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Release characteristics of anionic drug compounds from liquid crystalline gels Part II. The effects of ion pairing and buffering on the passive delivery of anionic drugs across non-rate-limiting membranes

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Abstract

This is the second in a series of papers that report on the release and transport of a range of anionic drugs (diclofenac, salicylic acid) from liquid crystalline gels and ultimately on their use in transdermal delivery. The previous paper [Fitzpatrick, D., Corish, J., 2005. Release characteristics of anionic drug compounds from liquid crystalline gels for transdermal delivery. Part I. Passive release across non-rate limiting membranes. Int. J. Pharm. 301, 226–236] investigated passive release profiles across a non-rate-limiting membrane: here we report on the search for a suitable model enhancer (benzyl dimethyldodecyl ammonium bromide) for the transdermal delivery of anionic compounds. The results presented reveal a significant role for ion pairing and for buffering, analogous to those found in the investigations of cationic species (salbutamol) by Nolan, L.M.A., Corish, J., Corrigan, O.I., Fitzpatrick, D., 2003. Iontophoretic and chemical enhancement of drug delivery. Part I. Across artificial membranes. Int. J. Pharm. 12, 41–55. The method of vehicle preparation is also investigated. It is shown that ion pairing of the drug with the enhancer decreases the amount of drug available for transport from the liquid crystalline gels into aqueous receptor media. This decrease is directly related to the ratio of the concentration of drug to that of the enhancer. Buffering the vehicle inhibits the ion-pair formation to some extent. Vehicle preparation was also found to influence the degree of ion-pair association. The inclusion of a similarly charged enhancer (oleic acid) to the drug was found not to impede the diffusion of the drug from the gels.

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

1. Introduction

In the last 15 years there has been an increased effort to find new enhancer molecules, which have the ability to reversibly reduce the barrier properties of the skin or facilitate the diffusion of the drug molecule in a mechanistic way. The roles of ion pairing and buffering of the gel and/or receptor media in preliminary release studies remain undefined in the literature for more complex vehicles. Initial studies should always first assess the effect on its release profiles of incorporating a new constituent into the vehicle. In this study, particular attention is paid to these parameters with the objective of optimising enhancement techniques for the release of a range of anionic drugs from liquid crystalline gels (LCG) across non-rate-limiting membranes.

It was initially assumed that the enhancement by oleic acid of the delivery of salbutamol was due to the opposite charge exhibited by the drug and the enhancer when ionised under vehicle conditions (pH 7.2) (Nolan et al., submitted for publication, in review). This assumption was the main criterion used here in the selection of analogous model enhancers to assist the delivery of anionic drug compounds. Molecules with similar properties to oleic acetate but with a positively charged instead of a negatively charged head group were evaluated. As oleic acetate possesses a long alkyl chain so too should the selected molecule for investigations involving anionic diclofenac. It was

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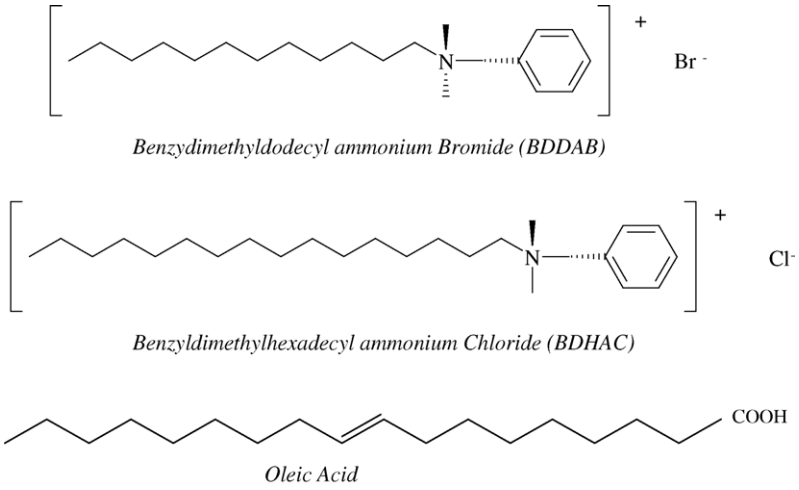

Fig. 1. Chemical structures of enhancers incorporated into the LCG.

decided to use derivatives of benzalkonium chloride, which best fit the selection criteria. The derivatives chosen are shown in Fig. 1. The molecules are tertiary ammonium salts, which vary in counter ion type and in chain lengths. The main focus of the investigation was benzyl dimethyldodecyl ammonium bromide (BDDAB) which has a chain length of 12 carbons. The other molecule used was benzyl dimethylhexadecylammonium chloride (BDHAC) that has four additional carbons in its chain and also differs in its counter ion. BDDAB has six fewer carbons in its chain compared to oleic acid, however aside from oleic acid, skin permeation enhancing effects have been shown to be greatest for the C_{10} and C_{12} fatty acids (Aungst et al., 1986; Ogiso et al., 1995).

