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Percutaneous local anaesthesia: drug release characteristics of the amethocaine phase-change system

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Summary

Differential scanning calorimetry has been used to demonstrate that amethocaine base, when formulated as a percutaneous anaesthetic gel, undergoes a phase change at or below normal skin temperature. Under aqueous conditions the melting point of amethocaine was lowered by approx. 10°C. The influence of the phase change on drug release characteristics was investigated in respect of both gelled, saturated amethocaine solutions and formulations containing a reservoir of undissolved drug. Drug release from the formulation, and subsequent penetration of lipophilic barriers, was shown to proceed from the aqueous diffusion layer at the formulation/barrier membrane interface. A more rapid replenishment of the diffusion layer can be achieved after the phase change has occurred. Under these conditions the drug is present both in solution and as undissolved oil droplets, the latter having an enhanced dissolution rate compared to solid drug particles in suspension. Given the low solubility of amethocaine base, and therefore the comparatively low concentration gradient established across the diffusion layer, the proven percutaneous anaesthetic efficacy of amethocaine is largely related to its lipophilicity and anaesthetic potency. An overall scheme is proposed for the drug release characteristics of the amethocaine phase-change system.

Introduction

Local anaesthetics do not readily penetrate intact skin (McCafferty and Woolfson, 1988). Therefore, the formulation of an effective percutaneous anaesthetic presents a difficult challenge (Akerman, 1978), which has been successfully met only in recent years. This point is well illustrated by the time interval of about 30 years between the first literature references to percutaneous anaesthesia and the first appearance of a commercial percutaneous anaesthetic product, a eutectic mixture of lignocaine and prilocaine free bases in an emulsified topical delivery system (Woolfson and McCafferty, 1989).

It has now been clearly established that a gel formulation of amethocaine free base (McCafferty and Woolfson, 1988) possesses many of the characteristics of an ideal percutaneous anaesthetic preparation, in particular a relatively short application period and a prolonged duration of anaesthetic activity. (Woolfson et al., 1990). The thermal behavior of this system is unusual in

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that amethocaine undergoes a phase change when applied to the skin, thereby complicating the interpretation of its drug release characteristics. Solid, solution and oil phases may all be present at various times after the system is applied to the skin. The present study, therefore, considers the influence of this system on the drug release characteristics of amethocaine in relation to its known percutaneous anaesthetic properties.

Materials and Methods

Chemicals and formulations

Amethocaine base U.S.P was obtained from Orgamol Ltd (Switzerland). All other reagents used were of analytical quality. The amethocaine phase-change system was formulated as a percutaneous anaesthetic gel containing from 4 to 30% w/w of drug, as previously described (Woolfson et al., 1988).

Differential scanning calorimetry

DSC studies were made using a DSC-4 differential scanning calorimeter (Perkin-Elmer Ltd, Beaconsfield, U.K.) calibrated with indium (m.p. 156.6°C). For the determination of melting points, scanning was at 1.00°C min^{-1} between 15 and 100°C at 0.5 mcal full sensitivity. Amethocaine was dried over silica in a vacuum dessicator for 48 h. Dry samples (5.6 mg) were placed in an aluminium sample pan and a DSC scan obtained. The effect of water on the DSC scan was observed by adding one drop of water to dry amethocaine in a sample pan directly before scanning commenced.

In vitro penetration studies

Amethocaine flux was determined across a polydimethylsiloxane (Silastic®) membrane (thickness 0.005 cm), using a modified Sartorius absorption simulator (Sartorius Instruments U.K. Ltd), as previously described (Woolfson et al., 1988). The receiving fluid was pH 7 phosphate-buffered saline with a volume of 200 ml, ensuring the maintenance of sink conditions over the sampling period. Drug analysis, using a previously prepared linear calibration ($R > 0.99$), was by ultraviolet spectrophotometry (Perkin-Elmer 554 Spectrophotometer; Perkin-Elmer U.K. Ltd, Beaconsfield) at a wavelength of 310 nm.

