curves, obtained using standard shearing cycle (10^{-1}–500 s^{-1}) with a 5 min sweep time to investigate the apparent viscosities (obtained from the apex of the up and down flow curve). All experiments were conducted at room temperature (~28 °C).

2.9. X-ray diffraction (XRD)

A powder X-ray diffractometer (Bruker 8 Advances, Germany) was used for the analysis of the lipogels prepared from magnesium stearate (S1–S5). The samples were irradiated with X-rays from a copper target using the following conditions and parameters: Filter Ni, Generator 40 kV, voltage 40 kV, current 20 mA, λ 0.15410 nm using a Soller slit. The samples were continuously scanned from 2.3 to 40 at a rate of 2.5°/s with a step of 0.025 s^{-1}. The XRD spectra were analysed using Diffract Plus software. Cu$K_{\alpha 1}$ values were used for the analysis of each peak.

3. Results

3.1. Physical appearance

Lipogels prepared were either stable semisolids, unstable solids showing syneresis of oil or mobile liquids depending on the type of MgSt and method of preparation.

Lipogels prepared from the three samples of mixed homologue MgSt (S3–S5) formed stable semisolids when prepared by methods 1 (~1–2% water) and 2, but gave unstable solids (syneresis of oil over time) when prepared by method 3. In contrast, the systems containing ~3–4% water (method 1) were structured fluids, which changed to semisolids upon storage for three months.

Systems containing pure MgSt (anhydrous or trihydrate) prepared by methods 1–3 were generally structured fluids. The exception was the lipogel containing pure MgSt trihydrate (S2) prepared by method 3, which was initially semisolid, but reverted to a liquid when stirred gently. The data are schematically summarised in Fig. 1.

3.2. Polarised microscopy

Fig. 2 shows selected photomicrographs of the lipogels containing MgSt (S2 and S3) prepared by methods 1–3. All lipogels showed different types of anisotropic structures against dark background. The stable semisolid lipogels showed existence of "Maltese crosses". In contrast, unstable solids or mobile fluids did not show "Maltese crosses", but rather crystals.

The lipogels containing mixed homologue MgSt prepared by methods 1 (~1–2% water) and 2 were similar showing numerous "Maltese crosses" (Fig. 2a and b). In contrast, liquid systems prepared by method 1 containing ~3–4% water (not shown) and solid systems prepared by method 3 (Fig. 2c) were different from semisolid lipogels and from each other showing numerous anisotropic crystals. No "Maltese crosses" were seen in these systems. The systems prepared using MgSt (S4 and S5) showed similar microstructure as that of S3 for all three methods (not shown).

In contrast, systems containing pure homologue MgSt (S1 and S2) prepared by methods 1–3 generally showed numerous

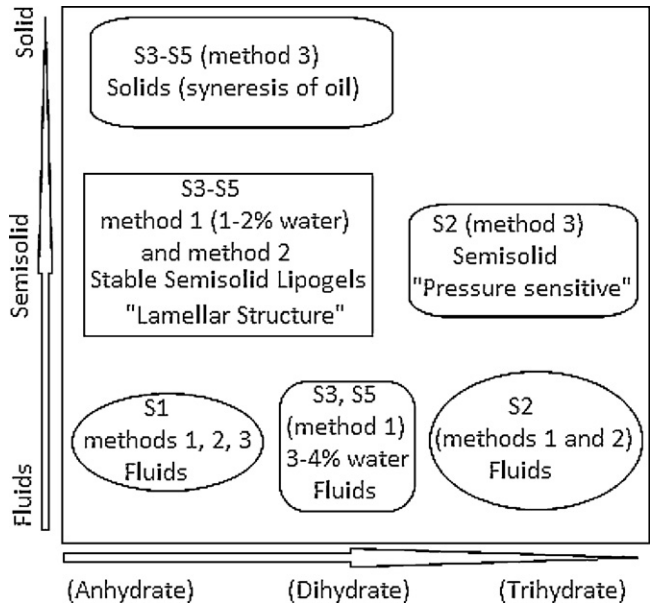

Fig. 1. Schematic diagram showing appearance of systems prepared by methods 1–3 using MgSt (S1–S5) and liquid paraffin.

anisotropic crystals (not shown) similar to the one seen in system containing MgSt (S3) prepared by method 1 containing ~3–4% water (not shown) with one exception (S2, method 3), which showed numerous anisotropic clusters of crystals and characteristic plate like crystals in addition to many "Maltese crosses". However, "Maltese crosses" disappeared, when system was gently stirred and showed only anisotropic clusters and plate like crystals (Fig. 2d).

