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Ketoprofen: release from, permeation across and rheology of simple gel formulations that simulate increasing dryness

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Abstract

The migration of ketoprofen through a series of simple gels that varied in solvent composition to simulate snapshots of a dynamically drying topical formulation was studied. Firstly, the release rate of ketoprofen was determined from formulations based on Cabosil® and PEG 400, the proportion of which was varied to mimic progressively dryer states. Secondly, the apparent permeability of ketoprofen across the corresponding blank Cabosil® gels was determined. Thirdly, the effect of macro viscosity on these data was probed by comparing permeation of ketoprofen across Cabosil® and hydroxypropyl cellulose (HPC) gels of equal viscosity. Linear release profiles were produced for all formulations suggesting first-order release and the rate of ketoprofen liberated was inversely to the proportion of Cabosil®, suggesting that the drier the film, the slower the rate of release. At the lowest level of thickener used (5%) the release rate was reduced to 45% of the control. At 25% the release rate was reduced to 24% of the control. The presence of the Cabosil® had an even more dramatic effect on the apparent permeability of ketoprofen across the gels. At 5% Cabosil® the apparent steady state flux was reduced to 4% of the control. At 25% the apparent steady state flux was reduced to <1% of the control. Although the 0.5% HPC gel and the 1% Cabosil® gel possessed identical macro viscosities, the permeation of ketoprofen through the HPC gel was almost double that of the Cabosil® gel. The data from these experiments demonstrated that migration of active molecules through a gel is significantly affected by the amount of solvent present in, or lost from, the system. It is proposed that increased adsorption of active to the thickener plays a more important role than increased macro viscosity for reduced active release as the formulation becomes increasingly dry. Furthermore, such affects are profoundly influenced by the chemical nature of the thickener.

Keywords: Ketoprofen; Gel; Cabosil®; PEG 400; Topical drug delivery; Release rate

1. Introduction

A large number of dermatological and transcutaneous formulations (cream, gel or ointment) are commercially available and their administration typically involves rubbing a dose onto the skin resulting in the formation of a thin film. A common assumption is that thereafter, the active will be released from the film and absorbed into the skin and that this process will occur at a more or less constant rate. However, a number of issues emerge from this simple paradigm stemming from the fact that the nature of the formulation will change immediately after application to the skin. Firstly, the film will increase in temperature to that of the skin surface, typically 32 °C. This will be accompanied by the absorption of the active (and potentially

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excipients) into the skin, changes in physical characteristics of the film and evaporation of the volatile components at the air interface. The ramifications of these changes are not easy to predict. On the one hand, one might anticipate an increase in release and permeation into the skin is feasible in response to the heightened thermodynamic activity of the system. On the other hand, loss of solvent could retard release due to increased viscosity and/or greater interaction between the active and remaining formulation excipients.

Published research involving topical formulations has tended to concentrate on the delivery of drugs from the formulation into the skin and their fate once they have been absorbed (Dayal et al., 2002; Fuji et al., 2002). Methods, including FDA guidelines, for studying the release of active from topical formulations (Addicks et al., 1998; Flynn et al., 1999) generally involve determination of the diffusional release of the active across a polymeric 'minimal-resistance' membrane. Typically, a relatively thin (finite) or thick (infinite) dose of formulation is applied to the upper surface of the membrane mounted in Franz-type diffusion cell for a period of 24 h at 32 °C (Pershing et al., 2002) to yield release data that purports to be representative of that formulation. However, we believe that these tests relate specifically to t_0 and fail to account for the fate of the active once the drying process has commenced. Very little research appears to have been published detailing what happens to the drug remaining in the formulation post-application and its consequent effects on delivery of active. In order to better understand diffusional release of an active from such formulations and the consequences for efficacy, it is important to consider release in relation to the dynamics associated with the drying process.

In this work, we examined a series of simple gel formulations in which the proportion of solvent was varied to represent snapshots of progressively dryer films. In the first experiment, diffusional release of the active (ketoprofen, a NSAID frequently used in topical formulations), was determined within the formulation. In the second experiment the apparent permeability of ketoprofen was determined across fixed volumes of blank gels. Finally, a Cabosil®-thickened gel and a gel with identical rheological properties, but thickened using hydroxypropyl cellulose, were compared to examine importance of formulation macro viscosity.

