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Investigation of the permeation of model formulations and a commercial ibuprofen formulation in Carbosil® and human skin using ATR-FTIR and multivariate spectral analysis

Wanessa Russeau[a], John Mitchell[a], John Tetteh[a], Majella E. Lane[b,*], Jonathan Hadgraft[b]

[a] Medway Sciences, University of Greenwich, School of Science, Central Avenue, Chatham Maritime ME4 4TB, UK
[b] The School of Pharmacy, University of London, 29-30 Brunswick Square, London WC1N 1AX, UK

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ABSTRACT

The purpose of the present study was to use attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR) and target factor analysis (TFA) to investigate the permeation of model drugs and formulation components through Carbosil® membrane and human skin. Diffusion studies of saturated solutions in 50:50 water/ethanol of methyl paraben (MP), ibuprofen (IBU) and caffeine (CF) were performed on Carbosil® membrane. The spectroscopic data were analysed by target factor analysis, and evolution profiles of the signal for each component (i.e. the drug, water, ethanol and membrane) over time were obtained. Results showed that the data were successfully deconvoluted as correlations between factors from the data and reference spectra of the components, were above 0.8 in all cases. Good reproducibility over three runs for the evolution profiles was obtained. From the evolution profiles it was observed that water diffused better through the Carbosil® membrane than ethanol, confirming the hydrophilic properties of the Carbosil® membrane used. IBU diffused slower compared with MP and CF. The evolution profile of CF was very similar to that of water, probably because of the high solubility of CF in water, indicating that both compounds are diffusing concurrently. The second part of the work involved a study of the evolution profiles of the components of a commercial topical gel containing 5% (w/w) of ibuprofen as it permeated through human skin. Although the system was much more complex, data were still successfully deconvoluted and the different components of the formulation identified except for benzyl alcohol which might be attributed to the low concentrations of benzyl alcohol used in topical formulations.

1. Introduction

The study of membrane permeation is of great interest in pharmaceutical research and development. The human body is composed of many different types of biological membranes or permeation barriers, examples being the skin, blood–brain barrier, intestinal mucosa, nasal and ocular tissues among others. These membranes act as barriers in the body as they affect the transport of drugs and influence the timeframe to act at the target receptor and/or the rate at which the receptor is reached. This may be related to their structure and chemical composition, most biological membranes being lipophilic and having one or more layers that result in slow drug diffusion (Camenisch et al., 1996). However, biological membranes are generally complex and variable. For the development of new permeation models it is advantageous to use less complex membranes such as synthetic polymers. In this study skin a biological membrane, and Carbosil® a synthetic membrane, previously used to mimic skin (Feldstein et al., 1996, 1998), have been considered. The skin is divided into different layers, but it is the stratum corneum (SC), the outermost layer, which controls absorption (Hadgraft, 2001). Carbosil® membranes are composed of polydimethylsiloxane (PDMS)–polycarbonate (PC) and have an heterophase domain structure (Feldstein et al., 1998).

Attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR) has become a well established technique to study drug permeation into membranes (Trifonov et al., 1975; Pellett et al., 1994; Farinas et al., 1994; Margarida et al., 1995; Cantor, 1999; Sammon et al., 2000; Tantishaiyakul et al., 2004; Wartewig and Neubert, 2005), to investigate the SC at the molecular level and to evaluate the influence of penetration enhancers on the skin (Watkinson et al., 1995; Pellett et al., 1997a,b; Dias et al., 2001, 2003). For permeation experiments using ATR-FTIR, the membrane is sandwiched between a zinc selenide (ZnSe) crystal and a formulation that provides an essentially constant concentration of the permeate (C_v), in the vehicle (C_v), on the upper surface of the mem-

* Corresponding author. Tel.: +44 207 7535821; fax: +44 870 1659275.
E-mail address: majella.lane@btinternet.com (M.E. Lane).

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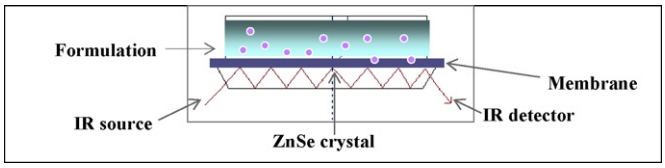

Fig. 1. Schematic of the ATR-FTIR membrane diffusion experiments.

brane. This is schematically illustrated in Fig. 1. The permeate will then diffuse into the membrane and will accumulate at the membrane/crystal interface. The build up continues until the membrane is saturated by the permeate, at which time a plateau is reached. The variation of the concentration of the permeate and vehicle as well as changes in the membrane can then be monitored as a function of time. Values for the partition (K) and diffusion (D) coefficients can be obtained, since the rate at which the plateau is obtained is related to the speed of the permeate moving through the membrane and thus to D. The plateau level is related to the solubility of the permeate in the membrane (K). The data are obtained by monitoring the increase in the IR absorbance associated with the permeate over the experimental time frame (Pellett et al., 1994, 1997a,b; Tantishaiyakul et al., 2004; Watkinson et al., 1995; Dias et al., 2003). An analytical solution describing the build up of permeate concentration at the membrane/crystal interface with time can be obtained using Fick's second law and the relevant boundary conditions as illustrated in Eq. (1), where C is the concentration at the crystal/membrane interface at any time t:

$$C = C_0 \left[1 - \frac{4}{\pi} \sum_{n=0}^{\infty} \frac{(-1)^n}{2n+1} \exp\left(\frac{-D(2n+1)^2 \pi^2 t}{4h^2} \right) \right] \quad (1)$$

Assuming that the Beer–Lambert law applies, the concentration terms of Eq. (1) can be replaced by experimental absorbance values (Farinas et al., 1994; Margarida et al., 1995; Tantishaiyakul et al., 2004; Watkinson et al., 1995; Dias et al., 2003; Pellett et al., 1997a,b; Watkinson and Brain, 2002).