Solubility determinations

Amethocaine base (0.003 g) was placed into a series of borosilicate glass vials containing 10.0 ml of distilled water. The vials were then incubated for 48 h at temperatures ranging from 22 to 42°C, in order to ensure equilibrium was obtained. The amethocaine concentrations of the saturated solutions, thus prepared, were determined by ultraviolet spectrophotometry. Samples for analysis were withdrawn from the saturated solution using a previously warmed needle, to prevent drug precipitation from the solution. The solution thus obtained (1.0 ml) was then diluted appropriately with pre-warmed distilled water and its absorbance determined at 310 nm.

Results and Discussion

Amethocaine has many of the characteristics of an ideal percutaneous anaesthetic agent. These include high lipophilicity and, consequently, good anaesthetic potency and extended duration of activity. For percutaneous drug absorption to occur the local anaesthetic base must be presented to the skin in a mobile, diffusible form. This will be the case if the drug is in solution. Amethocaine is approx. 96% ionised at pH 7. Although an aqueous solution can, therefore, be prepared from the base at low to neutral pH values, the amount of drug in the uncharged, lipophilic form will be reduced. It is this latter form which is required for significant percutaneous absorption to take place. If the solid base is formulated as a solution in an inert oil, or if this oily solution is emulsified as the internal phase of an o/w emulsion, the thermodynamic activity of the drug will be substantially reduced, since it will be partitioned between the inert oil and skin phases. This leads, in turn, to the use of unacceptably high drug concentrations in order to achieve the desired level of clinical response.

Amethocaine base is a poorly defined crystalline compound, a fact supported by its melting

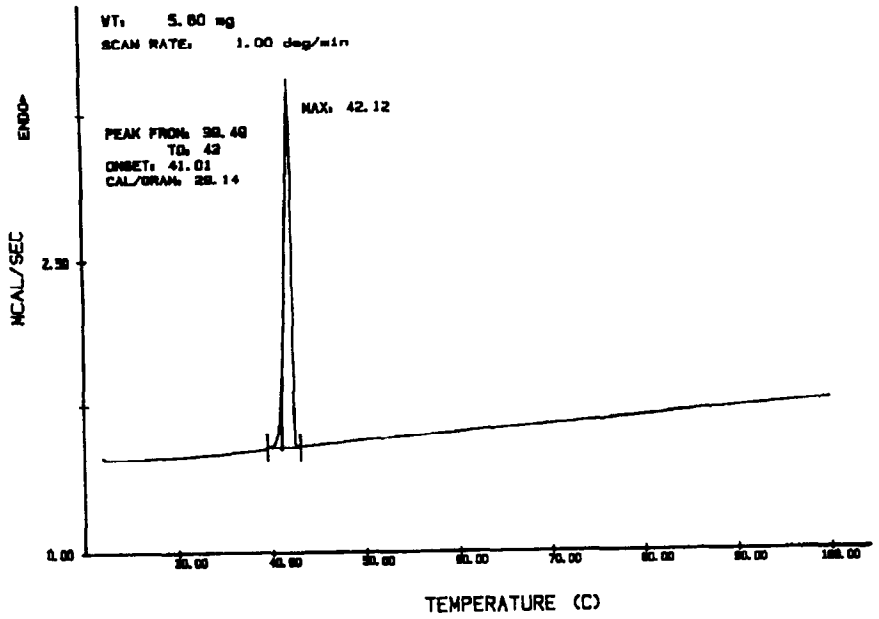

Fig. 1. Differential scanning calorimetry of amethocaine in the dry state.

point range of 40–42°C. A crystal structure of this type, with a low heat of fusion and a low melting point, is bound together by weak forces and readily lends itself to eutectic formation with solids that have similar properties. Such solids need not necessarily be local anaesthetics themselves. The

