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International Journal of Pharmaceutics 301 (2005) 226–236
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Release characteristics of anionic drug compounds from liquid crystalline gels I: Passive release across non-rate-limiting membranes

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Received 31 January 2005; received in revised form 20 May 2005; accepted 29 May 2005

Abstract

Liquid crystalline gels (LCG) offer the formulator dynamic and flexible vehicles, into which actives, enhancers and other adjuvants with a wide range of physicochemical properties can be incorporated. This is achievable because of the biphasic oil/water composition of the gel. In this paper, the suitability of an isotropic liquid crystalline gel is investigated for a range of anionic drug molecules, with particular emphasis on sodium diclofenac. Parameters, which have been investigated, include the mode of vehicle preparation, the effect of the concentration of the drug and how buffering the gel and/or the receptor medium affect the release profiles. Such profiles have been measured for the sodium salts of benzoate, salicylate and indomethacin. The passive release from the standard system was found to adhere to matrix-controlled diffusion. An increase in concentration leads to a non-linear increase in the cumulative release of sodium diclofenac from the gels. In direct contrast to the result reported for cationic salbutamol base, optimum release from the gel was achieved when neither the receptor medium nor the aqueous phase of the gel was buffered. The percentages released of the sodium salts of benzoate, salicylate and indomethacin, after 24 h, were determined to be 25, 26 and 19%, respectively, and these are significantly greater than the release of sodium diclofenac. This suggests that diclofenac undergoes ion-pairing or complexation within the gel, which inhibits its diffusion from the vehicle. Future papers will report on the incorporation of enhancers and the effects of iontophoresis on the release profiles of drugs from these gels, and ultimately on the transdermal transport of drugs from these vehicles across human and porcine skin.

Keywords: Diclofenac; Liquid crystalline gel; Transdermal; Buffering; Vehicle preparation

1. Introduction

It is well established that small, neutral compounds will permeate the skin barrier more readily than will charged species. Drug compounds can be classified chemically as ionic, zwitterionic or neutral. Ionic

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doi:10.1016/j.ijpharm.2005.05.040

compounds can be further subdivided into cationic or anionic species. The proportion of the compound, which exists in the ionic state depends on whether the compound is a salt, an acid or a base, on its associated pK_a or pK_b values, and the pH of the solution/matrix in which it exists.

The two main investigative aspects of transdermal drug delivery are, firstly, the determination of the release characteristics of the drug from the chosen vehicle and, secondly, the quantitative evaluation of the transport of the drug across the *stratum corneum* (SC) and its availability to the systemic system.

This investigation focuses on the former aspect of release studies in carrying out diffusion experiments using a non-rate-limiting membrane while varying several relevant experimental parameters. These include the nature of the receptor medium and the use of buffer solutions in the aqueous phase of the vehicle: the work extends over a range of model anionic drug molecules.

This work follows previous studies by Bannon et al. (1989) and Nolan et al. (2003), which investigated the transdermal transport of neutral (nicotine) and cationic (salbutamol) model compounds, respectively. Here we concentrate on the release and the subsequent transdermal transport profiles of anionic drug compounds, which, as a class, are comparatively under-reported in the literature. The anionic drug molecules chosen are the sodium salts of diclofenac, indomethacin, salicylate and benzoate.

It is essentially a coincidence that most of the anionic drug compounds under investigation here are classified pharmacologically in the same group as NSAIDs (non-steroidal anti-inflammatory drugs). These compounds do not meet all the ideal criteria of suitability for transdermal delivery, which include low molecular weight, high lipophilicity, high potency to achieve therapeutic affect, and stability. However, neither are they ideal for oral administration. Approximately a quarter of adverse drug reactions reported to the UK committee on the safety of medicines, are attributed to NSAID's and weak analgesic drugs (Rainsford, 1984). Most frequent side-effects observed with the NSAIDs are related to the gastrointestinal tract (GIT) (Escribano et al., 2003). Based on an index of topical anti-inflammatory activity (ITTA) Cordero et al. (2001) have found that diclofenac and indomethacin are of acceptable potency for external use. Therefore, it would be of considerable benefit if it were possible to deliver these drug molecules systemically via the transdermal route thus avoiding side-effects. Added advantages would include increased predictability and reproducibility of drug release kinetics and pharmacokinetics. Potentially, transdermal drug delivery is superior to all other conventional methods of delivery, such as oral, intravenous or intramuscular administration, because it can be better controlled (Smith and Maibach, 1995).