While a typical ATR-FTIR experiment is relatively simple the data generated are complex. Large data sets are generated and the generated spectral data often have significant band overlaps. Because of these potential band overlaps data interpretation can be very challenging for complex formulations. Fortunately, the data matrix generated by such systems is suitable for multivariate analysis which enables more accurate data analysis and interpretation of such data sets. In the present work, factor analysis was used to analyse the data matrix on the assumption that (i) within a spectral window range, there is a unique spectral profile for each component in a mixture, (ii) at each point in time during the spectral data capture the total absorbance is a linear or near linear sum of each component and (iii) there exists relative absorbance differences at each point in time during data capture. The resulting data matrix M after a typical experimental run will consist of x, y and z directional data. Data for x (columns) are related to time points, y (rows) are related to wavelength points and z are related to absorbance at each wavenumber and time point simultaneously. An overview of the multivariate data decomposition and analysis used in this work is summarized below. The algorithms and methods are embodied in Insight [Insight User Manual] encoded in Matlab [Matlab Version 6]. All data analysis was performed with this software.

1.1. Multivariate factor analysis overview

The deconvolution of M by factor analysis aims to: (i) estimate the number of non-random permeation profiles during the experiment and (ii) identify and confirm the spectral identity of the permeating entities. In this work, we used a modified target factor analysis (TFA) technique to analyse the data (Tetteh, 1997). TFA is used to determine whether or not a hypothetical vector, gleaned from chemical principles or heuristic intuition, lies inside the factor space and thus contributes to the phenomenon. The analytical strength of such target testing lies in the fact that each hypothetical vector can be tested individually for significance in the presence of a host of other unknown factors. When a data matrix has been decomposed into abstract factors (also known as principal components) in the row and column space of the data M and the numbers of significant factors have been determined, these significant factors can be subjected to various forms of mathematical scrutiny to determine if they have real chemical or physical meaning. In this work the mathematical technique of singular value decomposition (SVD) was used for the decomposition process. Eqs. (2)–(7) summarize the mathematical principles used to deconvolute the spectral data, M. The principal factor matrices describing the row and column information of M are R and C, respectively. R and C are the significant components of the matrix after excluding E, the error or noise inherent in the experimental procedure. Recombination of the significant row and columns R and C produces a new matrix M_x, as indicated in Eq. (3). During target testing X_t represents hypothetical j key sets of vectors that fully describe the data M_x. Various schemes have been proposed to determine X_t. In this paper the so-called needle search method described elsewhere (Malinowski, 2002) was employed. In summary initial hypothetical test vectors are generated by setting all wavenumber points in a selected window to zero, except those that show significant power intensity for each of the j key factors identified. From these test vectors, prototype profiles are generated after target testing using Eq. (4). An iterative and interactive approach is then used to select the unique set of X_t that best describes the data. Operating the pseudoinverse of X_t yields T. The pseudoinverse of R is R^+ [$R^+ = (R^T R)^{-1} R^T$], where R^T and X^{-1} are respectively the transpose and inverse. T is the target transformation matrix indicated in Eq. (4) and is used to deduce X_j and A. X_n is the predicted test matrix based on the X_t key vectors (Eq. (5)) and describes the row domain real information, which are the predicted evolution profiles for each of the significant j key factors identified in the data matrix, M. A is the column domain real information matrix, equivalent to the predicted relative concentration profiles obtained from Eq (6). Recombination of X_n and A produces M_n the significant part of the data matrix, M. The differences between M_n (*predicted*) and M_x (*raw data*) are minimized. An extended treatment of theory and applications of TFA can be found elsewhere (Tetteh, 1997; Malinowski, 2002; Geladi et al., 2004):

$$M = [RC] + E \quad (2)$$

$$M_x = RC \quad (3)$$

$$T = R^+ X_t \quad (4)$$

$$X_n = R^T \quad (5)$$

$$A = T^+ C \quad (6)$$

$$M_n = X_n Y \quad (7)$$

The aim of the present study was to use attenuated total reflectance-Fourier transform infrared spectroscopy and target factor analysis to investigate the permeation of model drugs and formulation components through Carbosil® membrane and human skin. Simple model formulation systems were examined to test the applicability of the experimental design and data analysis strategy. Permeation studies of saturated solutions in 50:50 water/EtOH of three model compounds methyl paraben (MP), ibuprofen (IBU) and caffeine (CF) in 50:50 water/EtOH were investigated using Carbosil® membranes and human skin. The selection of these compounds was based on their physicochemical properties and specifically because they span a range of Log P values. Three runs for each set were

Table 1
Instrumental settings for the ATR-FTIR during diffusion experiments.

Detector	MCT/A
Number of scans per spectrum	10
Resolution	2 cm^{-1}
Experiment duration time for synthetic membrane	240 min
Time resolution for synthetic membrane	Every 240 s
Experiment duration time for skin	720 or 1440 min
Time resolution for skin	Every 900 s

performed in order to assess the reproducibility of an identical system. Reference spectra required for the TFA were collected for each component.