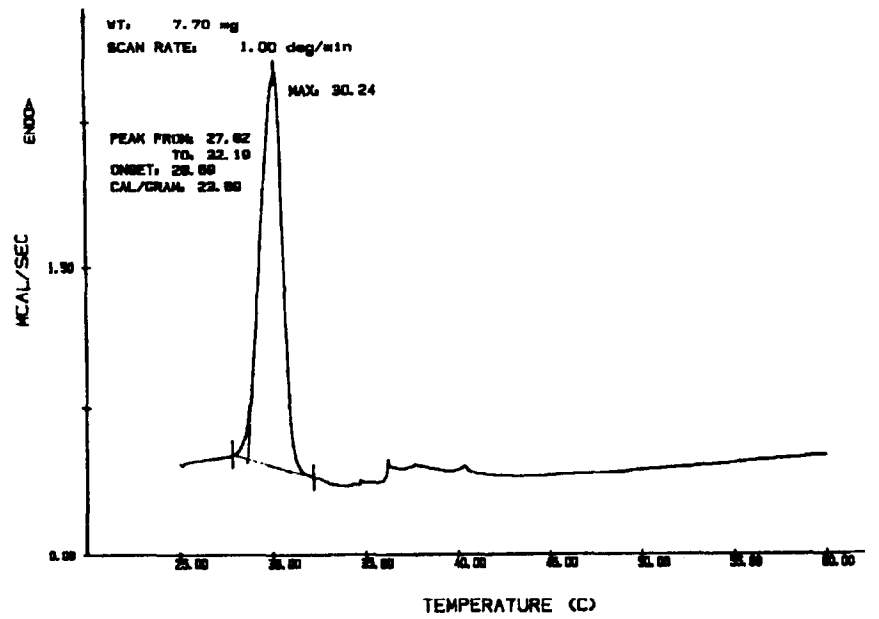

Fig. 2. Differential scanning calorimetry of amethocaine in the wet state.

combination of lignocaine and prilocaine bases in a eutectic mixture represents one formulation approach to the development of effective percutaneous anaesthetic preparations (Ehrenstrom-Reiz and Reiz, 1982). In the case of amethocaine, a novel formulation strategy is possible which does not require the formation of a eutectic mixture. This is based on the chance observation that amethocaine base, in the presence of moisture, undergoes a substantial depression of its melting point. Depression of the melting point in the presence of an impurity, in this case water, is, of course, well recognized. Amethocaine base, however, undergoes an unusually large change in melting point in the moist state. In fact, the melting range is lowered to 29–32°C, a significant occurrence since the moist drug melts at or below skin temperature, representing a melting point depression of approx. 10°C.

Confirmation of the melting characteristics of moist amethocaine base has been obtained by differential scanning calorimetry (DSC) of the drug in the dry and wet states. DSC of a sample of the base dried over silica in a vacuum dessicator gave a peak onset temperature of 41.01°C and an endothermic peak temperature of 42.12°C (Fig. 1). When one drop of water was added to the dry solid in the sample pan the onset temperature fell to 28.69°C and the endothermic peak temperature was reduced to 30.24°C (Fig. 2). Interestingly, these values gradually return to those corresponding to the dry state when DSC scans are obtained as the moist sample gradually dries out. Adulteration of the dry base with a very small amount of water appears to yield a metastable hydrate. A true hydrate is not formed since the original DSC characteristics of the dry base are gradually restored.

Lowering of the melting point of amethocaine base results in a phase change from a crystalline solid to an oily liquid. This observation can readily be made using heated stage microscopy. Thus, at skin temperature the drug undergoes a solid-to-liquid phase change which is the basis of its formulation as a percutaneous anaesthetic agent (McCafferty and Woolfson, 1988). Essentially, this amethocaine phase-change system may be formulated as an aqueous solid suspension. A viscosity builder is added to produce a preparation with semi-solid characteristics that allow the preparation to be located at the required skin site. In contact with the skin there is a rapid phase change, resulting in the formation of an aqueous suspension of fine oil droplets.

Amethocaine base is substantially more lipophilic than either lignocaine or prilocaine. Consequently, its aqueous solubility is much less than either of these amide local anaesthetics. Solubility characteristics of amethocaine are complicated by the phase change occurring around 30°C. Thus, there is a sharp, non-linear increase in aqueous solubility between 25 and 32°C. At 32°C, a saturated aqueous solution of amethocaine base contains, approximately, only 240 μg ml^{-1} of the drug. This means that, in an amethocaine gel containing 4% w/w of total drug (the clinically effective concentration), less than 1% of the total drug is present in the freely solubilised form.