The molecules chosen can be classified as surfactants, which are already known to have permeation enhancement characteristics, (Ruddy, 1995). Benzalkonium chloride and its derivatives are also considered to be clinically safe and are used as a spermicide in commercially available preparations and birth control products. All experiments were carried out in triplicate.

2. Experimental

2.1. Experimental method

Most of the experimental procedures are similar to those outlined in the previous paper (Fitzpatrick et al., 2005) but will be summarized here for convenience. In the experiments, the drug of interest is 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 utilized to ascertain the release characteristics of various drugs from the gel. The liquid crystalline gel used was formed using Myverol®, a commercially available emulsifier that forms an oil/water mixture. This was placed on the membrane across the top of the diffusion cell and a receptor medium poured into the cell which was then stoppered. It was important to make sure to exclude air from under the membrane. The cell was suspended at neck height in a thermostatted water bath at 310 K. Samples were taken at regular intervals and then injected from an autosampler through a HPLC column. A tunable detector gave a chromatogram from which concentrations of drug were determined by comparison with predetermined standards. The procedure was similar for the experiments with the potential chemical enhancers except that these molecules were also incorporated into the gel, along with the drug.

2.2. 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. Its sodium salt has a molecular weight of 318.1 and a melting point of 559 K. It is a commonly used non-steroidal anti-inflammatory drug (NSAID). 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.

Sigma–Aldrich Chemicals also supplied as analar grade the chemical enhancers; oleic acid, derivatives of benzalkonium chloride, namely: benzyl dimethyldodecyl ammonium bromide and benzyl dimehylhexadecyl ammonium chloride as well as potassium bromide and potassium chloride (both 99% purity). Sodium dihydrogenphosphate, di-sodium hydrogenphosphate (both 98% purity) and the following analytical grade solvents and acids were supplied by Riedel-de Haan; acetone, acetonitrile, methanol, sulphuric acid, nitric acid and phosphoric acid.

Myverol 18–92 was donated by Eastman Chemicals (UK) Ltd. Myverol is derived from rapeseed oil and consists mainly of monoglycerides. The material contained less than 5% diglycerides and is an off-white, odourless semi-solid which is a dispersing or foaming agent. Its melting point is 313 K and, on addition of water, it forms a liquid crystalline gel above 303 K.

2.3. Preparatory methods

2.3.1. Liquid crystalline gels (LCG)

Each vehicle had an approximate gel volume of 1.8 mL. These gels were prepared as described by Carr et al. (1997). A ratio of 71% myverol to 29% distilled water or buffer solution by weight was used. Carr established experimentally that this ratio was optimum for the release of drugs from the gel, the ratio is also the saturation point of water in Myverol. 4.69 g of myverol was carefully weighed and then heated gently over a bunsen burner until it melted. 196 mg of sodium diclofenac were then dissolved in this liquid myverol and 2.0 mL of triply distilled water or buffer are added to yield a 0.1 M solution. The liquid crystalline phase forms immediately and is thoroughly mixed to ensure a uniform distribution of drug. Vehicles containing enhancers were prepared in the same way, except for the addition of enhancer with the drug into the oil phase prior to the preparation of the liquid crystalline phase. Gels were used on the same day as preparation or the following day.

2.3.2. 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

2.3.3. 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 triply distilled water. The triply distilled water is filtered through a 0.2 μm filter to remove particulates. The solution is stirred and then sonicated to degas it before use. The mobile phase was degassed on a daily basis and renewed every 3 days.

2.3.4. 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, 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 centimeters and opened flat using a blade for use as a non-rate-limiting membrane. This membrane has previously been shown not to significantly affect the diffusion of a variety of drugs from agar or liquid crystalline gels (Bannon, 1989; Nolan et al., 2003).

2.3.5. Preparation of diffusion cells

Single compartment Franz-like diffusion cells were the standard apparatus for 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 quickly equilibrated. The first sample was taken after half an hour and subsequently on the hour up to 8 h. Samples were also taken at the 23 and 24 h intervals after the commencement of the experiment.