3.3. Hot stage microscopy

All lipogels showed melting of anisotropic structures at temperatures between 80 and 120 °C. Unstable solids (method 3) containing mixed homologue MgSt (S3–S5) showed clusters of crystals melting between 70 and 105 °C. In contrast, stable semisolid lipogels (methods 1 and 2) showed melting of anisotropic crystals at 95 °C whereas "Maltese crosses" showed phase changes between 110–125 °C (not shown).

In contrast, systems prepared using pure homologue MgSt (S1 and S2) showed melting of crystals between 80 and 105 °C. In contrast, plate like crystals in the systems containing pure homologue trihydrate (S2) prepared by method 3 and stirred gently showed phase transition between 70 and 100 °C.

3.4. Scanning electron microscopy (SEM)

Fig. 3 shows electron photomicrographs of the selected systems containing mixed homologue MgSt (S3) prepared by methods 1–3 in addition to the system containing pure homologue trihydrate (S2) prepared by method 3.

All semisolid lipogels showed rather similar structures containing numerous needle-like crystals (Fig. 3a and b). In contrast, the system containing mixed homologue MgSt (S3) prepared by method 3 showed complex structures (Fig. 3c). No needle-like structures were observed in this system.

The system containing pure homologue trihydrate MgSt (S2) prepared by method 3 also showed existence of needle-like crystals in addition to several plate-like crystals (Fig. 3d).

3.5. Differential scanning calorimetry (DSC)

Fig. 4 shows DSC data for selected samples. All mixed homologue (S3–S5) semisolid lipogels prepared by methods 1 and 2 showed similar thermal properties. Typical data using S1–S3 to illustrate