2. Materials and methods

2.1. Materials

Ketoprofen polyethylene glycol 400 (PEG 400) and hydroxypropyl cellulose were purchased from Sigma, Poole, UK. Nylon filter membranes (0.2 μm) were purchased from Phenomenex (Macclesfield). Cabosil® M-5 was a gift from Cabot Carbon Ltd., Barry, UK. All other reagents were of AnalR grade or equivalent.

2.2. Gel preparation

This work involved simple three-component systems, comprised of permeant (ketoprofen), solvent PEG 400 (frequently used in commercial topical formulations) and a silica-based thickening agent, Cabosil® M-5. Cabosil® was chosen as it is a commonly used as a non-matrix forming thickening excipient which exhibits its thixotropic properties solely via hydrogen bonding with solvent molecules. To simulate a formulation drying effect, a range of gels were prepared in which the only variable was the amount of solvent (w/w). Consequently, a fixed amount of Cabosil® was added to decreased amounts of PEG 400 that contained 5% ketoprofen of total gel (w/w). Firstly, the pre-determined amounts ketoprofen and PEG 400 were combined and sonicated for a short period to ensure complete molecular dissolution before being placed into ceramic mortar. The Cabosil® was then added and using a ceramic pestle and manually stirred until the Cabosil® was seen to have completely dispersed within the formulation. Care was taken to minimise introduction of air bubbles. The gels were then left to stand for 24 h, resulting in transparent, homogenous products. A control was included which lacked the thickening agent. Thus, a series of gels were formed (Table 1) containing 0, 5, 10, 15, 20 and 25% Cabosil® (w/w) mimicking 'snapshots' of progressively drier states. To examine the rheological properties of the Cabosil® gels, the range was 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 and 16% (w/w) Cabosil®. Using the same gel preparation technique analogous gels were formulated but using an alternative thickener, hydroxypropyl cellulose (HPC). This particular thickener was chosen due to its miscibility with PEG 400 and its thixotropic

Table 1
Formulae of gels (w/w)

Percent Cabosil®	Cabosil® (g)	PEG 400 (g)	Ketoprofen (g)	Total mass (g)
0	0	38.00	2.00	40.00
5	2	36.00	2.00	40.00
10	2	17.00	1.00	20.00
15	2	10.73	0.67	13.40
20	2	7.50	0.50	10.00
25	2	5.60	0.40	8.00

Ketoprofen (5%), Cabosil® and PEG 400 (variable).

chemistry, i.e. forms a polymer-matrix within the PEG 400.

2.3. Diffusional release of ketoprofen from gel snapshots

Diffusion experiments were performed using all glass Franz-type cells. The nylon membrane discs were soaked in the receptor medium (PEG 400) for 24 h then carefully wiped before being placed onto the pre-greased flanges of the receptor compartments. Earlier experiments had shown that the nylon membrane presented negligible resistance to the diffusion of ketoprofen (data not shown). The donor chambers were then placed onto the corresponding receptor compartments and pinch clamped in position. The receptor compartments were then filled with degassed PEG 400 and micro stirrers added. Infinite doses of the gel formulations were then applied, ensuring no air between gel and membrane surface, until the gel added reached the top of the donor chamber. The more viscous gels were worked into place using a spatula. Pre-greased glass cover slips were then placed onto each of the donor chambers to ensure the doses were occluded and with no entrapped air bubbles. A total of six replicates were carried out for each treatment. The cells were placed on a multiple stirrer plate in a thermostatically controlled water bath, where the temperature at the surface of the membrane was maintained at 32 °C. Two hundred microlitres of samples were collected at 1, 2, 4, 6, 12 and 24 h and replaced with equal volumes of PEG 400 equilibrated at 32 °C. Sampling experiments were carried out that validated equal distribution of ketoprofen within the receptor compartment (data not shown).

