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FORMULATION AND PHYSICAL PROPERTIES OF THIXOTROPIC GELS FOR HARD GELATIN CAPSULES

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ABSTRACT

Thixotropic gels for filling into hard gelatin capsules at room temperature were formulated using Miglyol 829 and colloidal silicon dioxide. Initial studies on several vehicles were undertaken prior to selection of Miglyol 829 for detailed study. The rheological properties of the gels and drug/gel formulations have been investigated in detail and the results are discussed with reference to capsule filling, stability and drug release of a model drug propantheline bromide (PPBr).

INTRODUCTION

It is generally accepted that the industrial scale filling[1,2] and if necessary, sealing technology[3], is now available such that liquid or semi-solid hard gelatin capsule formulations are a practical alternative to soft gelatin capsules. With developments in formulation and manufacturing technology,[4,5] the last decade has seen a great deal of interest in this area and a number of pharmaceutical and health food products have been introduced.[6] The potential advantages of these so-called semi-solid matrix (SSM) capsule formulations over conventional powder filled systems are well documented[7,8]. These include improved content uniformity and reduced handling risks for low

dose drugs where the properties and behaviour of the bases will be particularly important.

The problem of leakage from the capsule may be overcome by maintaining the capsule contents in liquid form only during the filling process. This may be achieved using either thixotropic formulations which are liquified by shear stress, or techniques which require heat to produce a mobile liquid. Much of the published work is concerned with the latter type of formulation where the drug is dispersed in the molten excipient followed by filling and solidification on cooling. This is due to a wide choice of solid excipients with melting points appropriate to capsule filling, together with continued interest in the enhancement of drug release by the formation of solid dispersions and in some cases solid solutions. However, the disadvantages of thermosoftened formulations include decomposition of thermolabile drugs, crystal structure changes during storage/temperature cycling and the manufacturing restrictions of handling bulk thermosoftened formulations during batch filling processes.

Thixotropic systems avoid the problems of thermal effects by filling at room temperature, however, their rheology, structure and drug release properties are not well understood. The work presented here is part of a detailed investigation of thixotropic semi-solid drug matrix systems.

MATERIALS AND METHODS

Selection of Excipients

Vehicle

Cuine and Mathis[9] created thixotropic systems with the addition of one or more thickening agents to oily vehicles including arachis, castor and olive oils. Less chemically complex, non-rancifiable materials were later employed, one of which required filling at 35°C. In this study, four semi-synthetic stable oils of defined composition were identified as possible vehicles for room temperature filling; a diglyceryl partial ester of caprylic acid (Imwitor 708), glyceryl mono-dicaprylate (Imwitor 908), isostearyldiglyceride succinate (Imwitor 780K) and a glyceryl ester of caprylic, capric and succinic acids (Miglyol 829) (all Hulls Ag).

Physical properties of the vehicles related to the product integrity of filled capsules were determined. For example, moisture uptake of the formulation has an important influence on gelatin shell stability, whilst viscosity and surface tension of the liquid vehicle will be important in terms of leakage. Moisture uptake was determined gravimetrically over a period of 28 days by storage at each of seven relative humidities (RH) ranging from 11 to 81% at 18-20°C. Viscosity at room temperature was determined using a rotational viscometer (Haake, RV3) with MV or SV concentric cylinder geometry. Surface tension was determined using a Du Nouy ring tensiometer (Cambridge Instruments) at room temperature.

Thickener

Various fats and waxes may be incorporated at the melt stage for thermosoftened formulations, but for systems to be formulated and filled at room temperature the choice is more limited. Two grades of colloidal silicon dioxide, Aerosil 200 and R974 (Degussa) were selected.

Gel Preparation.

The SSM bases were prepared by a defined procedure from the maximum silica content of 12%w/w, by dilution with oil to produce gels with silica content in the range 0.8-11%w/w.

Rheology of Bases.

The rheological properties of the SSM bases were investigated at 20 and 37°C using a constant stress rheometer (Carri-Med, CSL 100) and continuous shear flow, creep and oscillation techniques with 4cm, 2° cone and plate or parallel plate geometry.

In-Vitro Release Properties.

Propantheline bromide (PPBr), particle size <50μm (used as received; Sigma) was selected as a model drug. It was dispersed in the base and hand filled by weight into size 1 opaque hard gelatin capsules with drug content 50±1.5mg. In-vitro dissolution testing was performed in triplicate under sink conditions, not more than 24 hours after capsule filling.Using a BP beaker/basket type dissolution apparatus (Caleva), filled capsules were rotated

at 100rpm in 1000ml of distilled water at 37°C.Drug concentration in solution was determined spectrophotometrically at 243nm using a continuously sampling analytical system (Cecil Instruments).