Experiments were conducted using Carbosil® for 4 h and in skin for 24 h. A commercial topical pain relief gel containing 5% (w/w) ibuprofen was studied *in vitro* using human skin. Other components in the gel were isopropyl alcohol, benzyl alcohol, ethyl hydroxycellulose, sodium hydroxide and purified water. The reference spectra used for the TFA analysis were: (1) ibuprofen, the active ingredient of the formulation, (2) isopropyl alcohol a common enhancer in transdermal systems (Goldberg-Cettina et al., 1995), (3) benzyl alcohol which is normally used as a preservative and fragrance additive in pharmaceutical and cosmetic products (Nanayakkara et al., 2005) and (4) water.

2. Materials and methods

2.1. Materials

Methyl paraben, caffeine, isopropyl alcohol and benzyl alcohol were obtained from Sigma–Aldrich (UK) with a purity of 99% or greater. Ibuprofen was donated by Wyeth Consumer Health Care (UK). Ethanol (Analar grade) was purchased from BDH (UK). Silicone grease was obtained from Dow Corning (UK). Ibuprofen pain relief gel (Boots) 5% (w/w) was purchased from a retail outlet. Carbosil® was a donation from Pentapharm Ltd. (Moscow, Russia) and had a measured thickness of 50 ± 5 μm. Human skin was obtained from the International Institute for the Advancement of Medicine (IIAM) with informed patient consent and institutional ethical approval. Dermatomed human cadaver thigh skin samples with a thickness of 200 μm were used. All donors were Caucasian and female in the age range 45–65 years.

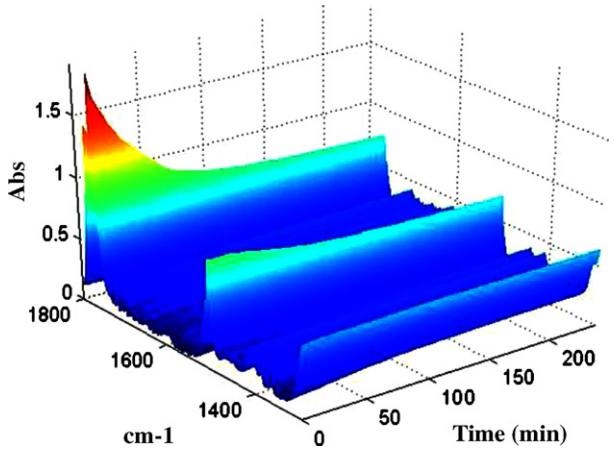

Fig. 2. A typical raw data set.

2.2. ATR-FTIR spectroscopy

The ATR-FTIR diffusion experiments were conducted on a Thermo Nicolet Nexus FT-IR system fitted with a Smart ARK™ ATR-FTIR ZnSe crystal accessory. The detector setting was selected as mercury cadmium telluride A band (MCT-A). The controlling software was Omnic® 7.2. The experiment involved placing the membrane in direct contact with the ZnSe crystal. The inner part of the skin sample was placed on the crystal. A PVC trough was placed on top of the membrane and silicone grease was used to produce a leak proof seal between the donor compartment (the trough) and the membrane. The formulation to be tested was placed in the trough above the membrane, and the trough was covered to avoid evaporation. Spectra were collected using the series analysis mode which allows automatic collection of a spectrum at desired time intervals for a set period. Table 1 shows the spectrometer settings used.

Reference spectra of the different components were also collected. For IR reference collections of MP, CF and IBU an ethanol

Table 2
IR regions selected for each component and their correlations with the reference spectra for the diffusion experiments, using Carbosil® membrane, of a saturated solution of methyl paraben in 50:50 water/ethanol.

	Methyl paraben	Water	Ethanol	Carbosil® membrane
Wavenumber region selected (cm^{-1})	1550–1650	1550–1750	1300–1500	1730–1800
Correlation between factors and reference spectrum ($n = 3 \pm$ S.D.)	0.986 ± 0.006	0.942 ± 0.006	0.924 ± 0.026	0.973 ± 0.003
R.S.D. from correlation (%)	0.6	0.6	2.8	0.3

Table 3
IR regions selected for each component and their correlations with the reference spectra for the diffusion experiments, using Carbosil® membrane, of a saturated solution of ibuprofen in 50:50 water/ethanol.

	Ibuprofen	Water	Ethanol	Carbosil® membrane
Wavenumber region selected (cm^{-1})	1650–1750	1550–1750	1300–1500	1730–1800
Correlation between factors and reference spectrum ($n = 3 \pm$ S.D.)	0.838 ± 0.029	0.929 ± 0.031	0.976 ± 0.002	0.950 ± 0.019
R.S.D. from correlation (%)	3.5	3.3	0.2	2.0

Table 4
IR regions selected for each component and their correlations with the reference spectra for the diffusion experiments, using Carbosil®l membrane, of a saturated solution of caffeine in 50:50 water/ethanol.