Table 2
Formulae of blank gels (w/w) containing Cabosil® or HPC and PEG 400 (variable)

Percent Cabosil® or HPC	Cabosil® or HPC (g)	PEG 400 (g)	Total mass (g)
0.00[a]	0	10.00	10.00
0.25	0.50	199.50	200.00
0.50[a]	0.50	99.50	100.00
0.75	0.50	66.17	66.67
1.00[a]	0.50	49.50	50.00
2.00[a]	0.50	24.50	25.00
4.00[a]	0.50	12.00	12.50
5.00	0.50	9.50	10.00
8.00[a]	0.50	5.75	6.25
10.00	0.50	4.50	5.00
15.00	0.50	2.85	3.35
16.00[a]	0.50	2.60	3.10
20.00	0.50	2.01	2.51
25.00	0.50	1.50	2.00

[a] Used in rheology study.

2.4. Permeation of ketoprofen across gel snapshots

In this part of the work, the body of gel was considered as the ‘membrane’. Gels were prepared generally as described in Section 2.1, but without the inclusion of the ketoprofen (Table 2). The same general procedure was used as described in Section 2.3 except that a fixed volume (1 cm^2) of gel was added to the donor chambers. Permeation experiments were only carried for the 0.5% HPC gel. The upper surface of the gels were then carefully dosed with 100 μl aliquots of 10% (w/w) ketoprofen in PEG 400 and rapidly occluded.

2.5. Rheology of Cabosil® and HPC gels

Up-curve rheology was carried out on the 0.5, 1.0, 2.0, 4.0, 8.0 and 16% (w/w) Cabosil® and HPC gels at 32 °C using a Bholin CS10 rheometer. A cone and plate angle of 4° and diameter 40 mm was used with the gap settings calibrated between each sample loading. Each gel was analysed using fixed step-wise stress increments (0.06–10 Pa) over a fixed time period with a 10 min equilibration time and replication of 3×. Since shear stress is constant (within 0.3%) the macro viscosity was calculated directly from the experimental torque/speed data.

2.6. HPLC analysis

HPLC analysis was performed using a Hewlett Packard 1100 HPLC automated system fitted with a Phenomenex Kingsorb 5 μm C18 Column (250 mm × 4.6 mm). The mobile phase consisted of 20 mM potassium phosphate solution (pH 3):acetonitrile (55:45). The UV detector was set to 258 nm and a 20 μl injection volume was used. The flow rate was 1 ml/min, the run time was 9 min and the retention time of ketoprofen was typically 6.8 min. Samples were diluted as appropriate with mobile phase. Standard calibration curves were constructed from standard solutions (range 0.1, 1, 10, 20 and 40 $\mu g\,ml^{-1}$) that contained the relative same proportions of PEG 400 and mobile phase used in the sample dilutions.

2.7. Data processing

The steady state flux of ketoprofen was calculated from the slope of the linear section of the cumulative amount of ketoprofen liberated ($\mu g\,cm^{-2}$) against time profiles (hours). The release rate was calculated using the method of Higuchi, from the gradient of the amount of drug liberated against the square root of time (Higuchi, 1962):

$$Q = 2C_0 \left(\frac{Dt}{\pi}\right)^{0.5} \quad (1)$$

where Q is amount of drug released per unit area, C_0 is initial concentration of drug in vehicle, D is the apparent diffusion co-efficient and t is the time elapsed. $Q24$ values are the release rates at 24 h and lag times were determined as the intercept of steady state flux to the time axis.

3. Results

Fig. 1 shows the release rates of ketoprofen from, and apparent steady state flux of ketoprofen across, the gel snapshots. Fig. 2 shows the same data as a percentage of the control (0% Cabosil®).

In the diffusional release experiment good linearities were obtained for each gel indicating that the kinetic profile of ketoprofen release from these gels were

