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Research Article

Microviscosity and Drug Release from Topical Gel Formulations

Khalil I. Al-Khamis,[1] Stanley S. Davis,[1] and Jonathan Hadgraft[1,2]

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Gel formulations are often used in topical drug delivery, and the drug release is controlled by two factors, the thermodynamic activity of the drug and the microviscosity of the gel. The latter property has been probed by observing the dynamic light scattering from polystyrene lattices of known particle size dispersed within Carbopol gels. The effect of gel concentration and temperature has been observed and related to the ability of the gel to release a series of salicylates.

KEY WORDS: microviscosity; gels; Carbopol; dynamic light scattering; diffusion.

INTRODUCTION

The rate of drug release from topical preparations can influence the bioavailability of the formulation (1). This is especially apparent if the product is used on diseased skin where the barrier function of the stratum corneum has been impaired. In order to optimize formulations it is consequently desirable to understand the basic physicochemical factors that influence their release properties. The main controlling factors are the thermodynamic activity of the drug and its diffusion through the preparation. It is difficult to separate the two effects (2) but in this publication we concentrate on the diffusional properties.

The diffusion coefficient of a solute in a base is inversely related through the Stokes–Einstein equation to the viscosity of the continuous phase. The main difficulty is to establish which rheological property should be used to predict the diffusion rate of the drug. In the case of the gel systems in which we are interested, it may be more appropriate to investigate the microviscosity of the formulation rather than any bulk properties. The microviscosity of gels may be investigated by a variety of spectroscopic techniques, including nuclear magnetic resonance and electron spin resonance (3), but little attention has been given to the use of photon correlation spectroscopy (PCS) (4).

PCS may be used to measure the diffusion coefficients of macromolecules or particles in solution, provided that the motion of the particle is controlled by random Brownian movement (5). If spherical particles scatter the light, their size can be estimated from their diffusion coefficient and the viscosity of the medium in which they are suspended. Polystyrene latices of known particle size can be incorporated into optically clear gels and their motion studied using PCS. Although large compared with the molecular structure of the gel network, the microviscosity of the gel appears to control the movement of the particles. Thus this technique can be used to study the microviscosity of optically clear gels and the results compared with the release properties of the formulation.

MATERIALS AND METHODS

Carbopol 940 was a gift from B. F. Goodrich and was used as supplied. It produces an optically clear gel when neutralized by the following procedure. Prefiltered triply distilled water was stirred at 100 rpm and the required weight of Carbopol 940 added slowly. Stirring was continued until the powder was completely dispersed. The mixture was allowed to stand for 6 hr to allow entrapped air to escape. Stirring was recommenced and the mixture adjusted to pH 7.2 with a solution of sodium hydroxide. For the light-scattering studies, polystyrene latices of diameter 0.642 μm [Dow Chemicals] were gently mixed into the gel to form a

Table I. Apparent Diffusion Coefficients (D_{app}) of 0.642-μm Polystyrene Latices in Carbopol 940 Gels and the Corresponding Microviscosity

% (w/w) Carbopol	D_{app}/cm² sec⁻¹ × 10⁹	η/cp
0	7.87	0.88
0.01	5.20	1.33
0.05	1.38	5.01
0.075	1.18	5.86
0.10	0.87	7.95
0.25	0.72	9.65
0.50	0.51	13.46
0.75	0.42	16.59
1.00	0.34	20.58
1.25	0.28	24.44
1.5	0.23	29.81

[1] Department of Pharmacy, University of Nottingham, University Park, Nottingham NG7 2RD, U.K.

[2] To whom correspondence should be addressed at The Welsh School of Pharmacy, UWIST, P.O. Box 13, Cardiff CF1 3XF, U.K.

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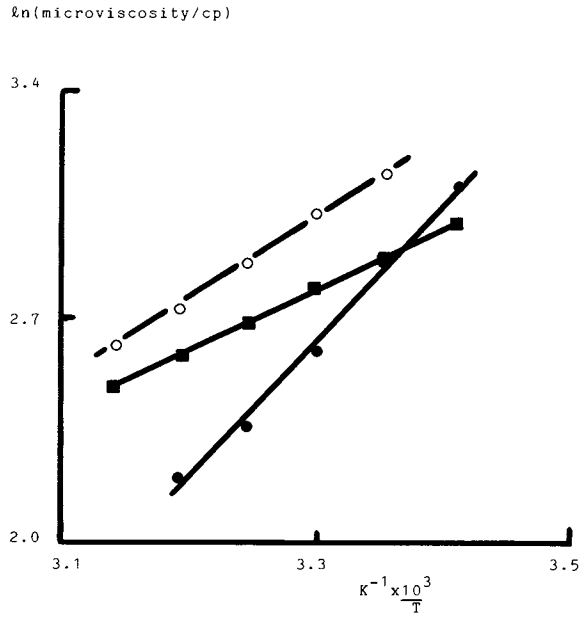