RESULTS AND DISCUSSION

Selection of Excipients.

A formulation for filling as a liquid into hard gelatin capsules can in most cases be developed using only two or three excipients. In addition to preventing leakage from the capsule during storage or handling, such formulations must be compatible with the gelatin shell and possess appropriate rheological properties to facilitate accurate pumping and hence good dosage uniformity.

Moisture Uptake by Oily Vehicles.

Moisture uptake by the vehicles is of prime consideration. Glycerol, propylene glycol, and sorbitol, commonly used in syrups and in soft gelatin capsules, are too hygroscopic. Higher molecular weight polyethylene glycols (PEGs) are successfully used in thermosoftened formulations for hard gelatin capsules,[10] but the increased hygroscopicity associated with the lower molecular weight liquid PEGs makes them unsuitable for room temperature filling. Hygroscopic fills would cause the capsule shell to dehydrate and exhibit characteristic splitting when protected from external moisture.[11]

The isotherms produced for the four selected vehicles were compared with that for PEG 600 (the least hygroscopic liquid PEG) under the same storage conditions.(Figure 1).Optimum shell moisture content is 14-16% and from this it can be estimated that moisture uptake of 2 to 3%, from the capsule by the formulation may cause splitting. The vehicles were hand filled into size 1 capsules, stored at 33, 55 and 75% RH and examined for splitting over a period of 28 days.

Table 1 compares the moisture uptake values for the vehicles with the tendency for capsules to split when stored at 55% RH. The moisture uptake values indicate that PEG 600 and Imwitors 708 and 908 sorbed more than 2.45% whereas Imwitor 780K and Miglyol 829 sorbed less than 0.25% at 55% RH. The former uptake values are large enough to reduce the shell moisture content to below 14% and cause capsule splitting.

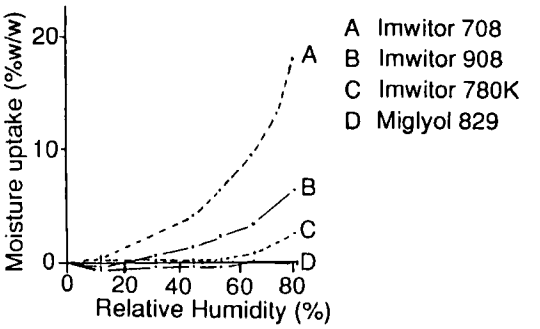

FIGURE 1.
Moisture Isotherms of Oily Vehicles and PEG 600

TABLE 1

Moisture Uptake (M) and Time to Capsule Splitting (T) for novel vehicles at 55% RH

	M(%w/w)	T(days)
PEG 600	12.18	<1
Imwitor 708	7.32	<1
Imwitor 908	2.45	<1
Imwitor 780K	0.25	>28
Miglyol 829	0.00	>28

The nygroscopicity of PEG 600 is well documented whereas the behaviour of Imwitors 708 and 908 has not been reported. The relative hygroscopicity of these two vehicles was attributed to the presence of hygroscopic impurities; 21% diglycerin and 6-10% glycerol respectively, and hence they would not be suitable for hard gelatin capsule formulation without removal or reduction of these impurities. The results for Imwitor 780K and Miglyol 829 show that these vehicles are of low hygroscopicity, do not cause

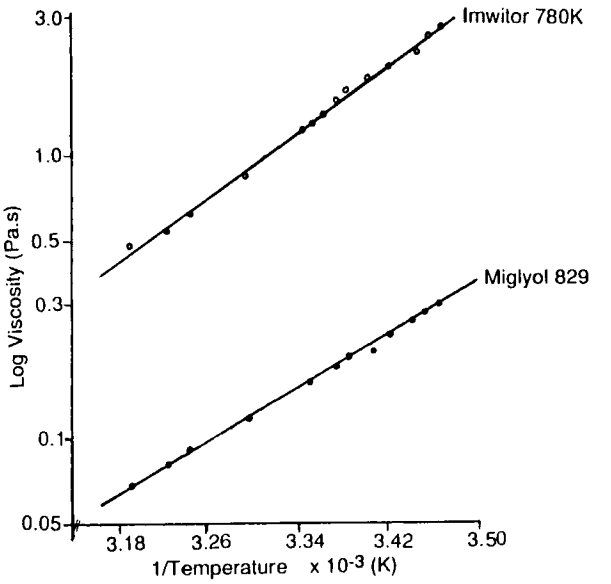

FIGURE 2.
Arrhenius Relationship Between Viscosity and Temperature for Miglyol 829 and Imwitor 780K.

capsule splitting and were therefore considered for further investigation.