Charged drug molecules are, in general, considered to be unsuitable for transdermal drug delivery (TDD). However, research continues into possible methods of enhancing the TDD of these particular species. Research previously carried out in this laboratory (Nolan et al., 2003), found that a combination of physical and chemical enhancement significantly improved the release of salbutamol base, a cationic drug from an LCG. Oleic acid was used to reduce the barrier function of the *stratum corneum*, i.e., chemical enhancement, and an electrical potential was used to attract the drug across to an electrode of opposite polarity, i.e., physical enhancement. For this type of iontophoretically assisted delivery, additional factors must be taken into consideration. The vehicle should not reduce the conductivity of the drug and afford it the highest transport number possible. Nolan et al. (2003) found it impossible to establish a current across a monoglyceride gel unless there was an aqueous component. The vehicles most commonly used for iontophoretic drug release studies are aqueous solutions and hydrogels (Burnette and Marrero, 1986; Bannon et al., 1989) but Carr et al. (1997) and Nolan et al. (2003) have shown the liquid crystalline vehicle to be used in this study to also be suitable for iontophoretically assisted transdermal drug delivery.

Many questions with regard to iontophoresis, arising in the last decade in the quest for rapid market success, still remain to be answered. Firstly, the profile, duration and intensity of current and interactions with local physiology need to be systematically examined in order to overcome limitations in terms of patient discomfort. Secondly, the formulations to be used in the vehicle must be optimised for drug delivery and stability, effective electrochemical assistance and skin compatibility. The balance between the need to reduce competition from other ions in the vehicle and the requirement in the case of ionic constituents for the stability of the drug species has to be established (Merino et al., 1997).

In this context, these current studies are a comparative investigation in which a suitable chemical enhancer and iontophoretic conditions are identified for an anionic drug, diclofenac, diffusing from a liquid crystalline gel.

2. Experimental

The bulk of the experiments consisted of studies in which the drug compound of interest diffused from a solid gel vehicle through a synthetic membrane into a Franz-like cell (Franz, 1978). The synthetic membrane used was Visking®, which acted as a non-rate-limiting barrier and so was utilised to ascertain the release characteristics of various drugs from the gel. The liquid crystalline gel used was formed using Myverol®, a commercially available emulsifier, to form an oil/water mixture. This was then placed on the membrane across the top of the diffusion cell. A receptor medium was then poured into the cell, which was then stoppered. It was important to make sure to exclude air from the receptor chamber just underneath the membrane. A star shaped magnetic stirrer was used in the cell to maintain an even concentration gradient throughout the cell through gentle stirring, whilst at the same time avoiding a vortex, which would affect steady state diffusion (Keshary and Chien, 1984). The cell was suspended at neck height in a thermostatted water bath at 310 K. Samples were taken at regular intervals, through a port, and placed in 1 ml HPLC vials. The samples were then injected from an autosampler through a column and tuneable detector to give a chromatogram from which concentrations of drug could be determined by comparison with predetermined standards.

2.1. Materials

The following analar grade chemicals were supplied by Sigma–Aldrich. Diclofenac, 2-(2,6-dichloroanilino) phenyl acetic acid is a white crystalline powder with a melting point of approximately 429–431 K and a molecular weight of 296.2 a.m.u. Its sodium salt has a molecular weight of 318.1 a.m.u. and a melting point of 559 K and its molecular structure is shown in Fig. 1(a). Indomethacin, [1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl] sodium is a pale yellow odourless solid. The compound is decomposed by light. Indomethacin exhibits polymorphism; one form melts

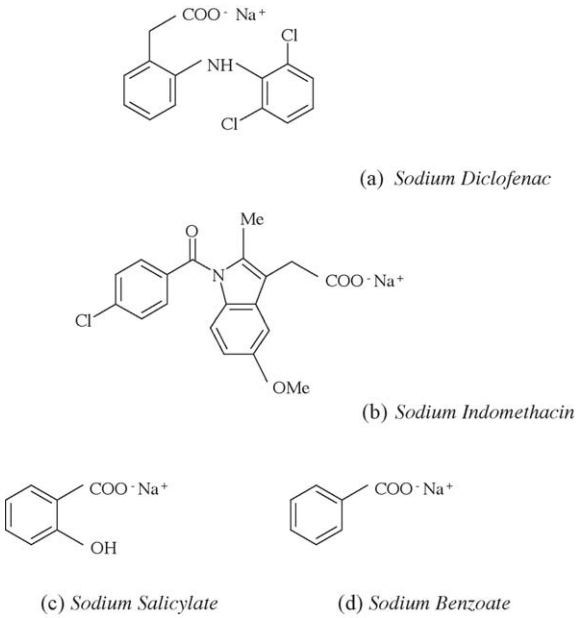

Fig. 1. Chemical structures of the sodium salts of the drugs investigated.

at about 428 K and the other at about 435 K. It may exist as a mixture of both forms, which melts between these two temperatures. Its structure is shown in Fig. 1(b). Salicylic acid, (2-hydroxybenzoic acid) and its derivatives is one of the earliest known and most widely used NSAID. The sodium salt is a white odourless compound. Its structure is shown in Fig. 1(c). Finally, sodium benzoate was also used as an anionic model compound. Although sodium benzoate is not a therapeutic compound, it was used because of its similarities to the other model compounds and because it is readily available. It is commonly used as a food preservative. The structure is shown in Fig. 1(d).