Fig. 1. Arrhenius plots for the microviscosity data of Carbopol 940 gels. (○) 1% (w/w); (●) 0.5% (w/w). Water (■) is included for comparison but the data (from Ref. 8) have been expressed as 3 + ℓn (viscosity/cp).

uniform suspension. The gel was then introduced into a sealed cylindrical PCS cell and allowed to stand for 24 hr. The formulations for the solute release studies were prepared similarly except the solute was added in place of the latices and the gel was mixed thoroughly in a Silverson homogenizer. The solutes used were:- methyl salicylate, ethyl salicylate, phenyl salicylate [BDH, Analar] and glycol salicylate which was a gift from Boots plc.

Dynamic light-scattering experiments were conducted using a Malvern Instruments photon correlation spectrometer, K7025, with 64 channels and a Liconix 14-mW HeCd laser. The correlator was interfaced to a Commodore 32K Pet, and the signal analyzed using the Malvern Application Program. Sample times were set using visual observation of the oscilloscope and the experiment duration was based on the scattering intensity of the gel formulation. Samples of gel without dispersed polystyrene did not produce correlelograms at the sample times used. Using the Stokes–Einstein equation,

$$D = \frac{kT}{6\pi r\eta} \quad (1)$$

where D is the diffusion coefficient, k is the Boltzmann constant, η is the viscosity, and r is the particle radius. The

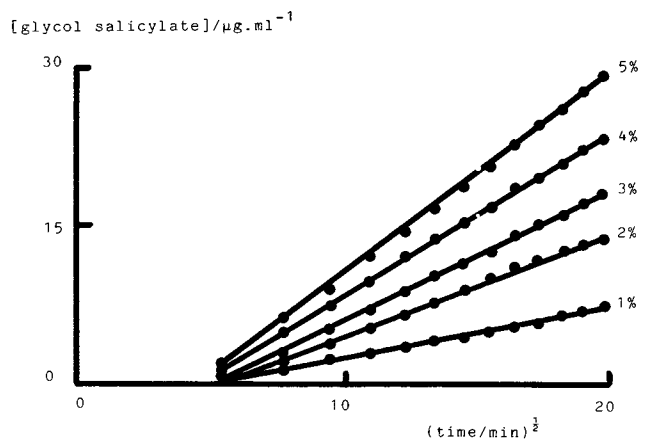

Fig. 2. Glycol salicylate release from 1% Carbopol gel at 30°C. The effect of varying the drug concentration is shown and the data are plotted according to Eq. (2).

effective viscosity of the preparation was assessed from the measured diffusion coefficient and the known particle radius.

The release properties of the gels were measured using the method described by Billups and Patel (6). The inert membrane used was polydimethylsiloxane of 0.13-mm thickness and was shown in all experiments to provide no contribution to the rate of release of the drug. The release rates from the gels were analyzed (7) according to Eq. (2):

$$Q = [2\,Dc_oc_st]^{1/2} \quad (2)$$

where Q is the amount of drug released per unit area at time t, c_o is the concentration of the drug in the gel, c_s is the solubility of the drug in the gel, and D is the effective diffusion coefficient of the drug in the gel. The appearance of the salicylate in the normal saline receptor phase was monitored by uv spectrophotometry on the removal of samples at 30-min intervals.

RESULTS AND DISCUSSION

Carbopol 940 gels containing different concentrations of the gelling agent were studied at 30°C. The results from dynamic light scattering are shown in Table I. The microviscosities of the gels compared with water (0.798 cp; Ref. 8) change by a factor of 30; this is considerably less than the bulk viscosity, which changes by five orders of magnitude as determined by continuous shear rheometry (9). Clearly the technique of PCS is probing the microstructure of the gel rather than the bulk properties.