Viscosity

The viscosities of the two oils selected for further study were 0.21 Pa.s (Miglyol 829) and 1.67 Pa.s (Imwitor 780K) at 20°C. In each case, Newtonian rheological behaviour was observed in shear flow within the normal ranges of storage temperature, (15 to 40°C). Arrhenius-type plots of viscosity versus the reciprocal of absolute temperature for the two vehicles indicate a greater temperature dependence for the more viscous oil, with activation energies for viscous flow of 43.79 and 60.16 kJ mol^{-1} for Miglyol 829 and Imwitor 780K respectively (Figure 2).

Surface Tension

Surface tension values for the two oils were 33.4 mNm^{-1} for Imwitor 780K and 32.4 mNm^{-1} for Miglyol 829 at 18°C. The role of surface tension in the filling and leakage processes is not fully

TABLE 2.

Comparison of Silicas

Product	Aerosil 200	Aerosil R974
Behaviour to water	Hydrophilic	Hydrophobic
Specific surface area (m^2/g)	200±25	170±20
Primary particle size (nm)	12	12
Pore size	none	none
SiO_2 (%)	>99.8	>99.8

understood, and is further complicated by the uncertain effects of viscosity. However, an examination of the literature suggests that values over 30 mNm^{-1} are likely to be satisfactory, but it is evident that further work is required in order that capsule leakage may be predicted from the physical properties of the vehicles.

Rheology of Bases

Since the oils in this study exhibit Newtonian behaviour, then any shear rate and/or time dependent rheological properties of the bases, including thixotropy, must result from the incorporation of thickening agent. Aerosil is an example of pyrogenic silica. This is a very pure form of silicon dioxide aerosol obtained by high temperature oxidation and flame catalysed hydrolysis of a volatile silane compound in an O_2/H_2 gas flame.

The degree of viscosity modification/gelation achieved when silica is added to a liquid depends upon the method of manufacture, impurities, pore characterisation, ultimate particle

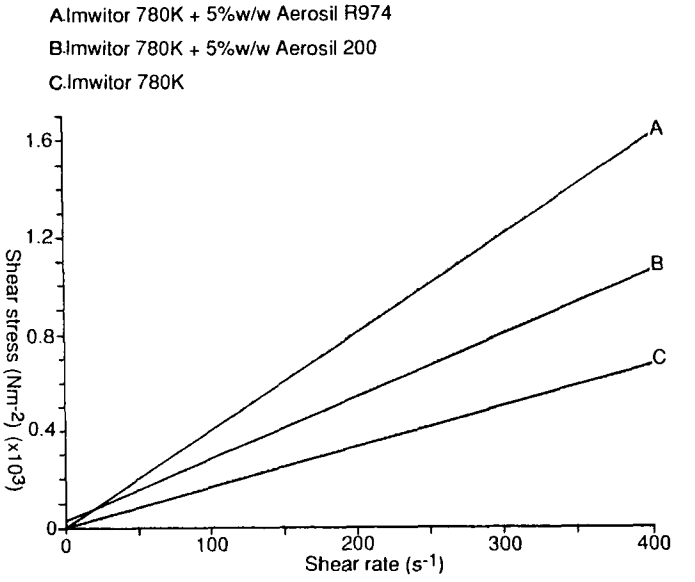

FIGURE 3.
Rheograms for Imwitor 780K gels with 5%w/w Aerosil R974 or 200

size, aggregate size and strength and the nature of the silica surface.[12] Table 2 compares the properties of the two Aerosil grades used in this study. These grades have the same particle size and approximate specific surface area but differ in the nature of their surface functional groups, i.e. Aerosil 200 has predominantly silanol surface groups, and is designated hydrophilic, whilst in contrast, Aerosil R974 has been chemically modified by treatment with silane to possess predominantly siloxane surface functional groups, and is thus termed hydrophobic.

Rheological classification of a system in simple shear flow produces a rapid evaluation of the effect of parameters such as shear rate, temperature and shear history on viscosity.The effect of each type of Aerosil on rheological classification of Imwitor 780K is first demonstrated for 5%w/w gels.