3. Results and discussion

3.1. The release of anionic drug molecules from a LCG incorporating benzalkonium chloride derivatives

The model enhancers at a concentration of 0.1 M were incorporated with the drug into the hydrophobic region of the vehicle during its preparation. The investigation first involved the use of the simple experimental protocol used in previous passive studies (Nolan et al., 2003; Fitzpatrick and Corish, 2005) where water as the gel solvent and receptor medium was proven to give the optimum release from the LCG for sodium diclofenac. The study was then extended to assess the effect of including physiologically adjusted buffer (pH 7.4) in both these parts of the system.

Fig. 2 shows the cumulative amount of sodium diclofenac released from the LCG containing 31.8 mg mL^{-1} of drug (0.1 M) and 0.1 M BDDAB. The release profile of sodium diclofenac from the LCG without any BDDAB is also shown. The stoichiometric ratio of drug to BDDAB in this experiment is 1:1. It is evident that the presence of BDDAB in the vehicle has a substantial effect on the release of the drug. As both the drug and enhancer are incorporated in their respective salt forms, it is expected that both will be fully ionised when diffusing through the aqueous domain of the gel. This introduces the possibility of ion pairing between the oppositely charged monovalent ions present in the vehicle. Both the drug and trial enhancer each bear one charge centre and consequently the association should result from a 1:1 interaction. An ion-pair association of this type in effect increases the lipophilic properties of the drug, which is of benefit with regard to transdermal drug delivery. However, it would appear that the apparent ion association between anionic

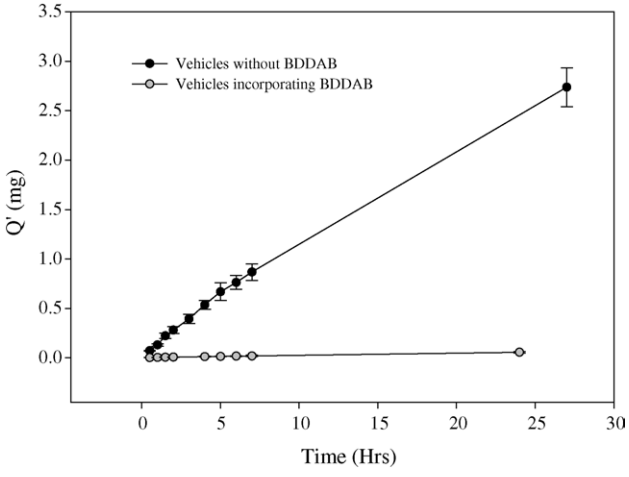

Fig. 2. The comparative release of diclofenac from a LCG with and without BDDAB in a water/water system.

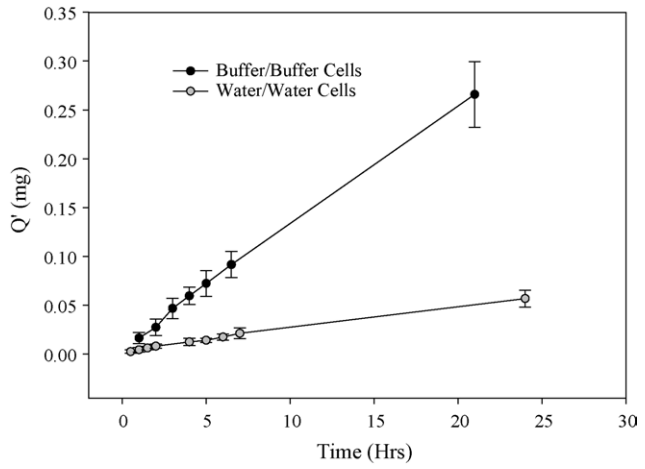

Fig. 3. The effect of buffering both the aqueous gel and receptor medium on the release of sodium diclofenac from a LCG incorporating BDDAB compared to the release rate using only triply distilled water.

sodium diclofenac and cationic $BDDA^+$ also reduces to almost zero the concentration of drug which can diffuse across the Visking membrane and into the aqueous receptor medium.

An analogous result was observed by Nolan et al. (2003) during their study of the passive release of salbutamol base (drug) and oleic acid (enhancer) from the same liquid crystalline gel. Because an acid and a base were used in the investigation, total association between the drug and the enhancer was not expected at vehicle pH. It was estimated that the quantity of salbutamol base that associated with oleic acid was approximately 66% and that the rate of release had decreased by a factor of three. The release of sodium diclofenac here may be affected dramatically by the greater association between ions of opposite charge and the increased number of ions from the dissociation of salts rather than incomplete dissociation of a weak acid and base. The results reflect this expectation as shown in Fig. 2. The release of sodium diclofenac was estimated at only 0.1% of initial drug loading after 24 h and this is essentially negligible in terms of its normal passive release from this vehicle.