The nature of the amethocaine phase-change system is of importance in determining the clinical efficacy of amethocaine percutaneous local anaesthetic preparations. In a typical 4% w/w gel formulation there will be a large reservoir of undissolved drug present, in addition to the small fraction of dissolved drug in the aqueous phase. The aqueous solubility characteristics of amethocaine base (Table 1) are such that there is little difference in drug solubility occurring as a direct result of the phase change. At temperatures in excess of 30°C, the undissolved drug reservoir will be present in the fluid state as oil droplets suspended in the aqueous gel. Fig. 3 shows the drug penetration properties, through a polydimethyl-

TABLE 1

Aqueous solubility of amethocaine base

Amethocaine concentration (mg ml^{-1})	Temperature (°C)
257.1	42
241.2	32
232.9	30
180.2	26
166.3	22

siloxane membrane, of gelled, saturated, aqueous amethocaine solutions at 25 and 37°C, these temperatures being, respectively, below and above the phase change in the system. Under these conditions there is no drug reservoir to replenish the aqueous diffusion layer at the barrier membrane interface. The resultant drug fluxes are, therefore, much lower than those resulting from a similar study using a 4% w/w amethocaine gel in which the drug reservoir is present. Indeed, the initial time period in Fig. 3 shows a higher, linear flux, which falls off rapidly in the absence of a drug reservoir capable of replenishing the diffusion layer. The drug flux across the barrier membrane is higher, and the depletion effect more rapid, at the higher temperature. These effects may be contrasted with Fig. 4 in which the gelled saturated amethocaine solution was replaced by a 4% w/w amethocaine gel with a large drug reservoir available. Here, the drug penetration profile remains linear throughout at both temperatures due to constant replenishment of the aqueous diffusion layer by the excess available drug in suspension. Consequently, the drug fluxes in this situation are much higher than for gelled, saturated aqueous solutions of amethocaine. Furthermore, the drug flux at 37°C is considerably higher than that at 25°C, an increase greater than would be accounted for by the increased rate of drug diffusion at the higher temperature. The increase in drug flux is due, in part, to the phase change in

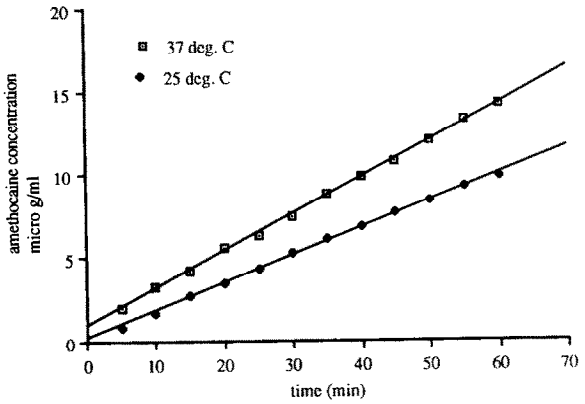

Fig. 4. Penetration of amethocaine from 4% w/w amethocaine aqueous gels through polydimethylsiloxane membranes, at 25 and 37°C.

the system above 30°C, at which point the undissolved drug is in the fluid, more rapidly dissolvable oil state. This may be compared to the situation at 25°C, in which the drug is present as suspended solid particles. The phase change, therefore, produces a more efficient system with respect to rapid replenishment of the aqueous diffusion layer. A similar effect has been reported for the lignocaine-prilocaine eutectic system (Nyqvist-Mayer et al., 1986).

Drug release in the amethocaine phase-change system, and subsequent drug penetration through the barrier membrane, proceed from the aqueous diffusion layer at the membrane interface. This

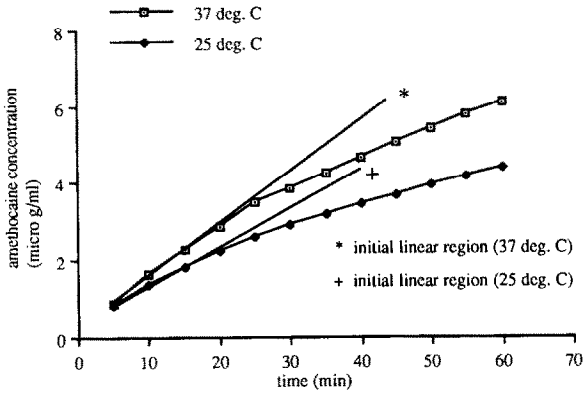

Fig. 3. Penetration of amethocaine from gelled, saturated aqueous solutions of the drug through polydimethylsiloxane membranes, at 25 and 37°C.