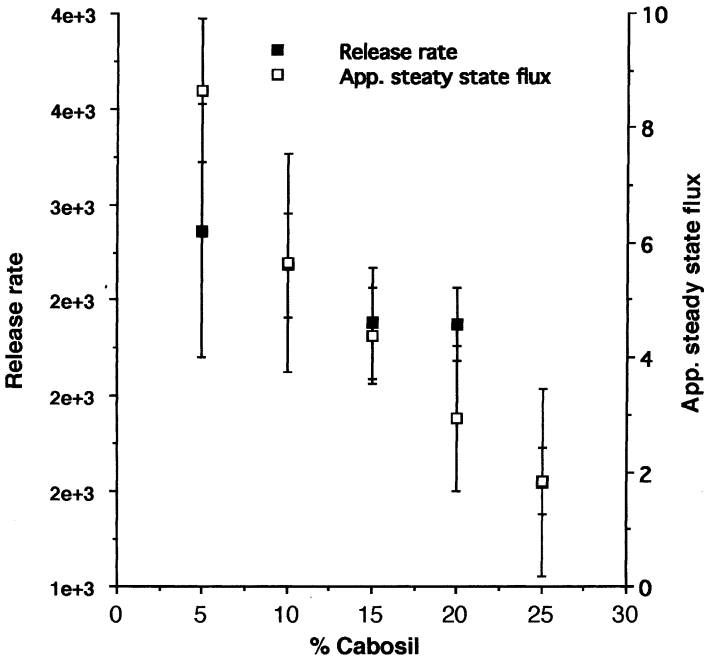

Fig. 1. Double *Y*-axis plot of release rate ($\mu g\,cm^{-2}\,h^{0.5}$) of ketoprofen from and apparent steady state flux ($\mu g\,cm^{-2}\,h^{-1}$) of ketoprofen across gel snapshots.

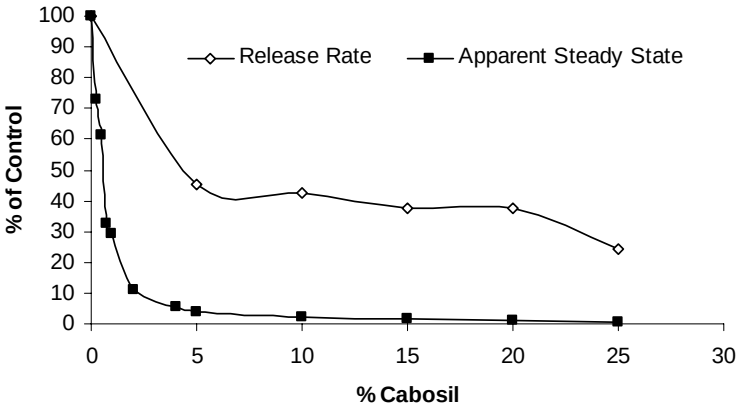

Fig. 2. Plot of diffusional release of ketoprofen from and apparent steady state flux of ketoprofen across gel snapshots as percentage of control.

first-order and followed the diffusion model as defined by Higuchi. Tables 3a and b summarise the release data for the formulations through the test membranes. The maximum concentration of ketoprofen observed in receptor phase was 50 mg ml^{-1}, which was some 25% of the solubility (194 mg ml^{-1}, data not shown). Therefore sink conditions were maintained throughout the experiments. There was a trend in that the rate of ketoprofen liberation was inversely to the proportion of Cabosil®, although the data were very close and statistically insignificant. Nevertheless, the release rate and *Q*24 data clearly suggests that the drier the film, the slower the rate of release. At the lowest level of thickener used (5%) the release rate was reduced to 45% of the control. At 25% (thickest gel practically achievable) the release rate was reduced to 24% of the control. Lag times were negligible (<1 h) as expected.

In the study of permeation of ketoprofen across gel snapshots (data presented in Table 3a) the presence

Table 3b
Summary of hydroxypropyl cellulose permeation data ($n = 6$)

HPC content (%)	Permeation of ketoprofen across snapshot		
	Mean lag time (h)	Apparent steady state flux (μg cm^{-2} h^{-1})	*Q*24 (μg cm^{-2})
0.5	1.2	139.88 ± 3.2	3357.2 ± 77

Table 3a
Summary of Cabosil® release and permeation data ($n = 6$, ±S.E.M.)