	Caffeine	Water	Ethanol	Carbosil® membrane
Wavenumber region selected (cm^{-1})	1600–1800	1550–1750	1500–1300	1800–1730
Correlation between factors and reference spectrum ($n = 3 \pm$ S.D.)	0.885 ± 0.035	0.847 ± 0.064	0.814 ± 0.042	0.925 ± 0.061
R.S.D. from correlation (%)	4.0	7.6	5.2	6.6

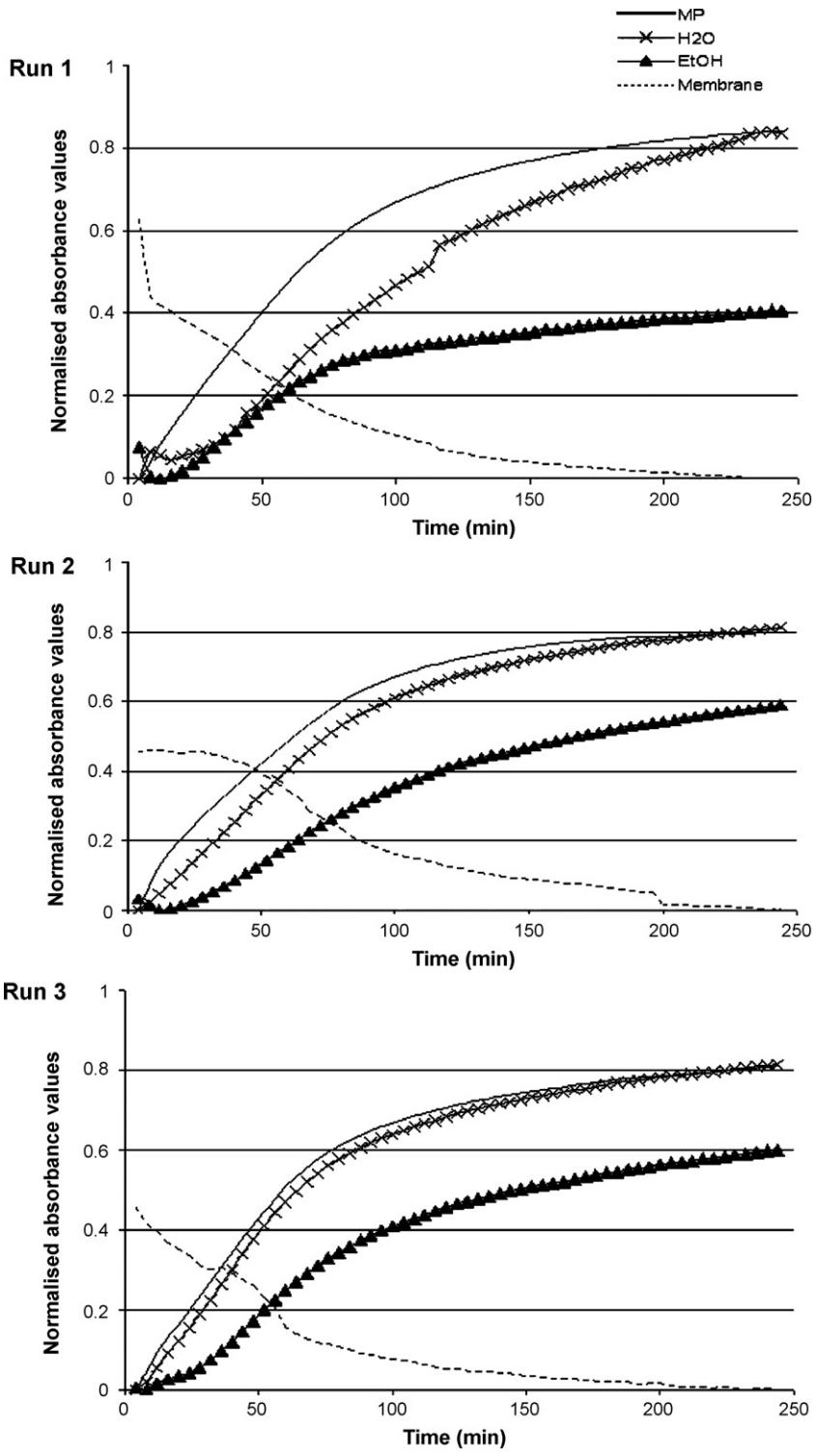

Fig. 3. Evolution profiles of the four components from the diffusion experiments in Carbosil® of a saturated solution of methyl paraben in 50:50 water/ethanol (methyl paraben (—), Carbosil® membrane (– – –), ethanol (▲) and water (×)).

paste of the compound was made and placed on the ZnSe crystal and after evaporation of the ethanol the spectrum was collected. For water, ethanol, Carbosil® and skin, the samples were directly placed on the crystal and the reference collected.

The experimental data were converted from the native binary format ASCII test to the comma separated values (CSVs) by Omnic® 7.2 software. The matrix dimension for Carbosil® runs were ~2000 rows of wavenumber points and 60 time points. Skin data sets were ~2000 rows by 96 columns. The core multivariate TFA were performed on the CSV files using InSight® software.

2.3. Data analysis

A wavenumber window was selected for each target compound, regardless of signal overlapping bands with other compounds. The TFA analysis was performed on each spectral window assigned to