Figure 3 compares the rheological behaviour of the Imwitor 780K gels up to approximately 400s^{-1} shear rate at 20°C. Aerosil R974 added to Imwitor 780K produced no deviation from Newtonian

behaviour, although the viscosity increased from 1.67 to 4.03 Pa.s at 20°C, whereas using the same concentration of Aerosil 200 non-Newtonian effects were observed. These gels exhibit time-independent shear thinning behaviour (i.e.no thixotropy), which over a limited shear rate range may be described by the Bingham derived equation:

$$\sigma = \sigma_y + \eta_p\gamma \qquad \text{Equation 1}$$

where σ is the shear stress, γ is the shear rate, σ_y and η_p are the constants yield stress and plastic viscosity respectively.

Determination of the flow properties of liquid or semi-solid pharmaceuticals is important at many stages of product development, but information regarding desirable rheological properties of SSM bases is unavailable. However, for non-Newtonian materials rheological parameters should be determined at a shear rate relevant to the process being investigated, before useful interpretation of experimental data can be made. The filling process is by controlled pressure precision pumping through dosing nozzles into the capsule bodies, where typical shear rates are likely[13] to be of the order of 10^{o} to$10^{3}s^{-1}$. McTaggart et al[14] reported good uniformity of fill weights with products of viscosity 0.1 to 270 Pa.s. More recently, other workers[15] found a viscosity of 0.027 Pa.s to be too low for optimum pumping.

The SSM bases also require sufficient consistency to prevent sedimentation of suspended drugs with particle size <50μm[16]. The drug/base mix should remain homogeneous throughout both the filling process (to ensure satisfactory content uniformity) and the longer term shelf life of the product (to prevent leakage or changes in drug release.) Typical shear rate ranges encountered in sedimentation of fine powders are of the order of 10^{-6} to$10^{-4}s^{-1}$. Despite the absence of thixotropic behaviour, whilst the very low shear rate viscosity of Imwitor 780K at room temperature was sufficient to prevent leakage from the capsules, the high shear rate apparent viscosity of the 5%w/w Aerosil 200 gel was shown to be suitable for filling on a capsule filling simulator (Hibar), producing a coefficient of fill weight variation of 0.44% (sample size 55).

A.Miglyol 829 + 4.5%w/w Aerosil 200

B.Miglyol 829 + 4.5%w/w Aerosil R974

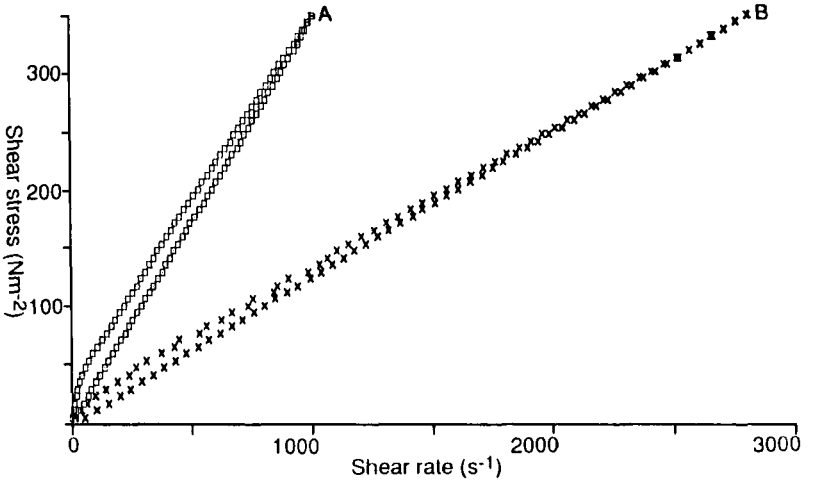

FIGURE 4.
Rheograms for Miglyol 829 gels with 4.5%w/w Aerosil R974 or 200

The effect of each type of Aerosil on the rheology of Miglyol 829 is demonstrated in the rheograms of Figure 4 for equivalent concentrations (4.5%w/w) at 20°C. Both systems show time dependent shear thinning behaviour. The up curves of the shear flow loops may be fitted to the Bingham equation over the shear rate range shown, and in general, Aerosil R974 gels exhibit much lower values for apparent viscosity, calculated yield value and thixotropic area between the up and down curves.