Potassium bromide and potassium chloride (both 99% purity) were also supplied by Sigma–Aldrich Chemicals. The following were supplied by Riedal-de-Haan: sodium dihydrogenphosphate, di-sodium hydrogenphosphate (both 98% purity); and the analytical grade solvents and acids: acetone, acetonitrile, methanol, sulphuric acid, nitric acid and phosphoric acid.

Myverol 18–92 was kindly donated by Eastman Chemicals (UK) Limited. Myverol is derived from rapeseed oil and consists mainly of monoglycerides.

The material contained less than 5% diglycerides. Some food grade antioxidants were also present. Myverol was used as the main constituent in the preparation of the liquid crystalline delivery vehicles. Myverol is an off-white, odourless semi-solid and is a dispersing or foaming agent. Its melting point is ∼313 K and it forms a liquid crystalline gel above 303 K on addition of water.

An aqueous gel vehicle, which was used for the purpose of comparison, was prepared from of purified agar, which was supplied by Oxoid (code L28) as yellowish granules. Agar is produced by using hot water extraction of selected seaweed to yield a polysaccharide mixture of agarose and agaropectin.

2.2. Preparatory methods

2.2.1. Liquid crystalline gels (LCG)

The following is a typical procedure for the preparation of a liquid crystalline vehicle containing, e.g., sodium diclofenac. Each vehicle had an approximate gel volume of 1.8 mL. The gels were prepared according to a method described by Carr et al. (1997). A ratio of 71% myverol to 29% distilled water or buffer solution by weight was used. Carr experimentally established this ratio as optimum for the release of drugs from the gel: the ratio is also the saturation point of water in Myverol. To prepare a 7 mL gel 4.69 g of myverol is required (density, 0.94 g/L). The myverol was carefully weighed and then heated gently over a Bunsen burner until it melts. 196 mg of sodium diclofenac were then dissolved in this liquid myverol or alternately in the aqueous phase. 2.03 mL of triply-distilled water or buffer were then added to yield a 0.1 M solution. The liquid crystalline phase formed immediately and was thoroughly mixed to ensure even distribution of drug.

2.2.2. Agar gels

The average volume of aqueous agar gel used was also 1.8 mL. The 4% agar solution was poured into a petri dish and allowed to set then stored in a fridge at 276 K. When set the gel is ready to be cut using a cylindrical cutter to produce disks with a cross-sectional area of 2.54 cm^2. The volume of agar required to fill the petri dish to a depth of 0.9 cm, in order to attain this volume was found to be 51 mL. The quantity of agar required to make a 4% gel is 2.04 g. 31.8 mg of sodium diclofenac are required to make a 0.1 M gel.

2.2.3. Buffer solution

Isotonic phosphate buffer solution (IPBS) is a physiologically adjusted buffer used to mimic diffusion into the systemic blood system. The buffer contains 2.2 g dm^{-3} NaH_2PO_4 A.R., 19.1 g dm^{-3} $Na_2HPO_4{\cdot}12H_2O$ A.R. and 4.4 g dm^{-3} NaCl. The pH of the resulting buffer is 7.4.

2.2.4. Mobile phase (for HPLC analysis)

The mobile phase was prepared using 1.96 g H_3PO_4, 600 mL of HPLC grade acetonitrile (ACN) and 400 mL of triply-distilled water. The triply-distilled water was filtered through a 0.2 μm filter to remove particulates. The solution was stirred and then sonicated to degas it before use. The mobile phase was degassed on a daily basis and prepared freshly every three days.

2.2.5. Visking membranes

Visking® 18/32 cellulose dialysis tubing is a synthetic membrane produced by the Visking Co., Chicago, IL, USA. It has an average pore size of 2.4 nm (Corrigan et al., 1980) and an average thickness of 20 μm (Bannon et al., 1989). Any soluble materials, such as sulphur compounds, were removed before use by repeated boiling in triply-distilled water (Molyneux and Frank, 1961). The tubing was cut into lengths of three centimetres and opened flat using a blade for use as a non-rate-limiting membrane. This membrane has previously shown not to significantly affect the diffusion of a variety of drugs from agar or liquid crystalline gels (Nolan et al., 2003).

2.2.6. Preparation of diffusion cells

Custom-made single compartment Franz-like diffusion cells were used in all experiments. The Visking membrane was securely held on the top of the Franz diffusion cell using parafilm wrapped around the neck of the cell. IPBS or triply-distilled water was placed in the receptor port of the cell. The 1.8 mL of the viscous gel-containing drug was syringed onto the membrane and covered with Parafilm™ to prevent water loss. The receptor port of the cell was then topped up to exclude air bubbles. The cell was now ready to be placed in a thermostatted water bath at 310 K with which it was allowed to equilibrate. The first sample was taken after

half an hour and subsequently on the hour up to 8 h and also at the 23rd and 24th hour after the start.