At two gel concentrations, 0.5 and 1.0% (w/w), the microviscosity was studied as a function of temperature. The

Table II. Solubility of Salicylate (mg/ml) in 0.9% (w/v) Sodium Chloride Solution at Different Temperatures

Temperature (°C)	Methyl salicylate	Ethyl salicylate	Glycol salicylate	Phenyl salicylate
25	0.67	0.64	9.08	0.16
30	0.95	0.77	10.57	0.18
35	1.23	0.89	11.98	0.20
40	1.52	1.02	12.89	0.24
45	1.81	1.14	13.72	0.27

Table III. Apparent Diffusion Coefficient of Salicylates from Various Concentrations of Carbopol Gel and Different Drug Concentrations at 30°C

Carbopol gel conc. (%, w/w)	Drug conc. (%, w/w)	Methyl salicylate ($D \times 10^{-5}$ cm^2 sec^{-1})	Ethyl salicylate ($D \times 10^{-5}$ cm^2 sec^{-1})	Glycol salicylate ($D \times 10^{-6}$ cm^2 sec^{-1})	Phenyl salicylate ($D \times 10^{-7}$ cm^2 sec^{-1})
0.5	2.0	0.96	0.55	—	—
	5.0	0.97	0.68	2.65	—
	8.0	1.32	0.94	—	5
1.0	1.0	—	—	0.55	—
	2.0	0.7	0.37	1.21	—
	3.0	—	—	1.36	—
	4.0	—	—	1.57	—
	5.0	0.8	0.38	1.97	2.43
	8.0	0.85	0.62	—	2.22
	10.0	1.05	—	—	5.57
2.0	2.0	0.58	0.09	—	—
	5.0	0.70	0.17	1.72	—
	8.0	0.77	0.25	—	3.08
	10.0	0.94	—	—	—

results are given in the form of an Arrhenius plot in Fig. 1. The gradients are used to calculate the energy of activation of particle movement and hence microviscosity. For the two gel concentrations 0.5 and 1%, the values are 32 and 23 kJ · mol^{-1}, respectively. These values may be compared with that of water, which is 20 kJ · mol^{-1}. This suggests that in the 1.0% gel the microenvironment which the particle experiences is very similar to that of bulk water.

Release studies from the carbopol gels were conducted on four salicylates, methyl, ethyl, glycol, and phenyl. The solubilities of these esters were determined in normal saline and are presented in Table II. Release was studied as a function of solute concentration, gel concentration, and temperature. The results were analyzed using the relationship given in Eq. (2) and typical results are reproduced in Fig. 2. The gradients of these lines give a value of the apparent diffusion coefficient of the drug in the gel matrix. Table III summarizes the results showing the effects of solute and gel concentration at a fixed temperature, 30°C. From the results it can be seen that the apparent diffusion coefficient of the salicylate decreases with increasing gel concentrations. This is in agreement with the microviscosity results. The diffusion coefficient of a solute within a polymeric gel network is influenced by the volume fraction of the polymer (ϕ) present. This obstruction effect can be described (10) by Eq. (3):

$$D_g = D_w/(1 - K\phi) \quad (3)$$

where D_g and D_w are, respectively, the diffusion coefficients of the solute in the gel and water. If the solute is not absorbed onto the polymer, the value of K assumes a value of 0.66. It is clear from the data in Table III that the diffusion coefficient of the solute is being influenced by more than a simple obstruction effect. It is possible that at the higher polymer concentrations, the solvent is trapped in smaller polymer cells and is structured by its close proximity to the polymer molecules. This increases the diffusional resistance

Table IV. Apparent Diffusion Coefficient of Salicylates in Various Concentrations of Carbopol Gel at Different Temperatures[a]

Carbopol gel (%, w/w)	Temperature (°C)	Methyl salicylate ($D \times 10^{-5}$ cm^2 sec^{-1})	Ethyl salicylate ($D \times 10^{-5}$ cm^2 sec^{-1})	Glycol salicylate ($D \times 10^{-6}$ cm^2 sec^{-1})	Phenyl salicylate ($D \times 10^{-7}$ cm^2 sec^{-1})
0.5	25	0.99			
	30	1.32			
	35	1.58			
	40	1.73			
	45	2.16			
1.0	25	0.73	0.33	1.56	2.81
	30	0.87	0.62	1.98	4.22
	35	1.0	0.77	2.49	5.41
	40	1.14	1.07	2.78	8.88
	45	1.31	1.3	3.11	11.25
2.0	25	0.52	0.2		
	30	0.66	0.22		
	35	0.78	0.33		
	40	0.93	0.35		
	45	1.16	0.48		

[a] Drug concentration 8% (w/w) except glycol 5% (w/w).