Following this conclusive result showing negligible release using BBDAB, buffer ions were incorporated into the vehicle and/or receptor medium, respectively, to investigate their effect on the association of drug ions and BDDAB. The most significant difference in quantitative release occurred in the comparison of water/water and buffer/buffer systems and is shown in Fig. 3.

Introducing buffer ions into the aqueous domain of the gel and/or receptor medium increases the number of extraneous ions that can associate with the drug or enhancer. Table 1 contains the data from all experiments using buffer as the aqueous domain of the gel and/or the receptor medium.

In general, the more buffer that was added to the system the greater the release of the drug. However, after 20 h the buffer/buffer system containing the model enhancer BDDAB showed just 22% release in the amount of sodium diclofenac in comparison to an LCG without BDDAB, whereas the unbuffered system containing BDDAB showed just a 2% release in comparison to an LCG without BDDAB. The effect of including buffer ions in the system is thus to increase the release of diclofenac. However, previous investigations (Fitzpatrick and Corish, 2005) have already shown that the inclusion of buffer as the aqueous domain of the gel without enhancers inhibits the release of sodium diclofenac. The data showed that the buffer decreased the release of diclofenac by a factor of three. Buffer has thus been shown so far to have two counter effects in the system: one effect is to inhibit the release of the drug by reducing the ion gradient between the domains of the vehicle which is non-beneficial to the release; and the other effect is to reduce ion pairing in the presence of BDDAB, which is beneficial.

Table 1
Effect of buffering aqueous gel and/or receptor medium on the percentage release of sodium diclofenac from a LCG incorporating BDDAB

Aqueous phase phase of gel/receptor	Release after 7 h, %	Release after 24 h, %
Water/water	0.04	0.11
Water/buffer	0.19	0.60
Buffer/water	0.14	0.47
Buffer/buffer	0.24	0.60

In order to further explore ion-pair formation a second different model enhancer was used. It was expected that the incorporation of BDHAC would have the same effect on the system as had BDDAB. The dissociation of the chloride salt produces cations with which diclofenac anions may be expected to pair. The release profiles of sodium diclofenac with BDDAB and BDHAC in the vehicle are shown in Fig. 4.

The inclusion of BDHAC in the vehicle also significantly inhibits the release of sodium diclofenac. This reduction in the cumulative release of sodium diclofenac is also due to ion-pair formation within the vehicle. Due to the 1:1 ratio of drug to model enhancer the ion-pair association is almost total. The inclusion of BDHAC in the vehicle accounts for a 93.2% decrease in quantitative release of sodium diclofenac in comparison to a 98% reduction in the presence of BDDAB in a similar system.

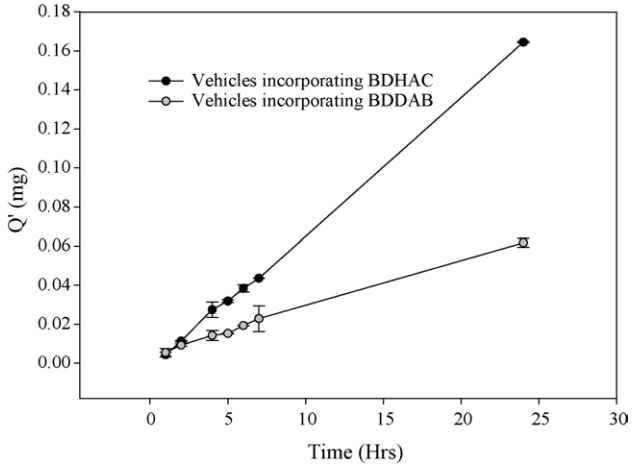

Fig. 4. Comparison of the passive release of sodium diclofenac from a LCG incorporating BDDAB or BDHAC.

3.2. Effect of vehicle preparation and ratio of enhancer to drug

The results of incorporating the long-chain benzalkonium chloride derivatives into the liquid crystalline vehicles are conclusive in that the release of sodium diclofenac is reduced to almost negligible levels because of ion-pair formation. It is likely that if both drug and enhancer could diffuse from the vehicle there will still be an enhancing effect whereby the enhancer reduces the barrier properties of the skin or ion-pairs with the drug to make it more lipophilic therefore increasing its skin permeability. Further investigations were undertaken to illustrate the effect of separately incorporating the drug in the aqueous phase and the enhancer into the myverol phase during preparation of the vehicle in an attempt to delay ion-pair association before diffusion of the drug or enhancer from the vehicle. The results are shown in Fig. 5

The release profiles show that separating the drug and enhancer (BDDAB) into different phases of the vehicle during preparation increases the amount of drug which diffuses from the vehicle. Although the effect of incorporating drug and enhancer into different phases results in a six-fold increase in release, the quantity released is still minimal in comparison to passive release from the simple gel.