Cabosil content (%)	Release of ketoprofen from snapshot			Permeation of ketoprofen across snapshot		
	Apparent steady state flux (μg cm^{-2} h^{-1})	Release rate (μg cm^{-2} h$^{0.5}$)	*Q*24 (μg cm^{-2})	Mean lag time h	Apparent steady state flux (μg cm^{-2} h^{-1})	*Q*24 (μg cm^{-2})
0.00	1050.5 ± 164	6334.2 ± 1358	25211 ± 3939	1.0	246.40 ± 13.8	5912.9 ± 291
0.25				1.2	179.72 ± 16.2	4313.2 ± 389
0.50				1.5	151.25 ± 11.1	3630.0 ± 327
0.75				1.7	79.77 ± 17.4	1914.4 ± 333
1.00				3.0	72.21 ± 173	1732.9 ± 415
2.00				4.0	27.32 ± 4.5	655.7 ± 202
4.00				4.5	12.84 ± 3.1	308.2 ± 77
5.00	478.5 ± 98.1	2862.6 ± 660	11484 ± 2358	5.0	8.65 ± 1.20	207.7 ± 15.0
10.00	450.8 ± 43.1	2682.1 ± 274	10820 ± 1034	7.5	5.65 ± 1.70	135.6 ± 42.2
15.00	391.3 ± 344	2379.4 ± 289	9390 ± 826	10.0	4.39 ± 0.80	105.3 ± 18.0
20.00	383 ± 17.8	2371.9 ± 190	9191 ± 427	11.0	2.93 ± 0.61	70.6 ± 28.0
25.00	257 ± 28.8	1542.5 ± 262	6168 ± 691	11.5	1.84 ± 0.40	44.1 ± 13.1

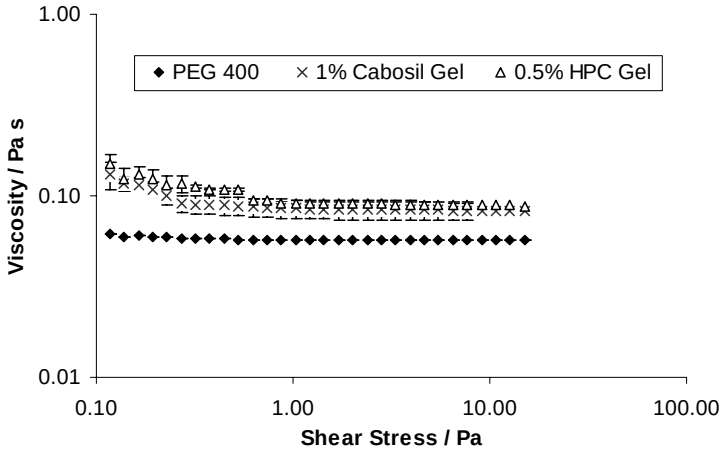

Fig. 3. Rheological profiles of 1% Cabosil® gel and the 0.5% HPC gel respective to their control.

of the Cabosil® had an even more dramatic effect on the apparent steady state flux of ketoprofen. At (5%) Cabosil® the apparent steady state flux was reduced to just 4% of the control. At 25% (thickest gel practically achievable) the apparent steady state flux was reduced to <1% of the control. As expected, lag times increased with increasing Cabosil® content.

The rheological study of both Cabosil®- and HPC-thickened gels showed a corresponding increase in macro viscosity with increasing percent Cabosil®

