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Controlled release of morphine from a poloxamer 407 gel

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ABSTRACT

Treatment of painful ulcers is discouraging. Topical morphine has been described as a useful therapeutic adjunct in some patients. In the development of a new analgesic product, we studied the in vitro release characteristics of a new topical formulation containing 0.5% (w/w) morphine–HCl in a poloxamer 407 (P407) based gel.

A diffusion cell was used for measurement of in vitro release characteristics. The donor compartment (DC) and the receptor compartment (RC) were separated by a 5000 Da cellulose acetate membrane.

The morphine–HCl release from this developed P407 based gel followed zero-order kinetics with a constant release of 150 $\mu g\,cm^{-2}\,h^{-1}$. Our results support the use of this P407 gel as a sustained release topical formulation in the pharmacological treatment of painful ulcers. Future research welcomes a formulation with release characteristics leading to less frequent application.

1. Introduction

It is generally accepted that opioid analgesics relieve pain by acting on receptors in the central nervous system. Their systemic use is often accompanied by significant side effects such as constipation, sedation and euphoria (Moore and McQuay, 2005). Recent work by Annemans showed that the pharmacoeconomic impact of these side effects warrants the reduction of the adverse-event profile of opioid analgesics (Annemans, 2011). Research suggests that in contrast to the analgesia induced via the central nervous system, similar analgesia can be achieved through peripheral receptors via a neuroimmune pathway (Machelska and Stein, 2002; Stein et al., 2003). Opioid receptors have been detected on peripheral nociceptive nerve endings after peripheral injury and at the onset of inflammation. Under normal conditions they are not detectable in healthy, intact tissue. Immune cells within inflamed subcutaneous tissue can release endogenous opioid peptides that interact with these receptors and produce pain relief. The experienced analgesia is reversible with an opioid antagonist e.g. naloxone (Hua and Cabot, 2010; Stein et al., 2009).

Similar pain relieving effects have been shown in numerous reports for locally applied exogenous opioid agonists to painful skin ulcers (LeBon et al., 2009). Most of these reports demonstrate an analgesic effect following this treatment, remarkably without the side-effects which are normally seen with systemic administration of opioids. In most published cases morphine solution was mixed with Intrasite® gel but other formulations have been used as well (Zeppetella and Ribeiro, 2005; Zeppetella et al., 2005).

Our clinical experience is that Intrasite® based morphine gel does not adhere very well to a moist wound surface. This is especially so the case with sacral pressure sores and more pronounced, excessive wound fluid production. To address the above mentioned unfavourable adhesive effects a more suitable formulation for topical use of morphine was developed by use of a poloxamer 407 (P407) thermo reversible gel. In this article we describe the release profile of morphine from this gel.

1.1. Objective

A slow, constant release of morphine from a gel that adheres well to an ulcer, could theoretically result in a protracted duration of action and a low frequency of application. The purpose of our work was to evaluate the in vitro release profile of morphine–HCl from the P407 gel.

2. Materials and methods

2.1. Morphine–hydrochloride poloxamer 407 formulation

Poloxamer 407 (Lutrol®/Pluronic® F 127 BASF) is a triblock copolymer consisting, by weight, of approximately 70% ethylene oxide and 30% propylene oxide with an average total molecular weight of 12,500 Da.

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Table 1
Formulation of 0.5% morphine–HCl poloxamer 407 gel.

Morphine–hydrochloride 0.5% (w/w) in poloxamer gel	
Morphine hydrochloride·3H_2O	0.5 g
Poloxamer 407 (Lutrol® F 127)	22 g
Glycerol	20 g
Carmellose sodium (HPMC) (1% visc 5000 mPa s)	0.075 g
Sterile water	Added until 100 g

Macgregor et al. were the first to describe the positive effect of such a gel in excoriating skin conditions (Beynon et al., 2003; MacGregor et al., 1994).

P407 gels show adequate bio adhesive properties and also have the ability to absorb serous secretion (Chang et al., 2002; Choi et al., 1998; Dumortier et al., 2006). At low temperatures they are in a liquid state which enables easy application. As a water soluble solution it is removable by any aqueous solution and easily rinsed from ulcers; on the other hand, the high viscosity of the gel at body temperature reduces the rate at which it is removed, making it more durable following application than for instance Intrasite® gel.

The original Lutrol® gel contains propylene glycol which is thought to be responsible for the occasional tendency for sensitization and/or stinging sensation on application. One study examining propylene glycol use in patients with a history of contact dermatitis reported that 1.5% of enrolled patients developed adverse reactions (Angelini and Meneghini, 1981; Catanzaro and Smith, 1991). For this risk of dermatologic adverse reactions, we substituted propylene glycol for glycerol. Replacement by glycerol changed the sol–gel transition temperature making the formulation almost liquid with room temperature. Addition of carmellose sodium (1% viscosity 5000 mPa s) lowered the sol–gel temperature to approximately 6 °C. The following approved pharmaceuticals were used for the formulation of the P407 gel. Poloxamer 407, Morphine hydrochloride (3 H_2O) (BUFA B.V., Uitgeest, The Netherlands), Glycerol (BUFA B.V., Uitgeest, The Netherlands), Cekol 50,000 (carmellose sodium), 5000 mPa s (Metsa Specialty Chemicals B.V. Nijmegen, The Netherlands). See Table 1 for the morphine containing poloxamer gel formulation.