3. Results and discussion

3.1. Passive release from LCGs

The cumulative amount of sodium diclofenac released passively as a function of time from a monoglyceride liquid crystalline vehicle, incorporating water as solvent, across a Visking membrane, is shown in Fig. 2. These results, and those for all other experiments reported here, were measured in triplicate and the appropriate error bars are shown. The total amount of sodium diclofenac released over a 24 h period was less than 6% of the initial loading of 0.1 M, increasing to a maximum release of 11% after 72 h.

This corresponds to the passage of 6.29 mg sodium diclofenac across the membrane. This is significantly lower than the quantities of many other drugs released under analogous conditions from this liquid crystalline gel. The release data in Fig. 2 show a non-linear relationship between the amount of drug released and time. At concentrations below saturation level lag times occur. The lag time can be obtained from the intercept with the x-axis when the data are plotted according to Eq. (1) below. The lag time is due in part to the presence of the Visking membrane and also the time required to establish steady state diffusion. For 0.1 M diclofenac the lag time was found to be 0.25 h and for 0.01 M it was found to have increased to 0.5 h. The increase in lag time with decrease in concentration is consistent with observations made by Nolan et al. (2003).

Several mathematical models have been developed and used to describe the release of drugs from matrix systems (Higuchi, 1960; Paul and McSpadden, 1976; Peppas and Korsmeyer, 1987). If a drug is uniformly dissolved in the gel, drug release from the gel in contact with the membrane can be described by the Higuchi equation:

$$Q = Kt^{1/2} \quad (1)$$

Here Q is the amount of drug released per unit surface area of the gel in contact with the membrane (mg cm^{-2}), t is the time in seconds and K is the release constant equal to $2C_0(D/\pi)^{1/2}$. Here C_0 is the initial concentration (mg mL^{-1}) and D is the diffusion co-efficient for the drug in the gel (cm^2 s^{-1}). The diffusion co-efficient of sodium diclofenac from the liquid crystalline gel was estimated from the slope of Fig. 3 and found to be 2.2×10^{-8} cm^2 s^{-1}. This is a significantly lower diffusion co-efficient than those measured for cationic salbutamol sulphate (9.70×10^{-7} cm^{-2} s^{-1}; Carr et al., 1997) or salbutamol base (1.32×10^{-7} cm^2 s^{-1}; Nolan et al., 2003) from the same vehicle.

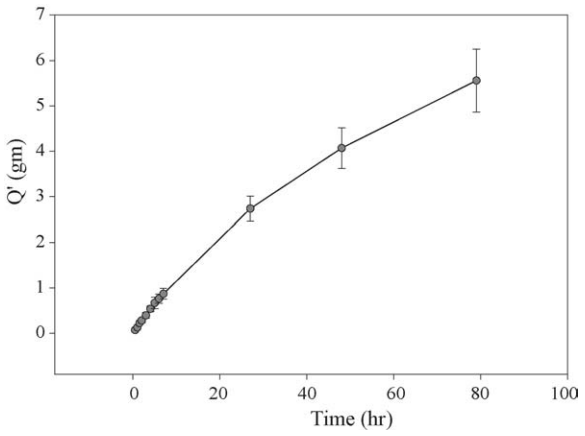

Fig. 2. The cumulative release of sodium diclofenac (Q', mg) transported from a liquid crystalline gel across a Visking® membrane, into an aqueous receptor medium. The initial concentration in all vehicles contained was 0.1 M.

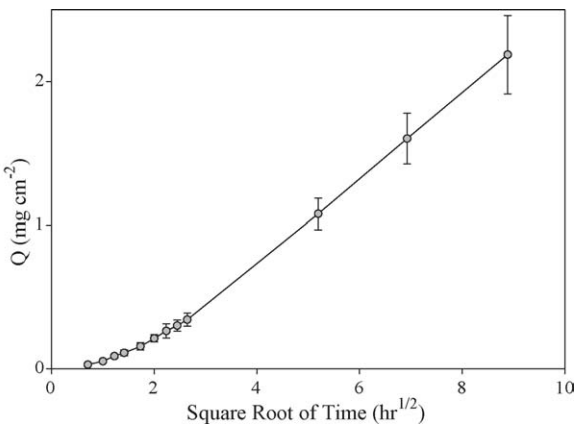

Fig. 3. Cumulative release data plotted according to the Higuchi model (Eq. (1)).

Nolan et al. (2003) suggested that the salt of a compound is more soluble in the aqueous phase of the biphasic vehicle hence its greater diffusion co-efficient. Sodium diclofenac has a high solubility in the aqueous phase and yet it has a diffusion co-efficient ~30 times lower that that of cationic salbutamol sulphate, which has a similar molecular weight, from the same vehicle. Therefore, the aqueous solubility of the salt form alone may not be considered as a good indicator in predicting the diffusion profile of a drug compound.