The effect of temperature on the apparent viscosity of these gels (taken from the apex of the shear stress/shear rate curves at a shear stress of 350 Nm^{-2}) is shown with Arrhenius-type plots in Figure 5. The activation energies for viscous flow of the 5%w/w Aerosil gels are 43.29 kJ mol^{-1} and 41.39 kJ mol^{-1} for Aerosils R974 and 200 respectively suggesting essentially the same mass transfer effect as for the unthickened oil.

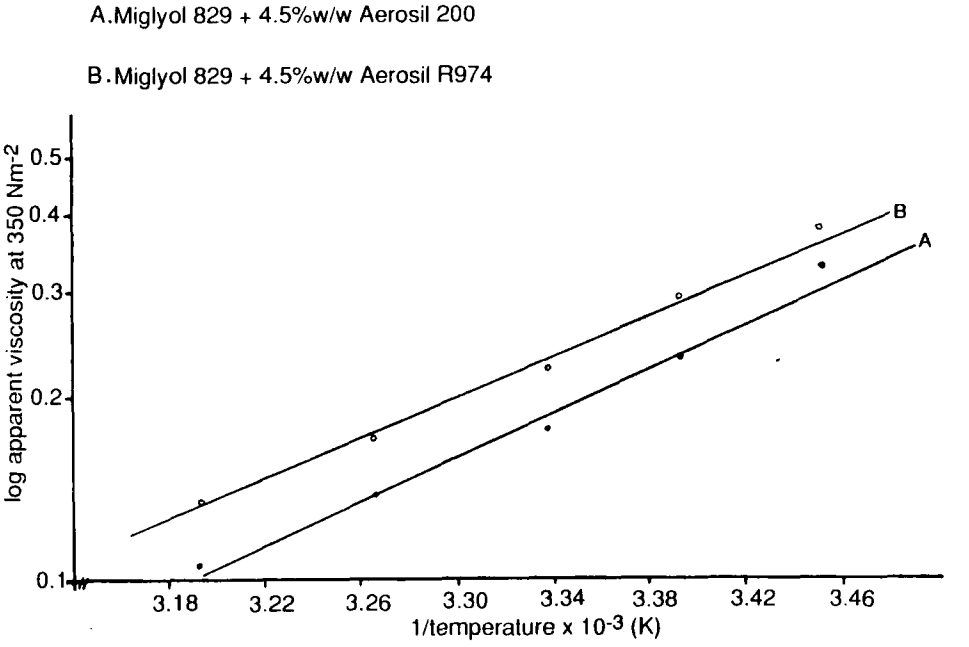

Figure 5.
Arrhenius-type Plots to Demonstrate the Effect of Temperature on Miglyol 829 Gels with 4.5%w/w Aerosil 200 or R974.

When Aerosil is dispersed into liquids the silanol groups may interact and the relationship between this disperse phase and the Miglyol 829 must be considered. Maximum network formation and thixotropy occur when small three dimensional aggregates link together through the polar areas of silica in the oil, to extend throughout the liquid in a three dimensional network, helped by traces of water. Such linkages involving hydrogen or hydrophobic bonding are readily broken down by shearing and are similarly re-established when the system is at rest. Thus a high degree of thixotropy is established with gel formation by Aerosil 200 in Miglyol 829, whereas less interaction, and therefore thixotropy, is possible with Aerosil R974.

Further rheological investigations of the Miglyol 829/Aerosil 200 system have been undertaken in order to examine the thixotropic behaviour of gels made with a range of silica concentrations from 1.5 to 10%w/w. Similar thixotropic behaviour