Table V. Apparent Activation Energy (kJ mol^{-1}) for Salicylate Release from Different Ointment Bases[a]

Gel	Methyl salicylate	Ethyl salicylate	Phenyl salicylate	Glycol salicylate
0.5% (w/w) Carbopol gel	28.93 (0.99)	—	—	—
1.0% (w/w) Carbopol gel	23.03 (0.999)	52.09 (0.99)	55.50 (0.995)	27.23 (0.99)
2.0% (w/w) Carbopol gel	30.72 (0.998)	—	—	—

[a] The figures in parentheses are the correlation coefficients of the appropriate Arrhenius plot.

by more than that expected. It is interesting that this effect is monitored by the laser light scattering technique. As the solute concentration increases, the apparent diffusion coefficient also increases. At the higher drug concentrations the diffusive barrier to drug release is reduced. This is probably a result of the drug loading influencing the gel structure by increasing the unit cell size.

The release properties of the gels were investigated as a function of temperature over the range 20–45°C. One percent Carbopol gels were used containing 8% (w/w) salicylate except the glycol derivative, where 5% (w/w) salicylate was employed. Additionally, the methyl ester was studied in 0.5% and 2.0% w/w carbopol. The apparent diffusion coefficients obtained were analyzed by employing the Arrhenius expression to calculate the energy of activation for diffusional release. The results are presented in Tables IV and V. It is interesting to note that the energies of activation for methyl and glycol salicylate are similar in magnitude to those found in the microviscosity experiments. The higher values for the ethyl and phenyl esters are possibly a result of their very low water solubility.

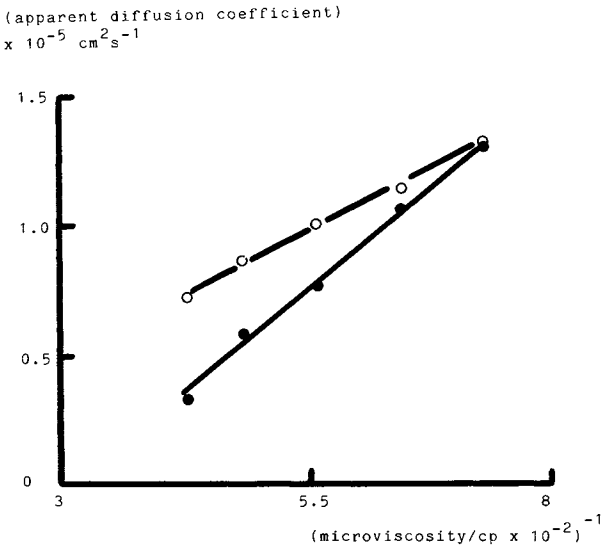

Fig. 3. Relationship between the apparent diffusion coefficient of methyl salicylate (○) and ethyl salicylate (●) and the microviscosity of 1% Carbopol gels at different temperatures.

It is possible to compare the apparent diffusion coefficients with the microviscosity as determined by dynamic light scattering. If the light-scattering experiments are producing a realistic measure of the microviscosity of the gel networks, there should be an inverse relationship between the viscosity and the apparent diffusion coefficient. This is predicted by the Stokes–Einstein equation. In all cases studied there was such a relationship and Fig. 3 shows typical data. We can conclude from this that the technique of photon correlation spectroscopy can be used to probe the microenvironment of optically clear gel networks. Consequently it should be possible to use this experimental procedure to aid the optimization of gel formulations used in topical therapy.

REFERENCES

1. J. Hadgraft. *Int. J. Pharm.* 16:255–270 (1983).
2. S. S. Davis and M. S. Khanderia. *J. Pharm. Pharmacol.* 24:176P–177P (1972).
3. P. Kearney, I. Kellaway, J. C. Evans, and C. Rowlands. *J. Pharm. Pharmacol.* 36:26P (1984).
4. E. J. Amis, P. A. Janmey, J. D. Ferry, and H. Yu. *Polymer Bull.* 6:13–19 (1981).
5. E. J. Derderian and T. B. MacRury. *J. Dispers. Sci. Tech.* 2:345–358 (1981).
6. N. F. Billups and N. K. Patel. *Am. J. Pharm. Educ.* 34:190–196 (1979).
7. W. I. Higuchi. *J. Pharm. Sci.* 56:315–324 (1967).
8. R. C. Weast (ed.). *CRC Handbook of Chemistry and Physics,* F40. CRC Press, Fla., 1982.
9. B. W. Barry and M. C. Meyer. *Int. J. Pharm.* 2(1):25 (1979).
10. G. L. Flynn, S. H. Yalkowsky, and T. J. Roseman. *J. Pharm. Sci.* 63:479–510 (1974).