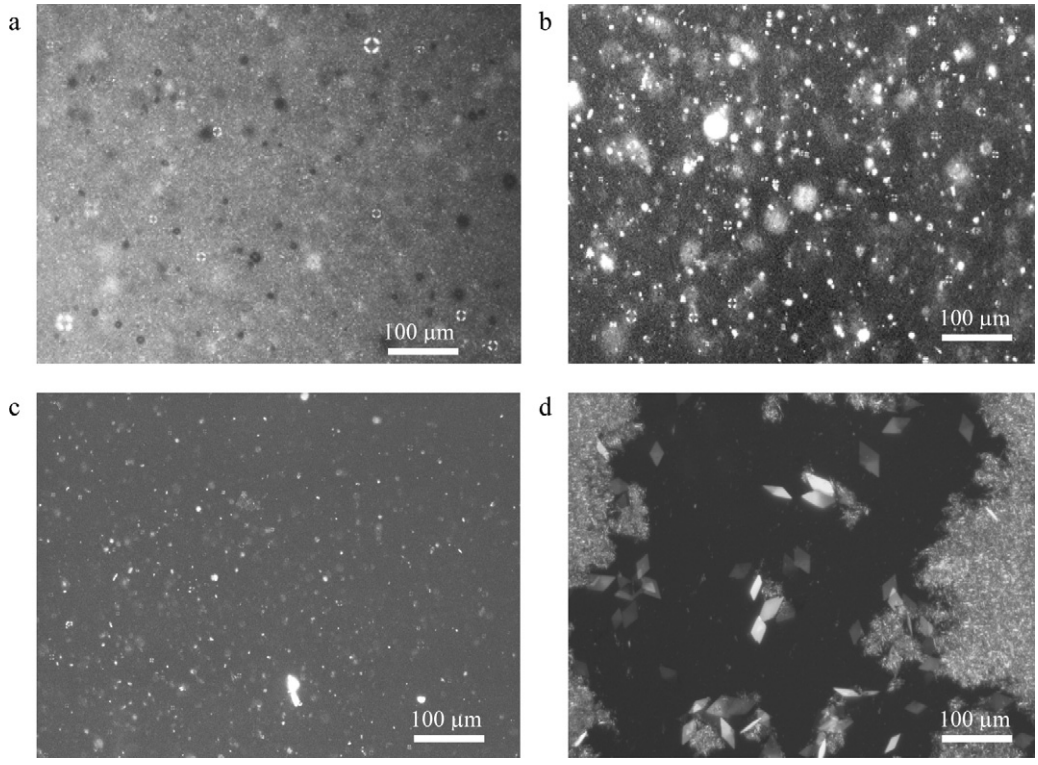

Fig. 2. Photomicrograph of the selected systems containing magnesium stearate (S2 and S3) and liquid paraffin prepared by the three methods: (a) S3, method 1 (2% water), (b) S3, method 2 (c) S3, method 3 and (d) S2, method 3.

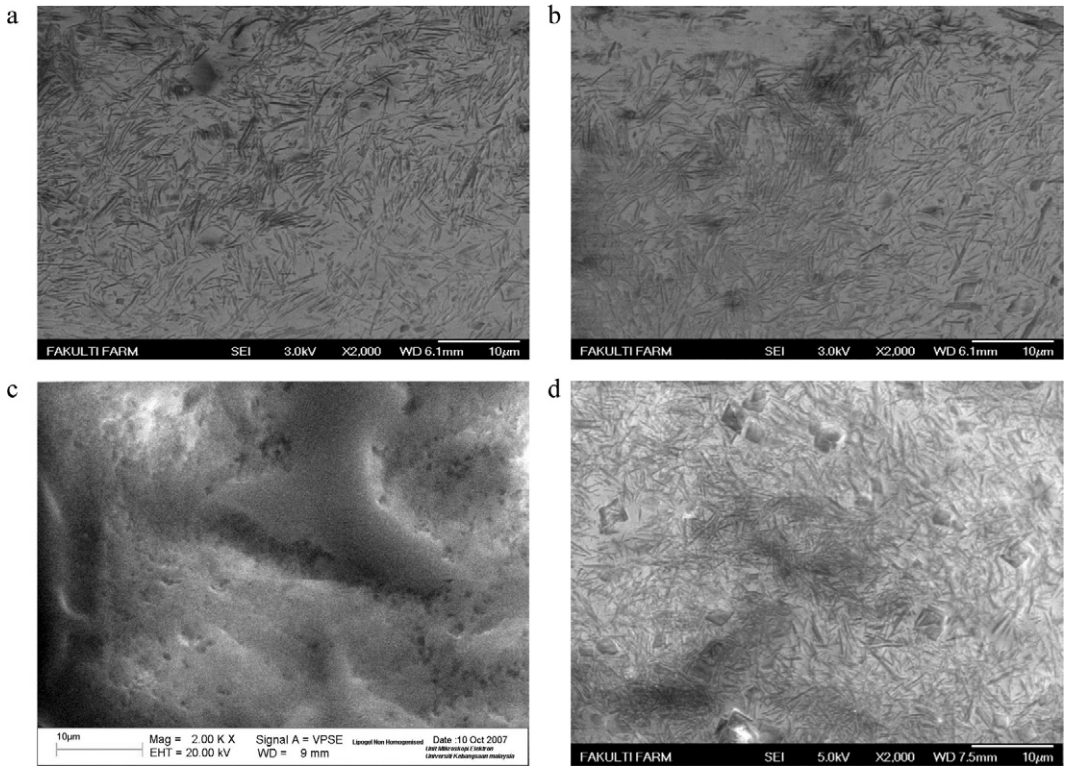

Fig. 3. SEM photomicrographs of selected lipogels prepared by methods 1–3 using MgSt (S2 and S3) in liquid paraffin (a) S3, method 1, (b) S3, method 2, (c) S3, method 3 and (d) S2, method 3.

this is shown in Fig. 4. The semisolid lipogels showed two high temperature endotherms peaking between 90 °C and 120 °C. The first broad endotherm peaked at 95 °C whereas second sharp endotherm peaked at 120 °C (Fig. 4).