To determine definitively that the inhibited release of sodium diclofenac was due to ion pairing with the model enhancer, investigations were instigated to quantify the effect of the enhancer concentration. A range of ratios of drug/enhancer were investigated to establish if there was a relationship between the amount of enhancer present in the vehicle and the cumulative release of drug.

It was first necessary to establish whether ion-pair formation would mask chromophores or in some way change or shift the absorption characteristics of the drug in the concentration range in which investigations were to be carried out.

UV studies showed that from a zero concentration of BDDAB to a 1:1 ratio of drug/BDDAB there is no decrease in the absorbance of sodium diclofenac in aqueous solution. As the ratio of enhancer increased above that of sodium diclofenac, a dramatic fall off in absorbance was noticeable. This was mainly due to an increase in the cloudiness of solutions and the subsequent dispersal of the light probably caused by micelle formation.

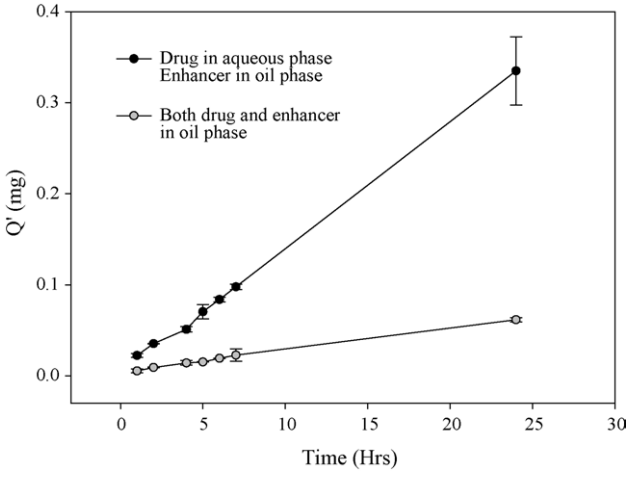

Fig. 5. Effect of incorporating the sodium diclofenac into the aqueous phase and enhancer (BDDAB) into the myverol phase compared to putting both in the myverol phase in the preparation of the gel.

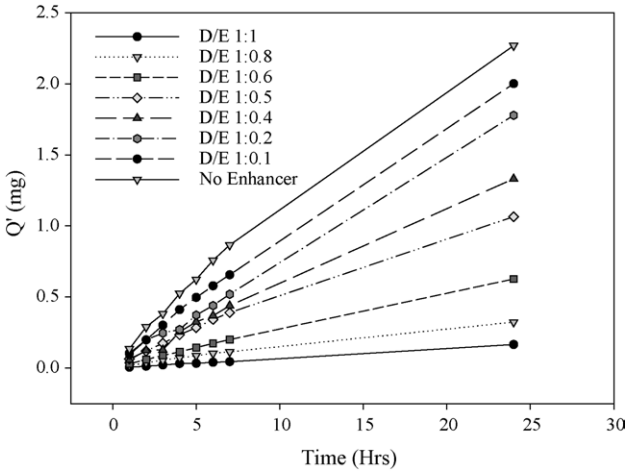

Fig. 6. Passive release of sodium diclofenac from the LCG incorporating incremental concentrations of BDDAB. The insert shows the ratio of drug (D) to enhancer (E). The experiments were carried out in triplicate and the standard deviation for all profiles did not exceed 8% after 24 h.

Fig. 6 shows the effect of varying the ratio of enhancer concentration from 0 to 1:1, whilst keeping the drug concentration at 0.1 M in the LCG. The graph indicates an obvious relationship exists between the ratios of drug/enhancer. A plot of percentage release after 24 h versus the ratio of drug/enhancer shows a linear relationship as shown in Fig. 7.