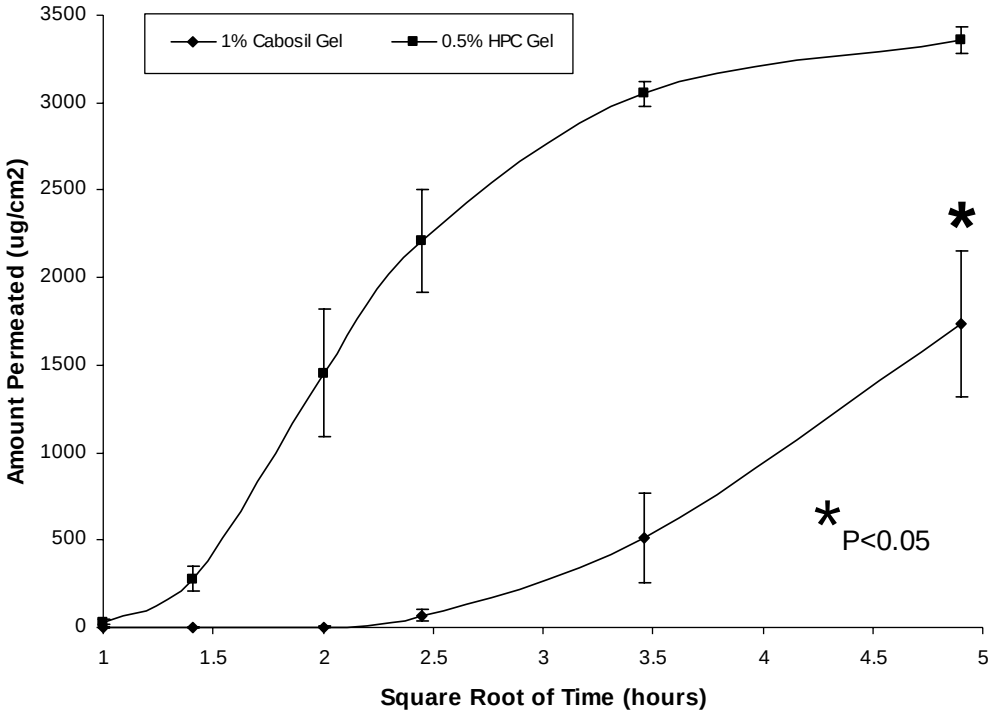

Fig. 4. Plot of diffusional release of ketoprofen through 1% Cabosil® gel and 0.5% HPC gel.

and HPC (data not shown). Both gel systems behaved in a thixotropic non-Newtonian manner acting as pseudo-plastic (shear thinning) fluids (Aulton, 1998). It was found that the rheological and viscosity properties of the 0.5% (w/w) HPC were almost identical to the 1% (w/w) Cabosil® gel (Fig. 3). A large difference was observed in that permeation of ketoprofen through the 0.5% HPC was almost *double* that observed through the 1% Cabosil® gel (Fig. 4). For example, the cumulative amount permeated across HPC gel was 1.94× that across the Cabosil® gel ($P = 0.008$).

4. Discussion

There appears to be a lack of consistency in the literature over the most appropriate model for determining release of actives from topical formulations. Franke et al. (1996) used a Cuprophan membrane, impregnated with the acceptor medium methanol/phosphate buffer (1:1, pH 5.0) to determine methyiprednisolone aceponate from ointment and cream. Parsaee et al. (2002) studied the release of diclofenac from Carbomer 934 formulations dialysed through Spectrapor membrane into phosphate buffer (0.2 M, pH 7.4). The effect of these receptor media in these, as well as other cases, is unknown. Broad FDA guidelines were issued in 1999 (Flynn et al., 1999), which unfortunately do not clarify the situation greatly. In the system we employed, the gel solvent and receptor phases were both PEG 400 and soaking the membranes in PEG 400 prior to cell assembly ensured the absence of phase boundaries and that the only net migration was the active. We believe this model was a significant improvement over previously published methods.

The use of relatively simple membrane transport models was recently reviewed (Kalia and Guy, 2001). Drug release kinetics into skin can be explained by Fick's second law of diffusion and generally, release from a topical formulation should be concentration-dependent (Bottari et al., 1974). For example, Pillai et al. (2001) found that release rate was directly proportional to the square root of the total concentration of hydrocortisone placed in the formulations. Certainly, such was the case prior to the formulation being applied, but what is not known is whether such relationships are maintained post-application.

Once a formulation has been applied, drug at the interface will begin to partition into the skin. The fate of the drug will thereafter be dictated by its relative skin permeability. It is known that in vitro drug release of active across synthetic membranes do not always correlate with skin permeation profiles (Dayal et al., 2002). This will be immediately followed by molecules of drug diffusing towards the interface to replenish the amount of drug partitioned at the formulation/membrane interface (this explains the greater lag times observed in the permeation experiment). However, this is occurring simultaneously with loss of solvent, which will either partition into skin, or evaporate at the air interface. The data shows that, the greater the loss of solvent the slower the rate of migration through the film (Fig. 2). This is seemingly at odds with the principles of thermodynamic activity, in that less solvent is present yet the amount of drug and thickener remain constant, the thermodynamic activity of the drug in the formulation will increase. This would be expected to result in an *increase* in the drug release from the formulation.