In contrast, the thermal properties of the unstable solids formed with mixed homologue MgSt (method 3) and the fluids formed with pure homologue MgSt were different from each other and from stable semisolid lipogels (Fig. 4). All solid and liquid systems showed only one high temperature broad endotherm peaking between 90 and 105 °C except the system containing pure homologue trihydrate (S2) prepared by method 3, which showed two broad endotherms peaking at 85 °C and 100 °C.

3.6. Rheology

Fig. 5 shows flow curves of selected lipogels containing MgSt (S2 and S3) prepared by different methods. All lipogels showed non-Newtonian behaviour with flow curves in the form of anti-clockwise hysteresis loops. Rheograms of all samples were different from each other showing varying hysteresis loops, *i.e.* lipogel containing mixed homologue MgSt (S3) prepared by method 1 showing the broadest loop (Fig. 5). In addition, all systems also showed certain amount of yield values.

All lipogels showed different apparent viscosities, which were calculated from the apex of the loop (500 s^{-1}). The lipogels containing mixed homologue MgSt (S3) prepared by methods 1 and 2 showed highest viscosities (Table 1). The systems containing S4 and

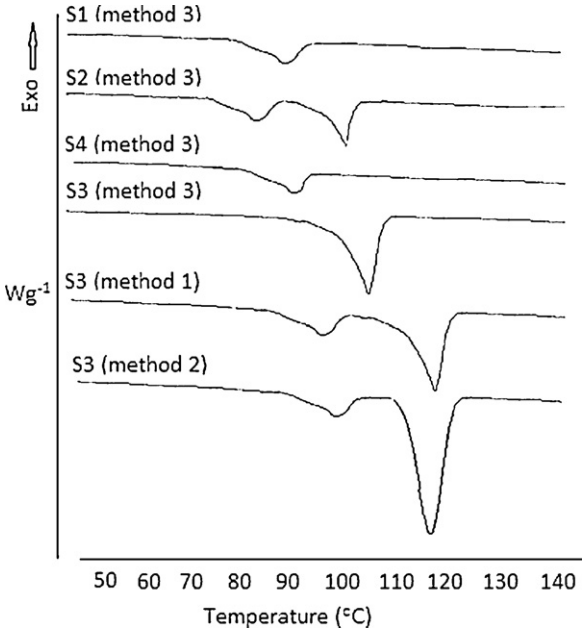

Fig. 4. DSC spectra of selected lipogels prepared by different methods.

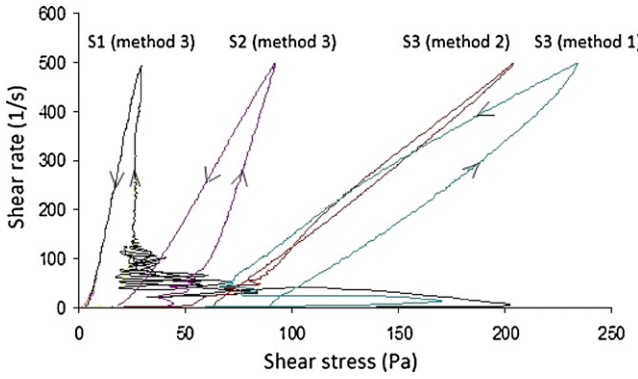

Fig. 5. Flow curves of selected lipogels prepared by different methods.

Table 1
Apparent viscosity of various lipogels prepared using methods 1–3.

Type of lipogels	Apparent viscosity (Pa s)	Yield value (Pa)
S3, M 1	0.47	134.0
S3, M 2	0.45	12.5
S2, M 3	0.16	38.5
S1, M 3	0.05	62.5

S: sample; and M: method.

S5 (not shown) prepared by methods 1 and 2 sowed similar apparent viscosities as that of systems containing S3. In contrast, the system containing pure homologue MgSt (S1) prepared by method 3 showed lowest apparent viscosities.