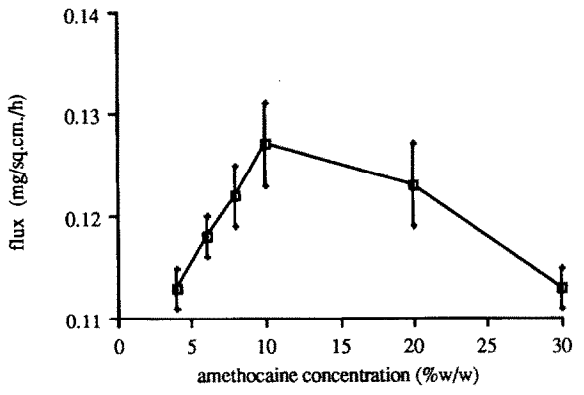

Fig. 5. Variation of drug flux with increasing amethocaine concentration in the phase-change system. Error bars show ±SD.

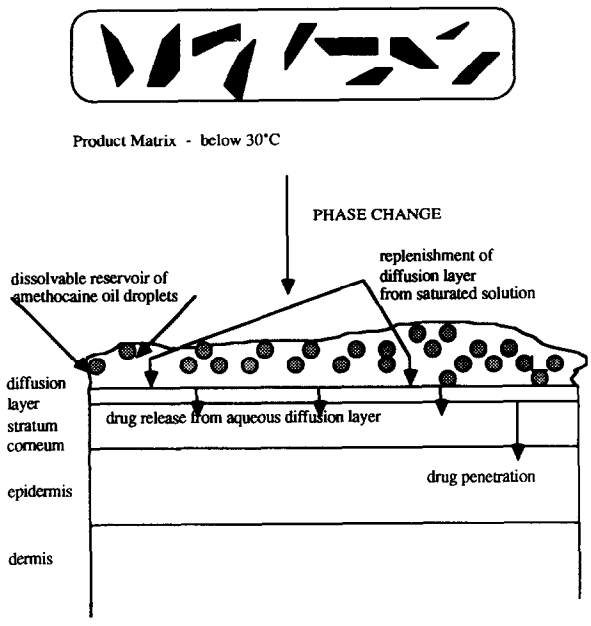

Fig. 6. Schematic representation of the drug release characteristics of the amethocaine phase change system.

observation is further supported by the data in Fig. 5. Amethocaine flux values were determined at increasing drug concentrations in the gel system. Although a small increase in flux is observed with increasing drug concentrations up to 10% w/w amethocaine, at higher drug loadings the flux was seen to decrease again. This may be attributed to the substantial increase in the viscosity of the system due to the high drug content present under these conditions. Consequently, there is a decrease in both the rate of drug dissolution and the diffusion of soluble drug towards the aqueous diffusion layer at the barrier membrane, with an overall decrease in the rate of replenishment of drug dissolved in this layer.

Together, these observations on the characteristics of the amethocaine phase-change system are particularly significant, given the much lower aqueous solubility of amethocaine compared to either lignocaine or prilocaine bases and, consequently, the lower concentration gradient which can be established across the barrier membrane. Despite this, the amethocaine phase-change system requires a shorter application time and has a longer duration of anaesthetic effect compared to the lignocaine-prilocaine eutectic mixture (McCafferty et al., 1989). Essentially, this is due to the greater lipophilicity of amethocaine, which results in substantially increased anaesthetic potency and, probably, better diffusion characteristics through the stratum corneum (Woolfson et al., 1992), though the latter effect will be offset to some extent by the reduced drug concentration in solution in the diffusion layer. Overall, drug delivery from the amethocaine phase-change system can be represented schematically according to Fig. 6.

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