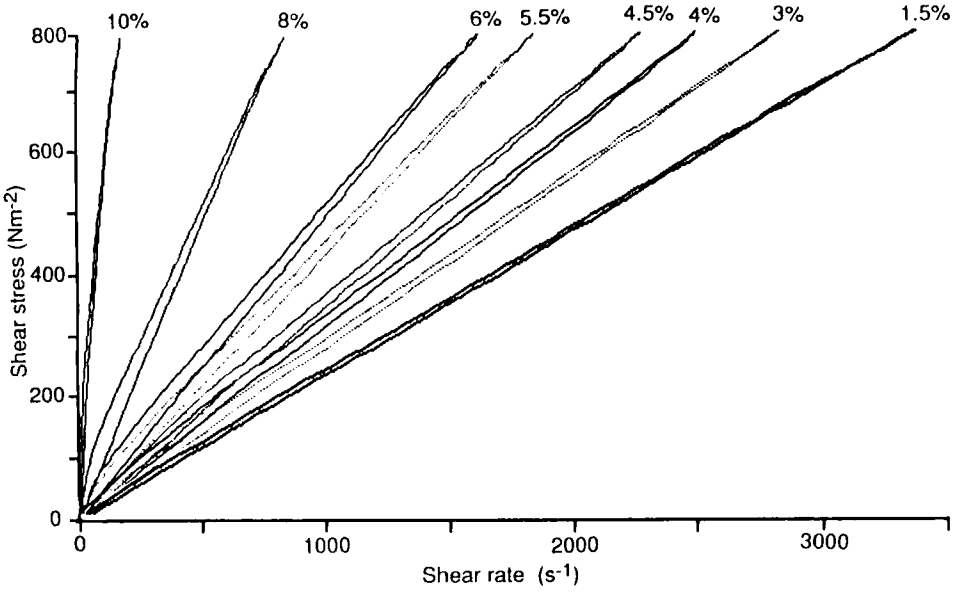

FIGURE 6.
Rheograms for Miglyol 829/Aerosil 200 gels

with apparent yield was observed for all Miglyol 829/Aerosil 200 gels and small changes in Aerosil 200 content (0.5%) affected the apparent viscosity, calculated yield and thixotropic area (Figure 6).

At a higher shear rate (13250 s^{-1}) apparent viscosity was shown to be log-linearly related to Aerosil 200 concentration both with and without PPBr (12.5%w/w). The high shear rheological parameters were also observed to increase during room temperature storage. This may have the advantage of preventing leakage from the capsule shell, but must not significantly reduce drug diffusion rate and hence release of the drug from the gel. This high shear data enables optimization of silica content and temperature for efficient preparation and filling.

High-shear measuring methods are useful for predicting the behaviour of products during the normal processes of manufacturing where significant breakdown occurs, however for efficacy evaluation and quality control they may be less meaningful. Sophisticated rheological methods such as creep

(transient) testing and oscillatory (dynamic) techniques enable the almost undisturbed viscoelastic properties of such semi-solid systems to be studied.[17,18] With creep tests the steady state viscosity η_o may be determined at very low shear rates. For example, an 8%w/w Aerosil 200 gel has an apparent viscosity in shear flow at $734s^{-1}$ shear rate and 37°C of 0.48 Pa.s, yet from a creep test at the same temperature the steady state viscosity at $8x10^{-5}s^{-1}$ shear rate is 12520 Pa.s.

Oscillatory testing provides a convenient way of determining both the viscous and elastic components of a material independently. In this case the material is subjected to a small amplitude sinusoidal stress and the resulting strain recorded. The amplitude ratio of the stress to the strain gives the complex modulus G*, and using the phase angle shift δ, the storage and loss moduli G' and G'' are calculated from the relationships

$$G' = G^* \cos d \qquad \text{Equation 2}$$

$$G'' = G^* \sin d \qquad \text{Equation 3}$$

$$G^* = G' + iG''$$

$$\text{where } i = (-1)^{0.5} \qquad \text{Equation 4}$$

Investigations in the linear viscoelastic regions of the Aerosil 200 gels show that at low concentrations of silica the viscous component of the modulus, G'', is greater than the elastic component, G', indicating weak interaction between the particles (Figure 7). As the Aerosil concentration is increased, a reduction in the slope of the G' line reflects the increase in solid-like behaviour. The magnitude of these parameters also increases with increased silica concentration, as G' becomes much greater than G'' and close to the complex modulus G*, indicating strong interaction and significant gel structure.

Figure 8 shows the rate of reformation of structure for an 8%w/w Aerosil 200 gel at 1 Hz following a period of high shear rate thixotropic breakdown at 20°C typical of that which the system would experience during the capsule filling process. This very low shear rate study illustrates the initial phase of the longer term viscosity increase observed by continuous shear techniques, and the rapid redevelopment of structure suggests