This linear relationship is conclusive evidence for the relationship between the concentration of enhancer in the vehicle and the percentage release of sodium diclofenac from the system. An r^2 value of 0.98 was obtained for the linear regression of the two variables. Fini et al. (1996) have reported that the diclofenac anion has the ability to form complexes and also possesses colloidal properties due to its structure which somewhat resembles that of a common anionic surfactant. These properties

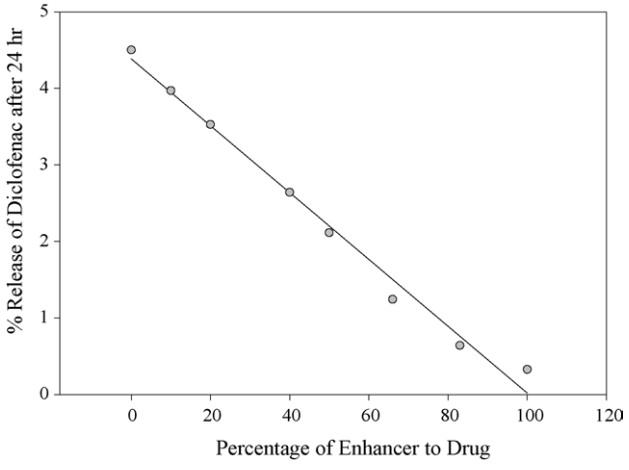

Fig. 7. Relationship between the ratios of the concentrations of the drug to those of the enhancers to the percentages of drug released after 24 h.

may be responsible for the unexpectedly low percentage release in the absence of enhancer but are unlikely to be the reason for the decrease of release in the presence of the model enhancer.

3.3. The passive release of the salt form versus the acid form of an anionic drug from an LCG in the presence of a model enhancer

Variables, which have been investigated so far include; effect of buffering the system, changing counter ion and chain length of the enhancer, and method of preparation of the vehicle. In an attempt to more fully understand the effect of incorporating BDDAB into the vehicle, it was decided to exchange sodium diclofenac with the sodium salt of another drug: sodium salicylate was chosen for these investigations. Measurements also included the use of the acid form of the drug (salicylic acid) to establish whether an increase in release is observable due to decreased ion pairing, as a result of incomplete dissociation of the weak acid.

The release of the salt form of the drug from the vehicle is over twice that of the acid form as shown in Fig. 8. This indicates that the salt form of the drug partitions more readily from the hydrophobic domain of the gel into the aqueous domain of the vehicle and continues through the non-rate-limiting membrane. The acid form of the drug would appear to be more stable in the oil domain of the gel and does not dissociate to the same extent into its constituent ions, which are more hydrophilic and would thus partition more readily from the oil domain. Nolan et al. (2003) also noted the same release profile trend associated with the salt and basic form of salbutamol sulphate.

When the model enhancer is incorporated into the vehicle the decrease in the amount of sodium salicylate observed was 67% compared to cumulative release in the absence of BDDAB from the simple gel. The decrease in the release of salicylic acid in comparison was 60%. The difference of 7%, although not significant, may be anticipated due to the incomplete dissociation of the acid, so that all of the acid is not available to form ion-pairs.

Compared to the >90% association of diclofenac anion and BDDAB, the reason is unclear as to why the association of the salicylate anion with BDDAB is ∼67% when there are equal concentrations of both compounds in the vehicle. However, Nolan et al. (2003) measured a decrease in the cumulative release of salbutamol base in the presence of oleic acid at ∼66%. This represents a similar degree of ion-pair association in both studies for the acid and base forms of the respective drugs. In the latter system the drug (salbutamol) is cationic and the enhancer (oleic acid) is anionic.

What is clear is that BDDAB and other benzalkonium salt derivatives associate strongly with anionic drugs. In the case of the acid form of the drug, the ion-pair association may be expected to be pH-dependent. Association is more likely to occur where the pK_a of the drug is below the vehicle pH (6.8 or 7.2 buffered). For most weak acids this tends to be the case.

3.4. The release of sodium diclofenac from the liquid crystalline gel incorporating oleic acid

It has been demonstrated in this laboratory (Nolan et al., submitted for publication, in review) that the presence of oleic acid in the vehicle has a dramatic effect on the delivery of salbutamol base across full thickness skin under iontophoretic conditions. This is in direct contrast to the effect of oleic acid on the transport of Salbutamol across non-rate-limiting membranes, (Nolan et al., 2003). In order to establish whether the action of oleic acid is drug specific i.e., actively facilitates the transport of cationic salbutamol, or whether its enhancing qualities are more general, it was essential to carry out preliminary investigations into the release characteristics of an anionic drug in the presence of oleic acid across a non-rate-limiting membrane. Passive release of sodium diclofenac from a liquid crystalline gel incorporating oleic acid is shown in Fig. 9. Its transport across full thickness skin will be reported in a later paper.