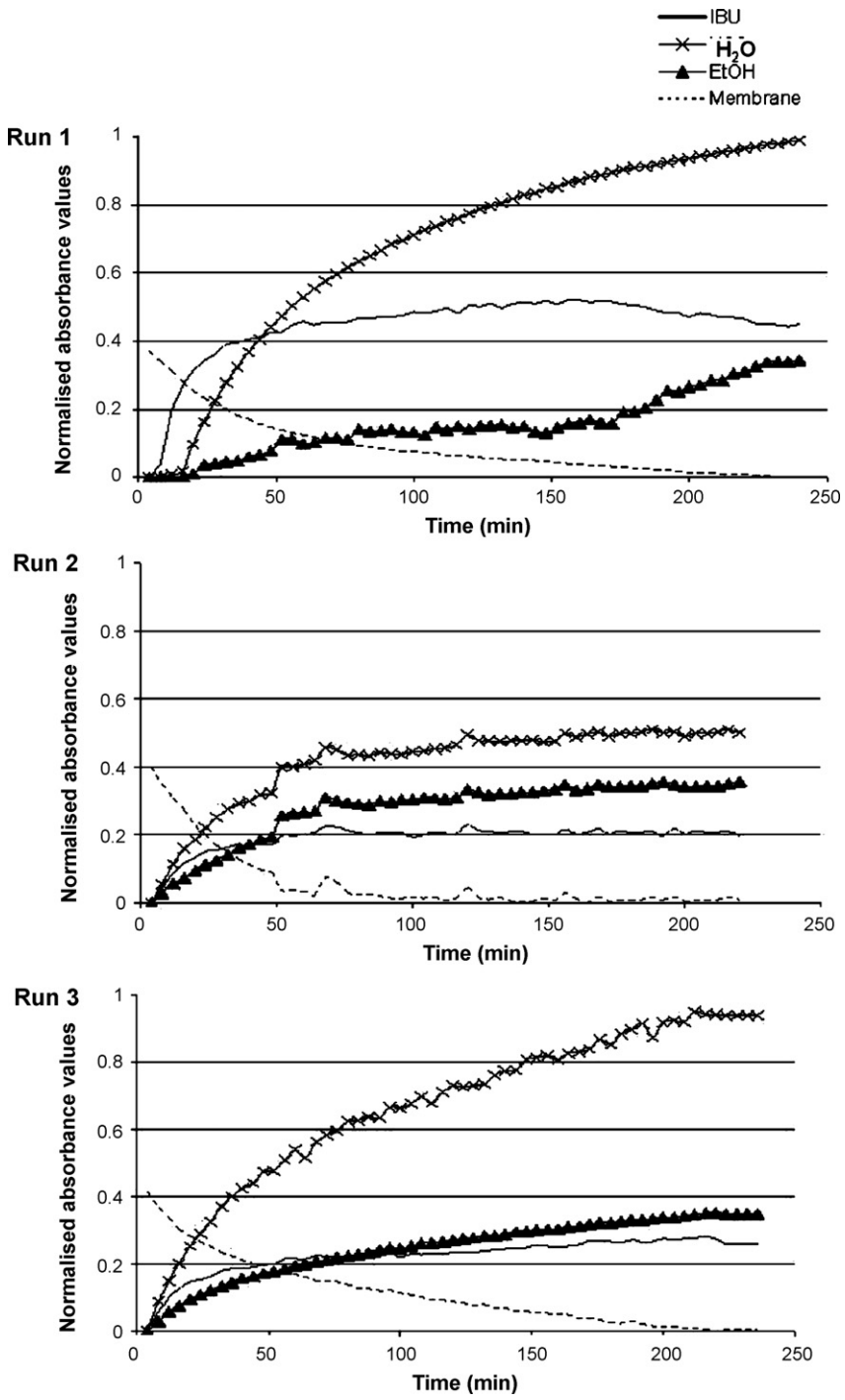

Fig. 4. Evolution profiles of the four components from the diffusion experiments in Carbosil® of a saturated solution of ibuprofen in 50:50 water/ethanol (ibuprofen (—), Carbosil® membrane (– – –), ethanol (▲) and water (×)).

each reference target. A typical raw data set is shown in Fig. 2. The only data pre-treatment performed prior to decomposition and profile prediction is baseline zeroing. A predicted spectrum X_n (see Eq. (5)) with a correlation (r) greater than 0.8 relative to the references is considered as a successful identification. The choice of correlation is based on signal to noise ratio, degree of spectral target overlap in a selected wavenumber region, a visual comparison between reference and predicted spectral profiles as well as the relative amount of the target in the mixture. The degree of correlation can therefore range from 0.70 to 0.99 depending on the type of system under investigation. In this study a correlation of 0.8 was found to be an acceptable compromise based on visual inspection of the predicted spectrum and the calculated r value. An example of the use of correlation in TFA (or quantitative iterative target factor analysis [QITFA]) and curve resolution is illustrated in a recent paper by Richards et al. (2008). Permeation profiles A (see Eq. (6)) of all successfully identified references are then calculated.

3. Results and discussion

Permeation data were deconvoluted and the degree of correlation between the references and predicted spectra were used for