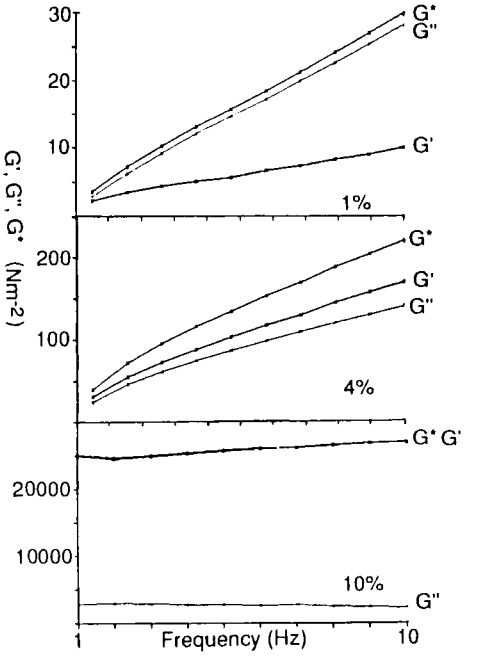

FIGURE 7.
Variation in Viscoelastic Behaviour with Aerosil 200 Concentration

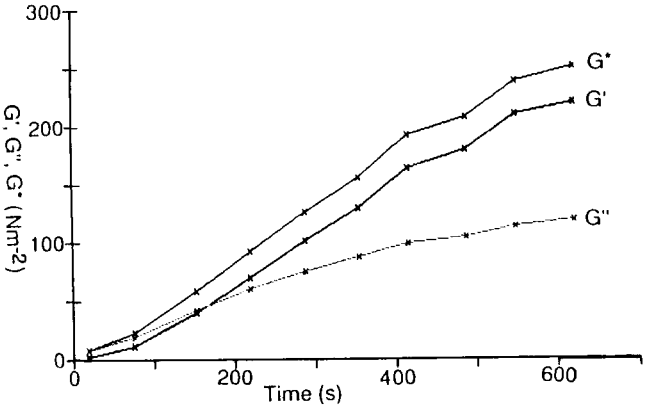

FIGURE 8.
Increase in Viscoelastic Parameters with Time for an 8%w/w Aerosil 200 gel

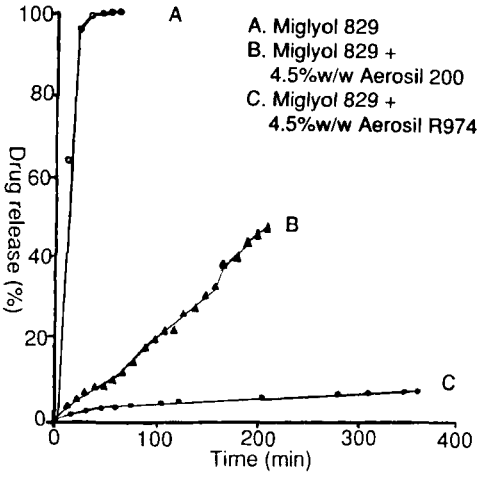

FIGURE 9.
In-vitro release of PPBr from Miglyol 829 and gels formed with Aerosil

that leakage would be unlikely in the immediate post-filling period.

In-Vitro Release of a Model Drug.

Figure 9 compares the drug release profiles of PPBr from unthickened Miglyol 829 and gels prepared with approximately equal concentrations of either Aerosil 200 or Aerosil R974. It is immediately apparent that drug release is significantly reduced in the presence of each thickener and that a greater reduction is shown with hydrophobic silica. Gels generally disperse more slowly than the oil and similarly reduced release rates have been observed by other workers.[19,20].

The effect of concentration of hydrophobic silica (Aerosil R974) in the base on PPBr release is demonstrated in Figure 10. A very low percentage (0.8%w/w) dramatically affects release rate and although approximately 25% of the PPBr is released from the base in less than 10 minutes, no significant further release is then seen within 2.5 hours. Initially, progressively increasing the concentration to 4.5%w/w reduces the release rate to a

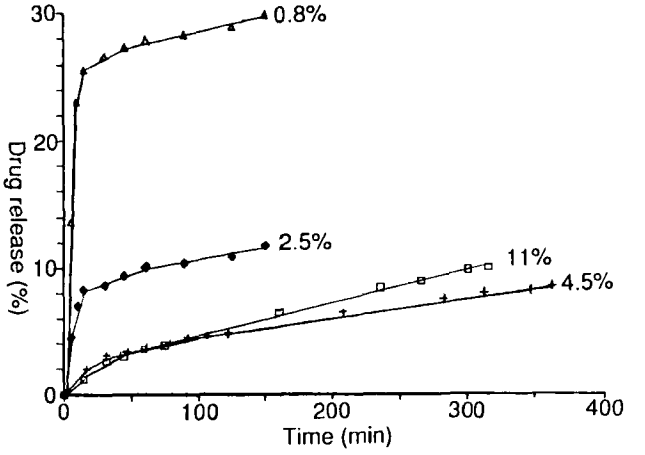

FIGURE 10.
In-vitro release of PPBr from Miglyol 829/Aerosil R974 gels

minimum, thereafter increase in concentration up to 11%w/w has no further effect.