The data displayed here indicate that incorporating oleic acid into the vehicle in a 1:1 ratio with diclofenac has an insignificant effect on the passive release of the drug from the gel. Oleic acid

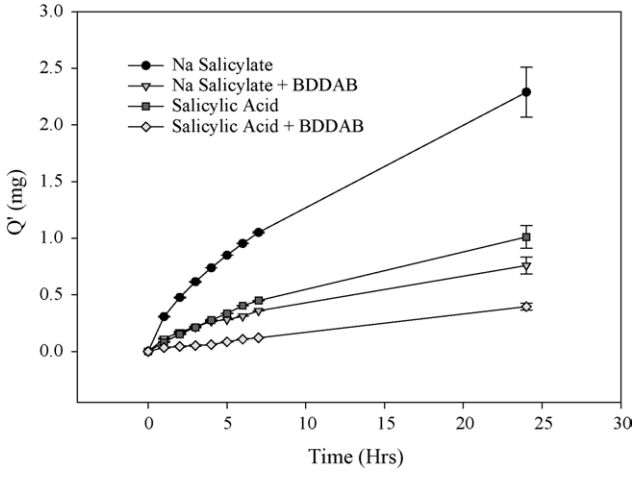

Fig. 8. The effect of incorporating BDDAB into the LCG on the passive release of salicylic acid and sodium salicylate from an LCG.

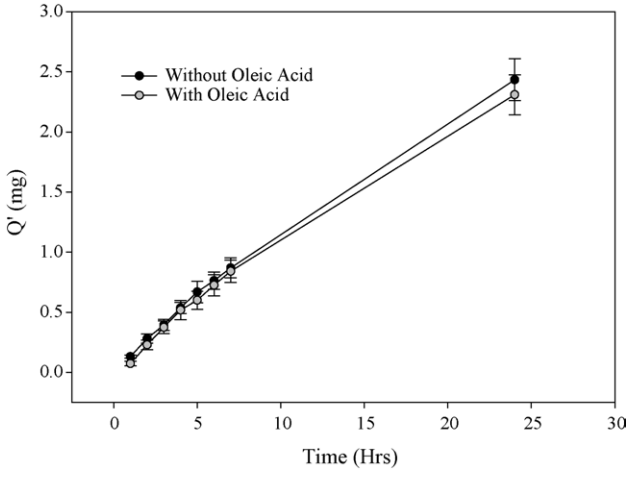

Fig. 9. The passive release of sodium diclofenac from the LCG with and without oleic acid. Each set of measurements was made in triplicate.

would not be expected to form ion-pairs as was observed in the presence of a cationic drug, because both sodium diclofenac and oleic acid produce anions. The fact that there is no association between the drug and enhancer not only leaves the drug free to diffuse across a membrane but the enhancer would also be available to disrupt the barrier properties of the skin. This result provides a firmer basis on which to continue investigations with this combination of enhancer and drug. Investigations by Maitani et al. (1986) used ethanol treated silicone membrane in studies involving the passive diffusion of sodium diclofenac in the presence of oleic acid. Results indicated oleic acid enhanced the diffusion of the sodium diclofenac through non-pore lipophilic routes. These results are not directly comparable due to the use of a non-rate-limiting membrane in this investigation. Also, the use of ethanol could be viewed as a chemical co-enhancement technique given the evidence of Hori's work, (Hori et al., 1990).

As discussed in Nolan et al. (submitted for publication, in review), it is essential to fully understand the nature of the vehicle and its adjuvants. The non-eroding cubic phase of the binary myverol/water system has the ability to solvate a wide range of drugs due to its very large interfacial area — in the order of 400 m^2/g (Ericsson et al., 1991). Incorporating a surfactant into a binary system effectively creates a tertiary system. The further addition of a drug could also be considered as producing a ternary system. It is known that the addition of surfactant to an oil/water mixture leads to the formation of a variety of phase structures (Attwood and Florence, 1983; Burrows et al., 1994) and a surfactant or micelle cannot be considered as an inert adjuvant.