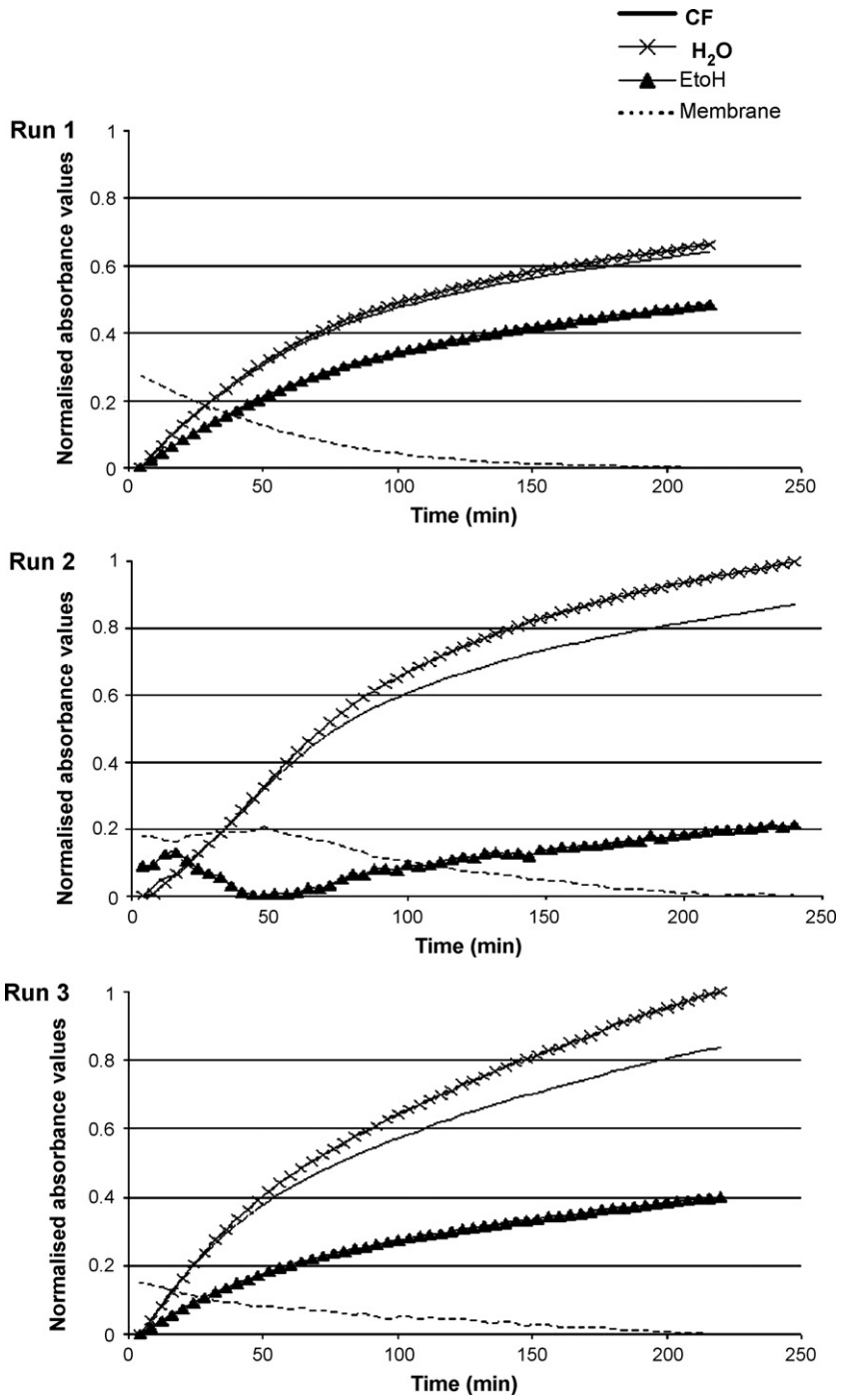

Fig. 5. Evolution profiles of the four components from the diffusion experiments in Carbosil® of a saturated solution of caffeine in 50:50 water/ethanol (caffeine (—), Carbosil® membrane (– – –), ethanol (▲) and water (×)).

identification of the components permeating the membranes. The evolution profiles were used for relative quantification over time for each identified target reference.

3.1. Model formulations in Carbosil® membrane

3.1.1. Data deconvolution

The regions selected for each set of experiments have been tabulated as well as the mean correlation and the relative standard deviations (R.S.D.), over three runs, of the references and the factors, in Tables 2–4. The IR regions selected for water, EtOH and the Carbosil® membrane did not vary from one set of experiments to another for the Carbosil® study. In monitoring ethanol, the region first selected was between 1000 and 1100 cm^{-1}, at about 1030 cm^{-1} ethanol has a strong absorbance band because of the C–OH stretching (typical of a primary alcohol). However, in this region Carbosil® also has an extremely high absorbance and it saturates the signal. Thus it was difficult to deconvolute the ethanol signal (or any other signal) in this region. The 1300–1500 cm^{-1} window was selected as an alternative. The ability to change flexibly windows in TFA is a major advantage compared to other less flexible (*hard*) multivariate systems such as partial least squares (PLSs) regression. Three medium to small bands are observed within this region corresponding mainly to the methylene ($-CH_2-$) bending

Table 5
IR regions selected for each component and their correlations with the reference spectra for the diffusion experiments, using human skin, of a topical commercial ibuprofen (5%, w/w) gel.

	Ibuprofen	Water	Isopropyl alcohol	Human skin
Wavenumber region selected (cm^{-1})	1650–1750	1550–1750	1058–1184	1471–1737
Correlation between factors and reference spectrum ($n = 3$)	0.894 ± 0.023	0.944 ± 0.001	0.962 ± 0.046	0.992 ± 0.013
R.S.D. from correlation (%)	2.6	0.1	4.8	1.3

and the methyl ($-CH_3$) symmetric and anti-symmetric bending modes. Carbosil® was monitored in the region between 1800 and 1730 cm^{-1}. Strong bands associated with the C=O stretching of the carbonyl group were characteristically present in this region. The IR region between 1550 and 1750 cm^{-1} is assigned to the OH bending mode of water. The region between 1550 and 1650 cm^{-1} was selected for MP. In this region MP has an IR band corresponding to the stretching mode of the aromatic ring. Ibuprofen was monitored between 1650 and 1750 cm^{-1}, where the characteristic carbonyl band is located. Finally, for caffeine the region between 1600 and 1800 cm^{-1} was selected as two characteristic bands of caffeine can be observed in this section, one at ~1700 cm^{-1} associated with the C=O stretching mode from the carbonyl group plus the stretching of the imidazole ring [26], and the second at a slightly lower wavenumber (~1660 cm^{-1}) associated with the carbonyl stretching mode.