Similarly, Figure 11 shows the in-vitro release profiles from unthickened Miglyol 829 and gels containing Aerosil 200 at concentrations up to 4%w/w. As with the hydrophobic Aerosil, increasing silica concentration appears to reduce the rate of drug release. However, in direct contrast, with further increase in silica content above 4%w/w (Figure 12) there is an increase in dissolution rate, until at maximum silica content (12%w/w) the drug release from the gel more closely resembles that from the unthickened oil.

Reference has been made to the influence that rheological properties may have on drug release and bioavailability. Cuine et al[19] demonstrated slowed dissolution of ferrous sulphate formulated in hard gelatin capsules, with the increased viscosity of oily vehicles, whereas Hunter et al[21] showed that increases in viscosity of PEG 1000 thickened with Aerosil 200 appeared to have little effect on the in-vivo dispersion and gastric emptying of the capsule contents. Most semi-solid systems exhibit complex flow behaviour dependent on the methods of rheological evaluation, and with topical semi-solids the choice of suitable

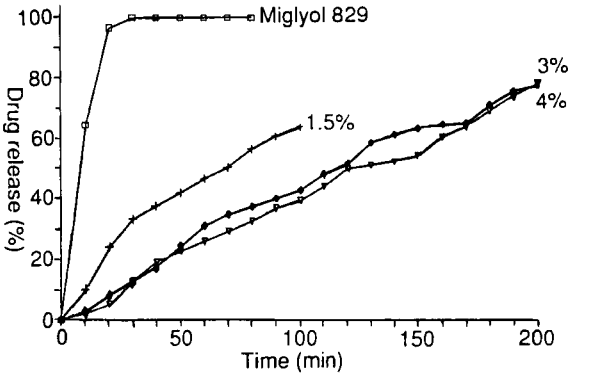

FIGURE 11
In-vitro release of PPBr from Miglyol 829/Aerosil 200 gels:
0 to 4% w/w

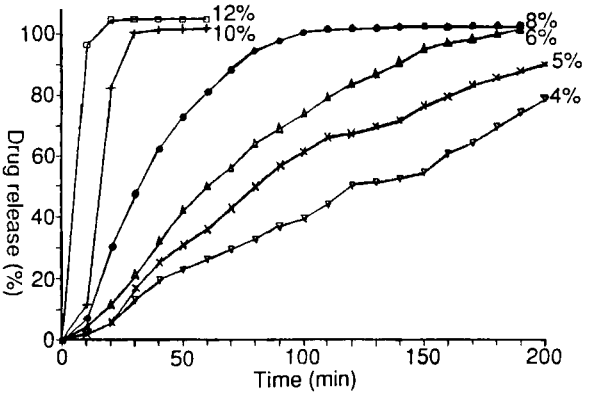

Figure 12
In-vitro release of PPBr from Miglyol 829/Aerosil 200 gels:
4 to 12% w/w

parameters that would lead to useful interpretation of various experimental data has been discussed.[22]

Previous attempts to relate drug release from semi-solid filled hard gelatin capsules with rheological properties have employed continuous shear techniques which cause extensive material deformation and alteration in structure. However, as with topical semi-solids[23], methods which observe the undisturbed structure of the system may prove more successful since they are more likely to represent the rheological environment of a diffusing drug molecule. Although it may be expected that an increase in viscosity of the base will lead to a reduceddiffusion coefficient for the drug in the SSM, it is often difficult to show any changes in drug diffusion and release that are wholly attributable to rheological factors[20].

The results for the release from gels in this work indicate that in some cases drug release is related to gel viscosity, whereas in other cases alternative physical properties control the release rate. It would appear that whilst the hydrophobicity of the system remains unchanged, rheological parameters control drug release (e.g., Miglyol 829/Aerosil R974 systems) up to the point where increase in viscosity has no further effect on release. However, with increasing Aerosil 200 concentrations the hydrophilic character of the silica becomes more important than viscosity in the control of drug release.

CONCLUSIONS

In-vitro release of a highly water soluble drug (PPBr) may be controlled by a thixotropic gel system. The rate of release was shown to be dependent upon the type and concentration of Aerosil in the gel and a wide range of drug release profiles from immediate to controlled release were observed. The release rate cannot simply be related to the viscosity of the gel and further investigations of the gel structure will be undertaken to elucidate the release mechanisms.

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