In contrast, when a comparison of the diffusion co-efficients of the compounds were measured from the monophasic aqueous vehicle of 4% agar gel, sodium diclofenac has a significantly greater diffusion co-efficient of 3.1×10^{-6} cm^2 s^{-1} compared to those measured by Nolan et al. (2003) for salbutamol sulphate (9.33×10^{-7} cm^2 s^{-1}) and salbutamol base (5.8×10^{-7} cm^2 s^{-1}). This represents a significant increase in the value of the diffusion co-efficient of the anionic compound over that of the cationic compound from an aqueous vehicle and it is also greater than that of the neutral nicotine molecule measured by Carr et al. (1997) and shown in Table 1. The use of the salt form of the drug as against the acid or base form may not be a significant factor in the large shift in magnitude of the diffusion co-efficients as illustrated by Nolan et al. (2003) salbutamol data. Other factors such as the partition co-efficient, complexation, viscosity and ionic radius may account for the lower diffusion co-efficient of sodium diclofenac from the LCG. A comparison of the release profiles of sodium diclofenac from the biphasic and monophasic hydrogel vehicles is shown in Fig. 4.

Table 1
Diffusion co-efficients of cationic, anionic and a neutral model drug from liquid crystalline gel and agar gel

Model drug	Diffusion co-efficient from liquid crystalline gel ($\times 10^{-7}$ cm^2 s^{-1})	Diffusion co-efficient from agar gel ($\times 10^{-7}$ cm^2 s^{-1})
Sodium diclofenac (anionic)	0.22	31.0
Salbutamol sulphate (cationic)	9.70[a]	9.33[b]
Salbutamol base (cationic)	1.32	5.80
Nicotine (neutral)	3.04[a]	26.0[b]

All initial drug loadings are 0.1 M.
[a] Data obtained from Carr et al. (1997).
[b] Data obtained from Bannon et al. (1989).

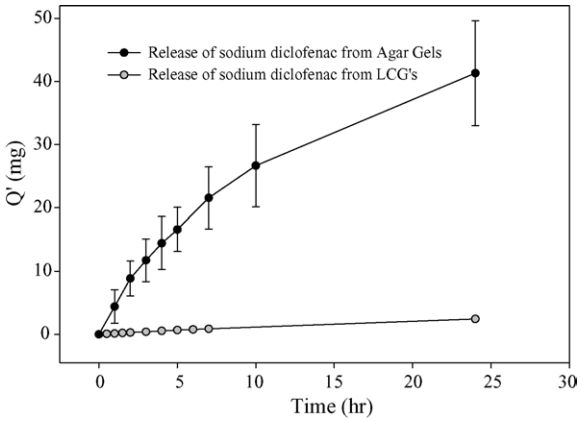

Fig. 4. Comparative release of sodium diclofenac from monophasic (Agar) and diphasic (liquid crystalline) gels over a 24 h period.

A fundamental parameter to be considered when investigating diffusion from a bi-phasic vehicle is the partitioning of the drug between the phases. This influences the release profile of the drug from the oil phase into the aqueous phase of the liquid crystalline gel and ultimately, in these studies, from the vehicle across the skin. The partition co-efficient ($\log P$) of sodium diclofenac is 13.4 (octanol/aqueous buffer) and 4.5 (octanol/water) (Maitani et al., 1994). In comparison, the octanol/water partition co-efficient of salbutamol base was found to be 0.43. The monoglyceride/water partition co-efficient of salbutamol base and of salbutamol sulphate have previously been measured in this laboratory and found to be $\log P = 0.8$ and $\log P = 0$, respectively. These values concur with release data, which show that the lower the partition co-efficient the greater the release from the liquid crystalline vehicles. The quantity of drug released over a 24 h period follows the trend salbutamol sulphate > salbutamol base > sodium diclofenac.

The reason for such a significant difference in partitioning between the salts of salbutamol and diclofenac is unclear. Bhattachar et al. (1992), reported on the ability of sodium diclofenac to form complexes with hydrogenated phospholipids. The oil phase environment of a liquid crystalline gel is not too dissimilar to the one presented by phospholipids, i.e., negative head group with long alkyl chain being the main composition of molecules in the oil phase.

Arellano et al. (1998) reported that the diffusion of sodium diclofenac across a synthetic membrane (0.2 μm cellulose nitrate) from a binary system of carboxypolymethylene (carbopol 940)/distilled water was best described by the Higuchi diffusion model. They reported a maximum release rate of 5.8×10^{-3} mg cm^{-2} min^{-1} compared to a release rate of 3.27×10^{-4} mg cm^{-2} min^{-1} from the myverol/water binary system used in this study. The reason for this almost 20-fold difference in release rates is most likely due to a larger ratio of aqueous phase in the carbopol system, which contained 98% water (w/w) compared to 29% (w/w) for the myverol system. This larger ratio insures that a greater proportion of sodium diclofenac is dissolved in the aqueous phase giving a more rapid and ready release.