3.7. X-ray diffraction (XRD)

Fig. 6 shows the XRD data for the unstable solids prepared with mixed homologue MgSt (S3–S5) by method 3 (Fig. 6a) and for stable semisolid lipogels formed by methods 1 (~1–2% water) and 2 (Fig. 6b). All unstable solids showed a broad peak at $2\theta = 20^\circ$ (Fig. 6a). No sharp peaks were seen in these systems. In contrast, all stable semisolid lipogels showed two sharp peaks at 2θ between 25° and 30° in addition to the broad peak at $2\theta = 20^\circ$ (Fig. 6b).

4. Discussion

Lipogels of pure (S1 and S2) and mixed homologue (S3–S5) MgSt were prepared in liquid paraffin by heating to 110 °C, holding at 110 °C for 1 h and upon cooling either by adding water at 90 °C (method 1), homogenisation upon cooling (method 2) or by cooling without addition of water or homogenisation (method 3).

Lipogels obtained from mixed homologue MgSt (S3–S5) were stable semisolids when prepared by methods 1 (~1–2% water) and 2 showing similar microscopic, thermal and rheological properties, but gave unstable solids (syneresis of oil over time) when prepared by method 3. The systems with mixed homologue MgSt (S3–S5), containing ~3–4% water (method 1) were structured fluids. In contrast, systems containing pure MgSt (anhydrate or trihydrate) prepared by methods 1–3 were generally structured fluids except the lipogel containing pure MgSt trihydrate prepared by method 3 (S2, method 3), which was initially semisolid, but changed to liquid when stirred gently, implying pressure sensitivity.

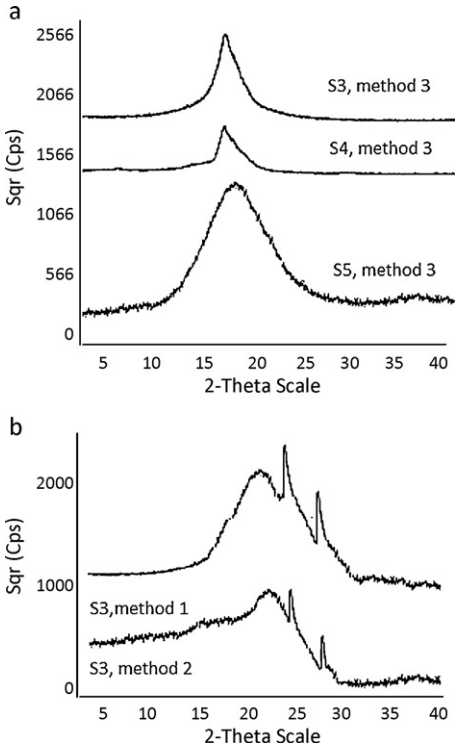

Fig. 6. Selected XRD spectra of lipogels prepared by three methods.

Rheological properties, *i.e.* semisolid nature is due to the swelling properties of α-crystalline lamellar gel network phase (Eccleston et al., 2000). The literature is confused because authors do not distinguish between α-crystalline lamellar phase and lamellar liquid crystals. Stability of colloidal dispersions has been associated with the formation of mesomorphic lamellar structures such as micelles, vesicles, liquid crystals, hexagonal or nanoparticle (Rao et al., 1992; Kriwet and Mueller-Goymann, 1993). Various liquid crystalline phases (hexagonal, cubic and lamellar) that are produced in concentrated surfactant solutions are known. Friberg (1965, 1966) proposed existence of non-aqueous lamellar micellar structure (liquid crystals) in systems containing aluminium soaps in hydrocarbons. In addition, Fukasawa and Tsutsumi (1990) also described semisolid formulations showing presence of liquid crystals formed from long-chain dialkyl phosphate salt of aluminium in non-polar (n-hexadecane) system. Scric et al. (1985, 1988) also described presence of micellar structures in the oily systems containing liquid paraffin and magnesium stearate. However, lamellar liquid crystals are fundamentally different that they do not swell significantly and convert to micelles instead forming liquids. The lamellar liquid crystalline structure may simply extend in the aqueous phase producing only two-dimensional systems showing little swelling and entrap the oil droplets forming liquid emulsions (Tadros and Vincent, 1983; Mueller-Goymann, 2004; Tadros et al., 2005; Savic et al., 2009).