As described in the manufacturers (BASF) technical information leaflet we used the so called "hot process" for preparation of the poloxamer gel. Distilled water was heated to 80 °C. Morphine was dissolved in a portion of this water. Following the P407 was gently added to the water–morphine mixture and mixed until homogenous (A). Carmellose sodium was mixed with glycerol (B). Solution A was added to B and mixed until homogenous. This mixture was left to cool to room temperature. Finally water was added to the desired total weight. Any remaining air bubbles were removed by cooling the gel to approximately 0 °C making the gel liquid so air could escape. The gel was sterilised for 20 min at 120 °C in a closed glass container. Upon use the gel was transferred in suitable amounts to a sterile syringe under aseptic conditions.

The formulation of the 0.5% (w/w) morphine–HCl in a 22% (w/w) P407 gel was developed in the department of clinical pharmacy at Rijnstate Hospital in Arnhem, The Netherlands. Stability tests with an HPLC method measuring morphine and pseudomorphine, the major degradation product of morphine, showed that morphine remained stable over a 12 month period when stored at room temperature protected from light. When exposed to light, rapid degradation of morphine ensued with approximately 10% in three to four months (data on file).

2.2. In vitro release study

Morphine–HCl release rates from the P407 gel were measured with a diffusion cell (Fig. 1). The donor compartment (DC) was separated from the receptor compartment (RC) by a non-limiting cellulose acetate dialysis membrane for morphine diffusion (dialysis membrane with a sieving coefficient of 1 for molecules smaller than 5000 Da). The diffusion area was 1.1 cm^2. Phosphate buffered saline with a pH of 7.4 (PBS) was pumped through the RC with a flow of 1.2 mL/h. The PBS in the RC was constantly stirred and the cell was maintained at 37 °C during the entire experiment. With each experiment 1 g 0.5% (w/w) morphine–HCl in P407 gel was placed on the diffusion barrier in the DC after which the DC was covered with parafilm® to simulate occlusion. The experiment was carried out in duplicate each time with a new, freshly prepared P407 gel. The receptor solution was collected during periods of 15 min for the first 2 h and furthermore every hour for a total of 24 h. "Sink conditions" were present throughout the experiment.

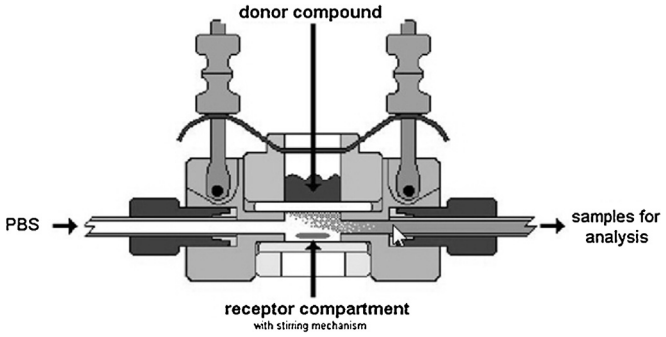

Fig. 1. Schematic of diffusion cell with donor compartment (DC) separated from receptor compartment (RC) by membrane.

2.3. Morphine measurement

Morphine levels were determined using an HPLC system with a variable wavelength UV detector operating at 280 nm and a C18 reverse-phase column (Varian ODS 3 Inertsil 5). The aqueous mobile phase with 1% acetonitrile and 10% of a 5% triethylaminephosphate buffer with pH 2.8 in water. The flow was set to 1 mL/min and the volume of injection was 20 μL. The method had a linear relationship between concentration and peak surface area for a concentration range of 1–500 mg/L with a correlation coefficient of 0.999. The lower limit of detection was 0.3 mg/L.

2.4. Data treatment

Each concentration measurement of morphine–HCl in the receptor medium was determined from a previously calculated standard curve. The cumulative amount of morphine–HCl penetrating through the membrane surface and diffusing into the receptor medium was calculated and plotted as a function of time. To understand the release mechanism of morphine–HCl, we described the release rate using the following equations

$$\frac{M_t}{M} = kt^n \quad (1)$$

$$\log\left(\frac{M_t}{M}\right) = \log k + n\log(t) \quad (2)$$

where M_t/M is the fraction of the released drug at time t, k is a constant of the formulation and n, the release exponent which is indicative of the release mechanism. The n value of 1 corresponds with zero-order release kinetics; $0.5 < n < 1$ indicative for a non-Fickian release model and $n = 0.5$ for Fickian diffusion (Higuchi model) (Higuchi, 1962; Peppas, 1985). From the plot of $\log(M_t/M)$ versus $\log(t)$, kinetic parameter n was calculated.