Ho et al. (1994) also reported the diffusion of sodium diclofenac across a synthetic membrane (Durapore) from a binary system of carbomer 940/water with a 1:90 ratio, respectively. They used 10% triethanolamine as a gelling agent and also found that the release was best described by the Higuchi model with a release rate of 14.66 mg cm^{-2} min^{-1}. Fang et al. (1999) have also reported that sodium diclofenac followed matrix-controlled release in the absence of rate-limiting membranes.

Another factor, which may influence the release profile of a drug, is the viscosity of the matrix. Mockel and Lippold (1993) investigated the release kinetics of proxyphilline from hydrocolloid matrices. The mechanism of release from the matrices depended on their viscosities. Gels of low viscosity exhibited zero-order release kinetics whilst those of higher viscosity adhered to matrix diffusion control.

Analysis of the diclofenac data measured here, using the Higuchi equation, reveals that the release kinetics conforms to matrix control for all initial drug loadings of sodium diclofenac. The data were also found to be linear for first-order kinetics when plotted according to the Schwartz equation (Schwartz et al., 1968)

$$\log W = \frac{kt}{2.303} + \log W_0 \quad (2)$$

where W is the quantity of drug left in vehicle, W_0 is the initial quantity of drug in the vehicle, k is the first-order rate constant and t is the time in seconds. However, consideration of a plot of the second derivative of both equations indicates the release conforms to matrix-controlled diffusion tending towards zero-order. This conclusion can be further confirmed by the use of Eq. (3), which is obtained by taking logs of Eq. (1). This predicts that a plot must not only give a straight line, but should have a slope equal to 0.5.

$$\log Q = \log K + 0.5 \log t \quad (3)$$

The co-efficient of determination (r^2 value) for the plot was found to be 0.99, which shows significant correlation between the variables, but the value of the slope is 0.82 instead of 0.5 as would be required by first-order release. Zero-order kinetics may prevail above a slope value of 0.66 (Mockel and Lippold, 1993).

3.2. Effects of concentration

The effects of concentration on the release profiles of sodium diclofenac were also investigated. The kinetic data measured in these studies allowed comparisons of rate constants to be made, and provided further confirmation of adherence to the Higuchi matrix-controlled diffusion model. Data from initial drug concentrations of 0.05, 0.01 and the previous concentration of 0.1 M are shown in Fig. 5. From the profiles, it is evident that an increase in the drug concentration leads to an increase in the quantity of drug released.

Diffusion co-efficients and rate constants, calculated using Eq. (2), at the different loadings are shown in Table 2. The rate constant values again confirm that the release of the drug from the liquid crystalline gel

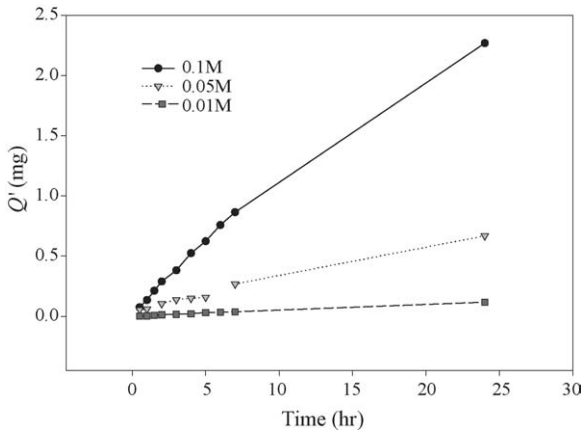

Fig. 5. Cumulative amount of sodium diclofenac released from liquid crystalline gels across a Visking^{TM} membrane with initial drug loading of 0.01, 0.05 and 0.1 M.

Table 2
Rate constants and diffusion co-efficients calculated from the release of sodium diclofenac from liquid crystalline gel across a Visking™ membrane

Initial drug loading (M)	Rate constant ($\times 10^{-6}$ s^{-1})	Diffusion co-efficient ($\times 10^{-7}$ cm^2 s^{-1})
0.1	2.55	1.60 ± 0.15
0.05	1.02	0.44 ± 0.03
0.01	1.54	0.90 ± 0.08

does not adhere to first-order kinetics, as variation is non-linear with concentration (Schwartz et al., 1968).

3.3. Effects of buffering vehicle and/or receptor medium

In line with possible use of the system for transdermal drug delivery, release characteristics of the model drug were also determined under physiological conditions. This was done by buffering the delivery vehicle and/or the receptor medium using isotonic phosphate buffer (pH, 7.4). The respective data are tabulated in Table 3 and reveal that the release of sodium diclofenac was greatest when neither the vehicle nor the receptor medium were buffered. There was a minimal decrease in the release when the aqueous phase of the vehicle was buffered and an almost three-fold decrease when the receptor medium was buffered.