Tables 2–4 show, in each case, a good correlation between the extracted spectral profiles and the references, within the selected IR regions. In all cases the correlation was above 0.80. Considering the complexities of such data sets and the degree of spectral overlaps, the predicted spectral profiles indicate that the different factors were successfully deconvoluted and identified. The R.S.D. was calculated, and for most of the cases the R.S.D. was below 5%, indicating good reproducibility of the deconvolution process from one run to another.

3.1.2. Permeation evolution profiles

The evolution profiles representing normalised absorbance values against time, for each extracted component are illustrated in Figs. 3–5. To assess the reproducibility of the data from one run to another, the graphs for each single run are given representing, respectively, the results for MP, IBU and CF. In general, good reproducibility between runs for each set of experiment was observed. The Carbosil® signal intensity decreased over time in all runs. This may be attributed to loss of contact between the membrane and the crystal, during the run, resulting in a lowering of the absorbance values. Another explanation is the possible build up of materials at the crystal and membrane interface over time, thus resulting in the decreased exposure of the membrane to the infrared radiation.

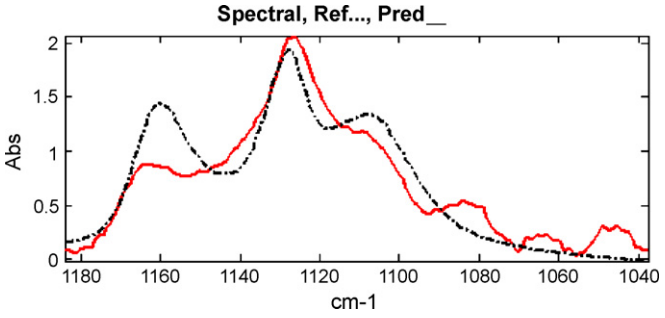

Fig. 7. Correlation between one of the extracted factors, from a diffusion experiment of a commercial ibuprofen formulation through human skin, and the isopropyl alcohol reference spectrum. Correlation $r = 0.925$. The discontinuous black line represents the reference spectrum profile and the plain red line the predicted factor spectrum profile. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of the article.)

The ethanol IR absorbance increased with time in all sets of experiments, such that its evolution profile almost mirrors that of the Carbosil® profile.

By comparing water and ethanol profiles, it appears that water diffused better through the Carbosil® membrane, as it had a larger initial slope than ethanol (Figs. 3–5). This indicates that the Carbosil® membrane used for these studies has hydrophilic properties. As noted by Feldstein et al. (1998) if stratum corneum is considered a lipophilic permeability barrier Carbosil® membrane exhibits an amphophilicity or moderate hydrophilicity.

For the model compounds studied, MP and CF diffused more rapidly through the Carbosil®. The evolution profile of CF was very similar to that of water, indicating that CF may be diffusing through the membrane concurrently with water. This can be explained by the high solubility of CF in water, and the affinity of the membrane for water, as illustrated by the water evolution profiles. IBU did not permeate as well as the other two compounds and this might be attributed to the low solubility of IBU in water.

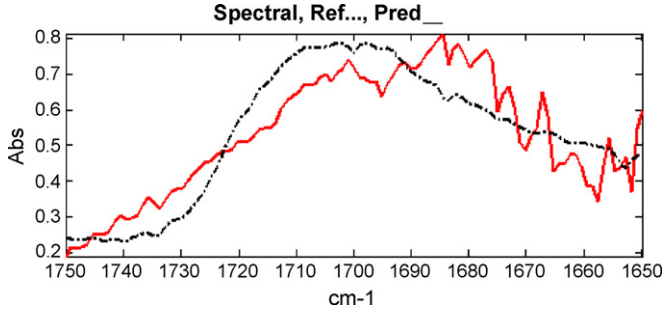

Fig. 6. Correlation between one of the extracted factors, from a diffusion experiment of a commercial ibuprofen formulation through human skin, and the ibuprofen reference spectrum. Correlation $r = 0.885$. The discontinuous black line represents the reference spectrum profile and the plain red line the predicted factor spectrum profile. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of the article.)

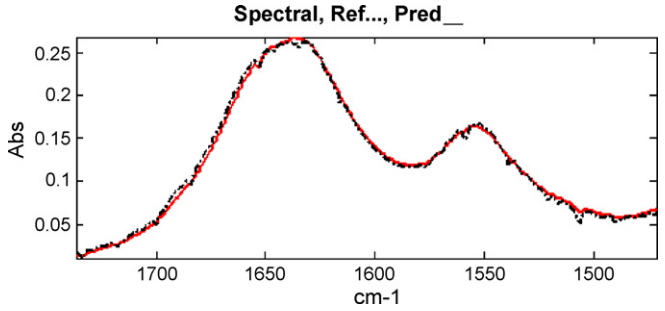

Fig. 8. Correlation between one of the extracted factors, from a diffusion experiment of a commercial ibuprofen formulation through human skin, and the human skin reference spectrum. Correlation $r = 0.998$. The discontinuous black line represents the reference spectrum profile and the plain red line the predicted factor spectrum profile. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of the article.)