Present work describes existence of α-crystalline inverse lamellar structures in the stable semisolid lipogels. This view was supported by the polarised microscopy where stable semisolid lipogels showed existence of "Maltese crosses" between crosspolars (Fig. 2a and b), which are indicative of α-crystalline lamellar phases (Eccleston, 1986; Eccleston et al., 2000). In contrast, unstable solids and fluids did not show "Maltese crosses", but rather clusters of crystals, suggesting absence of α-crystalline lamellar structures. The unstable semisolid lipogels obtained from pure MgSt trihydrate (method 3, S2) contained both plate like crystals and lamellar structures; the latter only disappeared on stirring producing liquids. Various researchers have reported significant effect of process variables such as stirring, temperature and solvent on the appearance and stability of the aqueous formulations containing stearic acid (Garti et al., 1980; Timmins et al., 1990; Lin et al., 1994; Eccleston, 1997). Eccleston (1997) showed that aqueous stearate creams are markedly affected by the mixing. She described the effect of stress on the swollen crystalline structures. It was shown that in some systems, the swollen lamellar structures appeared to be metastable and changed to non-swollen structures under pressure showing plate like crystals and attributed these differences to the marked polymorphism in the stearate creams. Therefore, pressure sensitivity of semisolid lipogel prepared using pure homologue MgSt trihydrate (method 3, S2) can be attributed to the plate like crystals.

The presence of needle-like crystals in the organogels has been associated to the tubules, suggestive of lamellar structures (Murdan et al., 1999; Jibry et al., 2004). Electron photomicrographs showed existence of needle-like crystals in all stable semisolid lipogels (S3–S5, methods 1 and 2). Therefore, same analogy can be used in the present work and the needle-like crystals (tubules) in lipogels may represent α-crystalline lamellar structures. Unstable pressure sensitive semisolid lipogels (method 3, S2) upon stirring, showed presence of plate like crystals in addition to the tubule, sug-

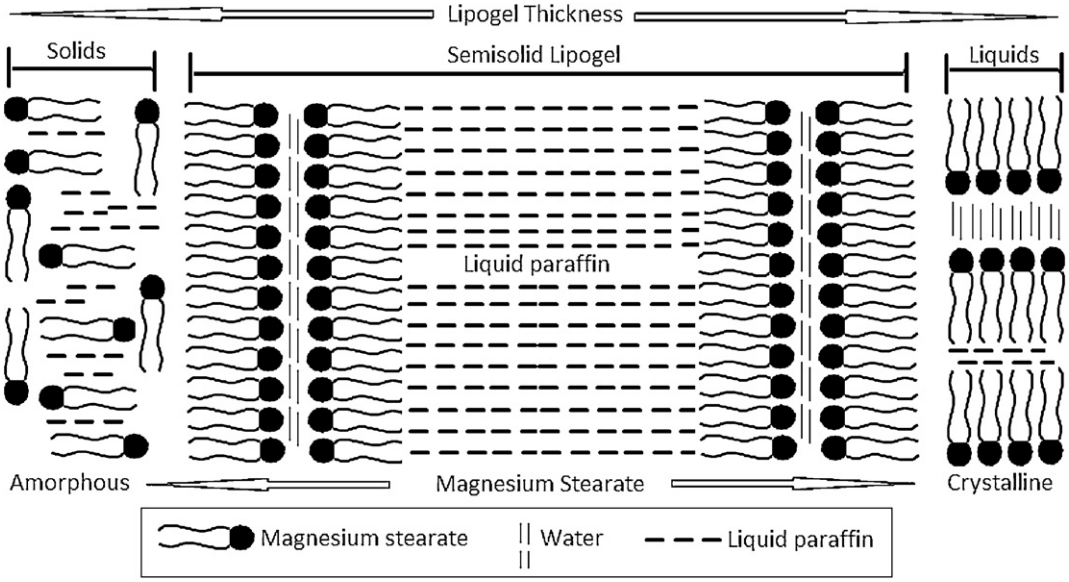

Fig. 7. Schematic diagram showing proposed lipogel structure based on the pseudopolymorphic changes in the magnesium stearate in the presence or absence of water.

gesting weakening of α-crystalline lamellar structures converting semisolids to mobile liquids (Fig. 3d).