This is in direct contrast to the trend observed for the release of salbutamol base from the same vehicle and the release characteristics for diclofenac and salbutamol base are distinctly different. After a period of 24 h the release of sodium diclofenac (4.5%) is approximately one sixth of that recorded (26.5%) for salbutamol base. The reasons for such significant differences in passive release profiles may be explained by factors such as the charges on drug ions, complexation, solubility, pK_a values and partition co-efficients. For example, the lower partitioning of diclofenac into buffer than into water can be attributed to an ion gradient between the two phases against which the drug must work when the aqueous phase is buffered. The concentration gradient favours transport of the drug in the required direction, as it is dissolved in the oil phase and must diffuse into the aqueous phase before being released. The presence of sodium ions in the buffered aqueous phase inhibits the free dissociation of sodium diclofenac from the oil phase due to sodium being the main counter ion to diclofenac. Whereas, the counter ion of salbutamol is sulphate and this is not a common ion in the isotonic phosphate buffer solution used.

Table 3
Effects of buffering vehicle and/or receptor medium

Aq. gel/receptor medium	% Release after 7 h	% Release 24 h
H_2O/H_2O	1.70	4.50
Buffer/H_2O	1.44	3.27
H_2O/buffer	0.63	1.80
Buffer/buffer	0.57	1.40

In the case of salbutamol base its octanol/water partition co-efficient was determined to be 0.43, i.e., it is almost 2.5 times more soluble in water. Salbutamol in its basic form is cationic, which will give it hydrophilic properties. Its pK_a value is 9.5 so it would not be appreciably dissociated at pH 7.0. Salbutamol sulphate partitions into water more strongly than does its basic form. Carr et al. (1997), observed a greater release of salbutamol sulphate passively than was observed for salbutamol base by Nolan et al. (2003).

Despite its ionic nature sodium diclofenac is more soluble in octanol than water. This may be due to the difficulty of the salt to dissociate in a lipophillic environment and also because the undissociated salt is neutral and well solvated in the neutral myverol phase. Fini et al. (1996), found that by changing the counter ion of diclofenac the partition co-efficient changes in favour of water. Using a diethyl amine cation they found a log P value = 0. It was found that the larger the counter ion the easier it is for the salt to dissociate. If this is the case it may explain why the sulphate salt of salbutamol dissociates so well in comparison with the sodium salt of diclofenac.

Nolan (1995) offered by way of explanation of these observations that the buffer ions may alter the "tortuosity" or "porosity" of the vehicle thus increasing the rate of release of the drug from the vehicle. However, in view of the results for diclofenac this is not likely to be is the case. It is more probable that a preferential cation-exchange process may be taking place between the buffered aqueous phase of the gel and the myverol.

3.4. Effects of varying the method of preparation of the vehicle

Carr et al. (1997) investigated the effect of varying the method used to prepare the vehicle. Their

Method I consisted of dissolving the drug in the aqueous phase while in Method II the drug was dissolved in the oil phase (myverol). Their results showed a 15% decrease in the apparent diffusion co-efficient using Method II. And, they suggested that the drug incorporated into the oil phase in Method II may be entrapped between the surfactant bilayers and hence tends to diffuse more slowly through the more lipophilic regions of the Myverol to the aqueous channels from whence it is released across the membrane. Similarly, an investigation of sodium diclofenac in the current study showed an average decrease of 11% in the cumulative release of the drug from gels prepared by Method II. Although this average result might be considered to add weight to the suggestion by Carr et al. (1997), the extent of the change observed here lies within the measured experimental error.

3.5. Comparison of release profiles of a range of anionic drugs

Due to the low diffusion co-efficients of sodium diclofenac and nicotine (Carr et al., 1997) from myverol/water liquid crystalline vehicles, an investigation of the release profiles of similar anionic model compounds were measured in order to ascertain whether this type of matrix is generally suitable for use as a delivery vehicle.

The model drugs chosen for comparison were the sodium salts of indomethacin, salicylate and benzoate. These molecules differ in physicochemical characteristics such as molecular weight, partition co-efficient, pK_a and solubility but all are related in having carboxyl groups, which produce negatively charged anions when dissociated. The release profiles of these compounds are shown in Fig. 6 where they are compared to that of sodium diclofenac over the first 25 h.

The data in Table 4 indicate, from a quantitative viewpoint, that sodium indomethacin has a very significantly greater release than those of the other model compounds. Indeed, in terms of percentage release, sodium diclofenac would appear to be anomalous.

The percentage release data, in Table 4, indicate that the three compounds, other than sodium diclofenac, are similar in magnitude. These similar percentage release data could indicate similar diffusion processes taking place for these particular compounds. In comparison, the release of sodium diclofenac from the LCG is retarded, which is due to an undetermined process yet to be identified.