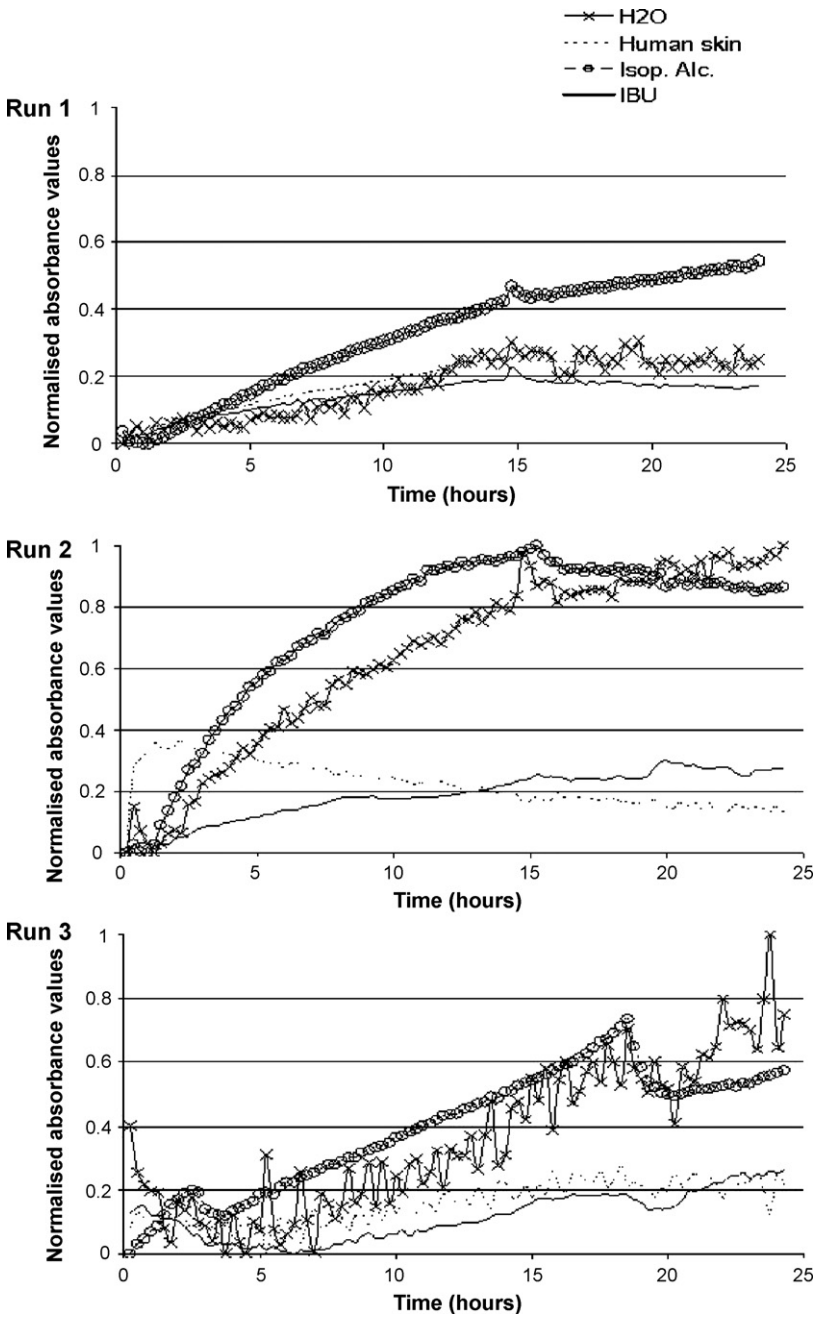

Fig. 9. Evolution profiles of the components from the diffusion experiments on human skin of Boots ibuprofen topical gel (5%, v/v) (ibuprofen (—), human skin (– – –), isopropyl alcohol (◯) and water (×)).

3.2. OTC topical gel through human skin

3.2.1. Data deconvolution

Table 5 shows the successful identification and deconvolution of the targets during the permeation study conducted with a commercial ibuprofen gel. A good correlation between the references and the components was observed as well as good reproducibility. Benzyl alcohol was not detectable in any of the runs. It is generally used as a preservative at concentrations of 2% (v/v) or less in pharmaceutical preparations (Handbook of Pharmaceutical Excipients, 2003) and therefore it may be present at amounts which are too low to enable detection. No description of the concentration of the excipients in the formulation was provided in the Manufacturer's Data Sheet. Figs. 6–8 illustrate examples of typical correlations between the predicted and the reference spectra.

3.2.2. Permeation evolution profiles

Fig. 9 shows the normalised evolution profiles for each extracted component. It shows the degree of reproducibility between runs. Similar trends were observed for the three runs, except for run 2 where the diffusion of water and isopropyl alcohol differs from runs 1 and 3. The rate of permeation of, water and isopropyl alcohol seems significantly higher than in the other two runs. This may suggest that the barrier function of the skin used for this particular run was compromised and thus the two components permeated much more rapidly.

In general, isopropyl alcohol seems to diffuse through the skin at the fastest rate. Water also permeates the membrane suggesting that this type of formulation helps to hydrate the skin. The profiles for IBU are very similar for all runs, reaching a plateau at about 15 h

after the beginning of the experiment, indicating that the skin is saturated with IBU.

4. Conclusions

All the spectral data sets were successfully analysed irrespective of the complexity of the systems studied. The discriminating power of multivariate data analysis for such systems has been clearly demonstrated. Although in many cases the infrared spectral window selected for a target component totally overlapped with other components, the permeation profiles of the target component were obtained. This enabled the monitoring of multi-component permeation, and also the observation of the effects that the components were having on the Carbosil® membrane and the skin. The deconvolution results in both Carbosil® and human skin, and the ability to monitor the impact of a formulation on the membrane, demonstrated the power of this experimental procedure to interrogate both synthetic and biological membranes. The complexity of the biological membrane did not pose problems during the analytical process. We believe that this experimental model offers promise as a rapid screening tool for permeation studies in general.

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