It was noted during the experiments with the salts of drugs that the vehicles in which BBDAB was incorporated had a cloudy appearance rather than being clear. There are several possible explanations, which account for this observation. It may be indicative of a phase change in the gel from cubic to one of a number of other phase types including hexagonal, lamellar or vesicles, all of which can form cloudy birefringent phases (Lawrence, 1994). A wide range of surfactant concentration is known to result in the formation of these phases. However, such a change of phase would cause a change in the diffusion profiles of the drug from the vehicles and this was not observed here (Lawrence, 1994). The low solubility of the drug/enhancer ion-pair within the aqueous domain of the vehicle may also account for the cloudiness. Birefringence (cloudiness) may also be due to anisotropic molecular orientations. It is known that temperature has an effect on the birefringence of liquid crystalline gels (Polymers and Liquid Crystals, Case Western Reserve University). It was noted that the cloudiness of the gels dissipated and that white crystals formed during the course of 24 h experiments, which were maintained at body temperature. This is 10–15 degrees above room temperature. At room temperature, the gels were observed over a period of days during which the cloudiness eventually cleared from all gels and the formation of solid crystals was seen to occur. The geometry and appearance of the crystals depended on the drug that had been incorporated. Gels containing sodium salicylate formed large snowflake-like crystals whereas those containing sodium diclofenac formed smaller more spherical crystals. Gels in which BDDAB and salicylic acid were present remained clear initially and became cloudy over a period of days. All gels were stored at room temperature and prevented from dehydrating during this period by encapsulation in parafilm.

The experimental evidence firmly suggests that an ion-pair association exists between the drug and model enhancer. The association can occur between the carboxylate group of the drug and the quaternary nitrogen head group of the surfactant. This association may have a beneficial effect on the transdermal permeation of the drug should the ion-pair form after both drug and enhancer have diffused from the vehicle. However, in this instance the ion-pair association occurs within the vehicle and results in the decrease in the transport of the drug out of the gel. The interface between the gel and the non-rate-limiting membrane is a very aqueous environment as the membrane allows the receptor solution through to be in direct contact with the vehicle. However, this contact does not adequately represent the in vitro contact between the vehicle and excised human skin which consist of a more lipophilic environment than that with a non-rate-limiting membrane. The release profile of a neutral ion-pair from the vehicle could therefore be expected to be less inhibited when in direct contact with human skin. Ion-pair association has been employed by many researchers to facilitate the percutaneous absorption of drugs. The lipophilicity of hydrophilic ionised drugs can be increased by ion-pair formation with lipophilic counter ions. The concept was first introduced by Bjerrum in 1926 to explain the decrease in electrical conductance of sodium chloride in liquid ammonia, (Smith and Maibach, 1995). Green et al. (1989) investigated the effect of long-chain fatty acids on the transdermal absorption of cationic drugs. The pH of the donor vehicle was >7.4 so that the ion-pair could dissociate into single ions.

The careful control of pH within the vehicle could be considered as a mechanism to prevent ion pairing of the drug and enhancer. To achieve this the pH must be at a value where either drug or enhancer is non-ionic in form. This may be possible by shifting the pH downward to make the drug a neutral acid or by shifting the pH upwards to make a tertiary ammonium head group neutral. The only option in the diclofenac/BDDAB system or salicylate/BDDAB system is to shift the pH downward. The problem in doing so is that the pH required to obtain a neutral drug would be unsuitable for transdermal applications. With a $pK_a = 3$ for salicylate the pH would have to be below 2 in order to have an appreciable quantity of drug as required.

4. Conclusions

It has been demonstrated that the incorporation of the cationic surfactants BDDAB and BDHAC into the liquid crystalline gel in the presence of an anionic drug greatly reduces the quantity of drug which is available to diffuse from the vehicle across a non-rate-limiting membrane. This is due to the formation of ion-pairs between the drug and model enhancer within the vehicle. This result may not be judged to be the basis for a decision not to carry out in vitro transdermal measurements. The formation of ion-pairs may result in the preferential diffusion of the ion-pair from the vehicle and into the skin.

The addition of buffer into the aqueous phase of the vehicle and the receptor medium increased the release of drug from the LCG. Buffer ions inhibited the formation of ion-pairs to a minor degree. The use of an alternative cationic model enhancer BDHAC resulted in a similar suppression of the release of diclofenac with a 93% reduction in the release of the drug compared to a 98% reduction for BDDAB. A linear relationship was established between the percentage release of the drug and the concentration of model enhancer incorporated into the vehicle. The separation of the drug and enhancer into the different phases of the vehicle during preparation also reduced the extent of ion-pair formation. The passive release profile of sodium salicylate was also significantly reduced by the presence of the cationic surfactant. However, the magnitude of the association was 67% which is not as great as that observed for diclofenac. The use of salicylic acid further reduced the association by 7%. As the dissociation of the acid is not complete it is not available in total to form ion-pairs. Finally, a 1:1 ratio of diclofenac/oleic acid was demonstrated not to inhibit the release of diclofenac from the LCG and forms the basis for further studies with this combination of drug and enhancer.

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