In solvent alone, the active molecules are able to diffuse relatively freely. Cabosil® M-5 has a fumed silica network that forms gels due to hydrogen bond formation with solvent molecules. As the film dries, there is an apparent increase in the amount of Cabosil® and the amount of solvent molecules not undergoing hydrogen bond interactions with the Cabosil®. However, when active molecules that also have the ability to bind to the Cabosil® are present, there will be competition for the binding sites on the Cabosil®. Again, the lower the proportion of solvent, the greater the interaction with active and such a retarding effect would work in the opposite direction to the greater release produced by increased thermodynamic activity.

In this work it was interesting to see that up-to 5% Cabosil® content there was a significant reduction in ketoprofen release and permeation through the gel formulations. Above 5% Cabosil® this observation was less apparent. As discussed previously this work suggests that Cabosil® exhibited a capacity to bind the active within the gel formulations. As with typical binding studies study at some point saturation of binding will occur and, as seen in Fig. 2, with increasing percent of Cabosil® up-to 5% there was a corresponding reduction in ketoprofen release rate. This may also be interpreted as a binding curve in which greater

amounts of the available ketoprofen (fixed amount) are being bound to the increasing amount of Cabosil® in the system therefore being unavailable for release from the system. As the system proceeds towards saturation, i.e. all Cabosil®-binding sites occupied with ketoprofen, then the amount of ketoprofen bound and subsequently unavailable for release from the system diminish as seen beyond approximately 5% Cabosil® (w/w).

A number of papers have discussed release from topical formulations in terms of viscosity, which in general propose that the greater the viscosity of the formulation the lower the release (Chi and Jun, 1991; Rafiee-Tehfani and Mehramizi, 2000). However, viscosity is a physical property, which at the molecular level can be rationalised in terms of an increasingly tortuous route of migration through the gel as a consequence of reduced solvent content.

Determination of the permeation of ketoprofen across two different gels with identical macro viscosity/rheological properties provided a direct test for the influence of bulk viscosity on the migration of active through drying films. One would presume that if bulk viscosity was the predominant factor over adsorption in the release of active, then two gels of equal rheological character would yield similar permeation rates, although the influence of potential differences in micro-viscosity remain to be established. Given that almost double the amount ketoprofen permeated through the HPC gel in comparison to the Cabosil® gel, *despite their rheological parity*, it suggests bulk viscosity on its own does not account for interactions between active and excipient (see Fig. 4).

We propose, at least in this case, that the extent of adsorption of active to the thickener is more likely to be the governing factor responsible for the reduction in the rates of release. The processes involved are somewhat analogous to the phenomena involved in adsorption chromatography.

If one accepts that the adsorption scenario best explains the data obtained, it still remains necessary to account for the reduced migration despite increased thermodynamic activity. It is likely that the two opposing effects were operating simultaneously, yet the driving force (thermodynamic activity) was overwhelmed by the retarding force (adsorption). In this case equilibrium was towards retention although it would be expected to shift according to the solvent in the system. Moreover, the position of the equilibrium would generally depend upon the nature of the excipient/thickener and the capability of the active to interact with it. This hypothesis is currently being tested.

Prior to skin application a topical formulation has a relatively high solvent concentration. At that time the topical system is both at its lowest level of thermodynamic activity and exhibiting lowest adsorptive effects from the Cabosil®. Once applied to the skin a topical formulation would begin to lose solvent through evaporation (and possibly absorption into the skin). A resultant increase in thermodynamic activity occurs, due to net increase in permeant concentration per unit area of the formulation occurs. Depending on where the equilibrium lies for a particular topical system then either thermodynamic activity or adsorptivity prevails as the dominating factor, and resultant effect on rates of release. This would shift in response to the changing nature of the increasingly drier system.

5. Conclusions

Data from these experiments have indicated that migration of active molecules through basic gel formulations was markedly affected by the amount of solvent present in, or lost from, the system. The data also point to increased adsorption to the thickener, rather than due to changes in viscosity, as being primarily responsible for reduced release as it becomes increasingly dry. It is evident that such behaviour can vary depending upon the nature of the thickener and its capacity to bind molecules of active. Further work is currently being carried out to evaluate this and to quantitatively deconvolute the relative effects of viscosity and binding.

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