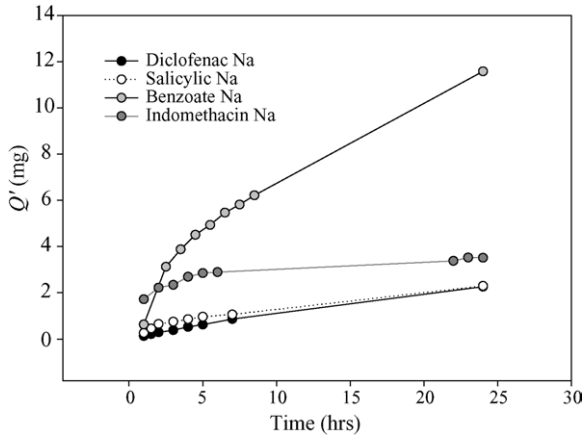

Fig. 6. Comparison of the release of anionic drugs from the liquid crystalline vehicle.

There is no direct correlation between partition co-efficient and percentage release, e.g., sodium indomethacin has the lowest log P value and the highest diffusion co-efficient yet is third on the percentage release scale. However, indomethacin has a significantly greater molecular weight than either salicylate or benzoate.

It is evident that sodium diclofenac has the smallest percentage release from myverol/water liquid crystalline vehicles. The reasons for this probably lie in an interaction with the myverol oil phase. The results of the current investigation can only serve to eliminate some of the more obvious parameters such as pK_a, partition co-efficient, concentration, molecular weight and solubility from the list of potential factors, which may inhibit the release of diclofenac. Factors, which have not been eliminated, are complexation and ion–paring,

Table 4
Quantitative release data and diffusion co-efficients of anionic drugs from liquid crystalline vehicles with an initial drug loading of 0.1 M.

Model drug	Diffusion co-efficient (10^{-7} cm^2 s^{-1})	% Release of initial loading after 24 h	Quantitative release after 24 h (mg)
Na benzoate	0.12	25.2	3.51
Na salicylate	0.37	26.0	2.29
Na indomethacin	1.50	19.1	11.6
Na diclofenac	0.22	6.0	2.27

which would change the properties of the drug, making it more stable within the cubic phase of the matrix.

The drug and other additives may, depending on the amount present, dramatically alter the type and range of aggregates formed in the gel (Lawrence, 1994). Little work has been performed in this area. Indeed, it is difficult to predict the effect of a drug or other additive on a phase structure of a gel as it is expected to vary according to whether the additive is water soluble, adsorbs at the aggregate surface, or co-aggregates with the surfactant or resides in the interior of the aggregate. Evidence suggests, however, that the phase structure experiences the most disruption when the additive is itself surface active. For example, the presence of the drug lignocaine hydrochloride at concentrations >5 wt.% converts the cubic structure formed from 10 wt.% monoolein in water into a lamellar phase (Engstrom et al., 1992). The influence of the presence of a drug is further complicated because most drugs are administered as salts, so that the amount of amphiphilic salt to lipophilic free drug varies according to the pH. Consequently, the effect of the drug on the phase structure may vary with the pH of the surrounding environment. However, balanced in favour of the employment of bi-phasic gels as delivery vehicles are the matrix diffusion control they offer and the ease with which the characterisation of release profiles can be obtained. Their ability to solvate a wide range of actives and adjuvants and also their non-toxic and non-irritant nature gives the gel ideal suitability.

The results of these investigations serve to demonstrate the release profiles of the selected ionisable compounds relative to each other. The moderate quantitative and percentage release from the gels into aqueous receptor media may not be a true measure of the transport of the drugs into a more lipophillic environment such as that which is found in human skin. Nonetheless, these studies represent a firm platform from which to further investigate the behaviour of the liquid crystalline gels with respect to their release profiles in the presence of enhancers and/or iontophoretic conditions. It is expected the gels will be robust and provide alternate phases both aqueous and organic in which additives can reside. The aqueous phase will also provide a conductive medium that can carry an assisting current in iontophoretic delivery.

4. Conclusions

The total amount of sodium diclofenac that was released from the LCG over a 24 h period was less than 6% of the initial loading of 0.1 M with an estimated diffusion co-efficient of 2.2×10^{-8} cm^2 s^{-1}. The data were found to adhere to a matrix-controlled release profile. The lower than expected release of the drug from the gel may be as a result of complexation with components of the oil phase of the gel. An increase in the drug concentration leads to an increase in the quantity of drug released.

The release of sodium diclofenac was greatest when neither the vehicle nor the receptor medium were buffered. There was a minimal decrease in the release when the aqueous phase of the vehicle was buffered and an almost three-fold decrease when the receptor medium was buffered. This is the exact reverse of the trend that was observed for the release of salbutamol base from the same vehicle (Nolan et al., 2003).

Incorporating the drug into the oil phase instead of the aqueous phase during vehicle preparation resulted in an 11% decrease in the cumulative release of the drug from the gel. This mimics a similar result found by Carr et al. (1997) investigating the release of salbutamol sulphate from the same gel.

The percentage release of the sodium salts of benzoate, salicylate and indomethacin, after 24 h, were determined to be 25, 26 and 19%, respectively. This is significantly greater than that of sodium diclofenac and again suggests that diclofenac undergoes ion-pairing or complexation within the gel, which inhibits its diffusion from the vehicle.

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