This view was further supported by DSC data as all stable semisolid lipogels prepared by methods 1 and 2 showed similar thermal properties suggesting that the microstructures were similar (Fig. 4). The high temperature endotherm (120 °C) in stable semisolid lipogels was related to the melting of "Maltese crosses", which was confirmed by hot stage microscopy, confirming existence of α-crystalline inverse lamellar structure. In contrast, unstable solids or liquids did not show this endotherm (120 °C), which confirms that these systems lacked α-crystalline lamellar structures. In addition, pressure sensitive lipogel (method 3, S2) showed broad endotherm peaking at 85 °C, which was related to the melting of plate like crystals as confirmed by hot stage microscopy, confirming weakening of α-crystalline inverse lamellar microstructure.

Apparent viscosity values measure the ability of any system to resist the structural breakdown during a shearing process (Eccleston, 1977; Realdon et al., 2001; Ribeiro et al., 2004; Tadros, 2004). Furthermore, viscosity determinations provide information about the structural organisation of the formulation (Kohler and Strand, 1990; Mueller-Goymann, 2004). There is an increased organisation of the α-crystalline lamellar structure with an increase in the viscosity (Tadros, 2004). It can be postulated that an increase in viscosity causes structural organisation mainly due to formation of α-crystalline lamellar structure. This postulation was confirmed by the rheology data as the stable semisolid lipogels showed significantly higher apparent viscosities than the liquid systems (Table 1).

XRD data showed that MgSt is present either mainly in amorphous or crystalline state. The broad peaks in the XRD spectra are generally related to the amorphous state and sharp peaks to the crystalline state (Gunstone, 1967). The mixed homologue MgSt stable semisolid lipogels showed existence of sharp peaks at $2\theta = 24–30^{\circ}$, suggesting that MgSt is present essentially in the crystalline state producing α-crystalline lamellar structures giving rheological strength to the systems. In contrast, the solid nature of unstable systems (S3–S5) can be attributed to the broad peak at $2\theta = 20^{\circ}$, suggesting existence of MgSt mainly in amorphous state. Therefore, it is suggested that hydrated (crystalline) mixed homologue MgSt (S3–S5) upon heating to high temperature (110 °C) may have been converted to mainly amorphous state giving the formulation solid appearance. Amorphous materials are easy to disintegrate and penetration of the vehicle is rather easier due to lack of any ordered structure compared to the crystalline materials (Garti et al., 1982; Leinonen et al., 1992). The solids were brittle, fragile and crumbled to touch. Due to lack of water, lamellar structure was not fully developed and the systems showed syneresis as a consequence.

Fig. 7 illustrates proposed lipogel structure depending on the pseudopolymorphic modification of MgSt brought about by addition of water. MgSt mainly in amorphous state produces solids whereas MgSt as a mixture of amorphous and crystalline states yields stable semisolid lipogels and pure crystalline materials give structured fluids.

5. Conclusion

i The formation of stable semisolid lipogels depends on the type of magnesium stearate used and preparation technique. Mixed homologue MgSt (commercial as-received, anhydrate and dihydrate) produced stable semisolid lipogels only by methods 1 (~1–2% water) and 2. Method 3 produced unstable solids showing syneresis of oil. In contrast, pure homologue MgSt (anhydrate and trihydrate) generally produced fluids except pure homologue trihydrate MgSt (method 3), which gave pressure sensitive semisolid lipogels that changed to mobile liquid upon gentle stirring.

ii The stable semisolid lipogels showed presence of "Maltese crosses", suggesting existence of α-crystalline lamellar structures. Unstable solids and fluids did not show "Maltese crosses", suggesting lack of α-crystalline lamellar structures. Furthermore, unstable semisolid lipogels prepared using pure homologue trihydrate MgSt (method 3) showed presence of plate like crystals, implying pressure sensitivity.

iii MgSt was essentially in the crystalline state in semisolid lipogels producing α-crystalline lamellar phases. In contrast, MgSt was mainly in the amorphous state in unstable solids.

Acknowledgement

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