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An investigation into the influence of drug lipophilicity on the in vivo absorption profiles from subcutaneous microspheres and in situ forming depots

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Abstract

Drug lipophilicity is known to have a major influence on in vivo drug absorption from intramuscularly and subcutaneously administered solutions. Indeed, chemical modification to increase drug lipophilicity is used to enable sustained drug release from solutions. In contrast to the wealth of knowledge on drug release from simple solutions, the influence of drug lipophilicity on its release from controlled release formulations, such as, microparticles and in situ forming depots, have not been systematically studied. Controlled release vehicles are designed to 'control' drug release, hence, in vitro studies show negligible influence of drug lipophilicity on release. The situation could however be different in vivo, due to interactions between the vehicle and biological tissue. We therefore investigated the influence of drug lipophilicity on its in vivo release in rats from two controlled release formulations, PLGA microparticles and in situ forming depots. Both systems exhibited a burst drug release. Subsequent to the burst release, we found that lipophilicity did not influence the rate or extent of drug absorption from the two formulations over a 10-day study period, which would imply that drug partitioning out of the depots was not the main mechanism of drug release from both formulations. This study must however be repeated with a greater number of animals to increase its power.

Keywords: Microspheres; In situ forming implants; Lipophilicity; Drug absorption; In vivo; Subcutaneous

1. Introduction

Sustained release of drugs from depot formulations has a number of advantages, such as, reduction in dosing frequency, increased patient compliance, optimisation of the drug's pharmacokinetic profile, hence increased efficacy with reduced toxicity and cost. Sustained release drug formulations range from simple oil solutions and aqueous suspensions to more complex formulations such as polymeric microspheres and in situ forming implants. The rate of drug release from the more complex vehicles depends on a large number of parameters, and in this paper, the influence of drug lipophilicity from polymeric microspheres and in situ forming implants is reported.

Polymeric microspheres have been extensively investigated as controlled release vehicles for the past decades and a number of preparations have been commercially available for a number of years. The formulations are available as lyophilised microspheres which are re-constituted with a diluent prior to subcutaneous or intramuscular administration. Drug is released from the depot over a period of weeks to months, by drug diffusion out of the polymeric matrix and/or by erosion of the matrix. Thus parameters which influence these 2 processes control the drug release profiles [1]; these include polymer chemistry and erosion mechanism, polymer molecular weight, copolymer composition, crystallinity, polymer–drug interactions, excipients, microsphere size and porosity, drug distribution [1,2].

More recently, an in situ forming drug depot – Eligard™ – was approved by the FDA. This consists of a solid component (the drug leuprolide acetate and the polymer PLGA) which is

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dissolved in an organic solvent (*N*-methyl-2-pyrrolidone, NMP) immediately prior to injection. Upon administration, the water-miscible NMP dissipates into the surrounding tissue, which leads to polymer precipitation into a depot (entrapping the drug) at the site of injection. The obvious advantage of such in situ forming implants over polymeric microspheres is their relative ease of preparation — a water-insoluble polymer (e.g. PLGA) and the drug are dissolved in a water-miscible solvent. The in situ forming implant is also easier to inject — we found injection of microsphere suspensions to be hampered by needle clogging by particulates. The obvious disadvantages are the fact that an organic solvent is administered (which can lead to toxicity) and the variable shape and size of the implant formed in vivo, which leads to variable rates of drug release [3]. Many parameters are expected to influence the drug release profile, and some of these have been investigated in vitro and/or in vivo. For example, the in vitro burst release was related to polymer molecular weight [4], solvent nature [4–6], presence of additives [7] and polymer concentration [4,6,8]. The duration of drug release in vivo was related to polymer molecular weight [9], polymer nature [10] and drug loading (3 vs 10% studied) [8]. Some of the parameters were found to have no significant effect on duration of implant efficacy when narrower ranges were investigated (3–6% leuprolide acetate drug loading and 40–50% polymer concentration studied [9]). To our knowledge, the influence of drug lipophilicity has not been studied and this is the first report on the effect of drug lipophilicity on release from in situ forming implants.

In addition, as mentioned above, the influence of drug lipophilicity on the in vivo release from microspheres is addressed in this paper. Despite the extensive literature on microspheres as drug carriers, the influence of drug lipophilicity on in vivo release profile has received scant attention. Thus, in this paper, the 2 depot systems (microspheres and in situ forming implants) are compared with respect to release rates. Despite the fact that polymeric microspheres and in situ forming implants are two of the most common complex sustained release parenterals, there is currently very little literature where the two systems have been compared. Comparison of the 2 depot systems could only be performed to a certain extent, as the 2 depot systems did not have the same drug:polymer ratio (the animals received 15 mg drug and 75 mg PLGA (in situ forming implant) or 150 mg PLGA (microspheres)). The smaller amount of PLGA used in the in situ forming implant formulation was due to the fact that volume of NMP required to administer the higher amount of PLGA (0.3 mL) was found to be irritating to experimental animals.

Rats were used as the experimental animals, and octanoate salts of the beta-blockers, metoprolol and alprenolol, which have similar molecular weights and pK_as, but different lipophilicities, were used as model drugs. Log *P* of metoprolol and alprenolol octanoates were experimentally determined to be 0.6 and 1.25 respectively [11]. The octanoate salts were used as these had a significantly reduced in vitro burst release from PLGA microspheres compared to the tartrate and hydrochloride salts [11], which enabled investigations into sustained drug release. The octanoate salts (hydrophobic ion pairs) were prepared and loaded into microspheres and in situ forming implants. Experimental animals were subcutaneously injected with drug-loaded microspheres or in situ forming implants, then bled at time intervals to determine the plasma drug levels. Subsequently, Wagner–Nelson deconvolution calculations were performed to obtain and compare the absorption profiles from the 2 depot systems. Control animals received subcutaneous injections of aqueous solutions of the octanoate salts to confirm the effect of encapsulation within microspheres and in situ forming implants. In separate experiments, the drugs were administered intravenously to rats to establish the pharmacokinetic parameters for use in deconvolution calculations.

2. Materials and methods

Alprenolol hydrochloride, metoprolol tartrate, propranolol hydrochloride, sodium octanoate, Tween 80, *N*-methyl-2-pyrrolidone (NMP) and formaldehyde 37–40% (molecular biology grade) were obtained from Sigma-Aldrich (Poole, UK). The polymer PLGA 5050 DL 2.5A was purchased from Alkermes Inc. (Medisorb® Ohio, USA). Disodium hydrogen orthophosphate, potassium dihydrogen orthophosphate and sodium chloride were all analytical grade and purchased from VWR International Ltd. (Poole, Dorset, UK). Acetonitrile (HPLC grade), methanol (HPLC grade) and formic acid were purchased from Fisher Scientific (Loughborough, UK). Hypnorm™ was supplied by Janssen Pharmaceutical (Oxford, UK). All chemicals and reagents were used as purchased.

Male Wistar rats weighing 162–265 g were purchased from Harlan (UK) and allowed to acclimatise for a minimum of 7 days prior to experimentation. Food and water were provided ad libitum before and during experimentation. All procedures had been approved by the School's Ethical Review Committee and were conducted in accordance with UK legal and Welfare standards.

2.1. Intravenous (IV) administration of drug solutions

Rats (lightly anaesthetised with intraperitoneally administered 0.2 mL of Hypnorm™) were intravenously dosed with solutions of the beta-blockers (0.5 mL, containing 1.15 or 1.28 mg alprenolol HCl and metoprolol tartrate respectively in phosphate buffered saline, pH 7.4, equivalent to 1 mg of free base) via the tail vein. The rats were then bled from the tail veins at time intervals over a 3-h period and blood samples (each approximately 150–200 μL) were collected into anticoagulant (EDTA)-coated centrifuge tubes (Microvette CB300, Sarstedt, UK). To separate the plasma, the blood samples were centrifuged for 10 min at 3000 rpm (Eppendorf Centrifuge 5415D, Eppendorf AG, Hamburg, Germany), after which the plasma (supernatant) was collected and frozen (ca −20 °C) until assayed. The last blood samples were collected by cardiac puncture, after the animals had been euthanised.

2.2. Preparation of hydrophobic ion pairs of metoprolol and alprenolol

The hydrophobic ion pairs, metoprolol and alprenolol octanoates, were prepared by the dropwise addition of an