International Journal of Pharmaceutics 472 (2014) 276–281

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical nanotechnology

A continuous flow method for estimation of drug release rates from emulsion formulations

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ARTICLE INFO

Article history:
Received 7 May 2014
Received in revised form 12 June 2014
Accepted 13 June 2014
Available online 16 June 2014

PubChem classifications:
Tetracaine (PubChem CID: 5411)
Triglyceride oil (PubChem CID: 5460048)
Lecithin (PubChem CID: 57369748)

Keywords:
Drug delivery
Emulsion
Drug release
Lipid
Colloid
Triglyceride

ABSTRACT

We present a continuous-flow method that allows the release of drugs from submicron colloidal carriers to be estimated on a millisecond timescale. The technique is applied to the study of release of a model drug (tetracaine) from lipid emulsions, and shows that the solute drug is released in this timescale, and thus is primarily controlled by the rapid diffusion of the drug within the oil droplet. This confirms our previous claims that existing methods, such as dialysis or centrifugation, are too slow to provide useful release data for drug-containing emulsions, and demonstrates that it is unlikely that a simple emulsion could be used as a circulating sustained-release formulation, as has been suggested by some workers.

1. Introduction

Emulsion formulations are a commonly-studied option for the formulation of lipophilic drugs (Davis et al., 1987). The active drug is dissolved in a suitable biocompatible oil, which is then homogenized using a biocompatible surfactant to form an emulsion in which the active drug is partitioned within the oil droplets. A particularly interesting application of this technology is the production of drug-loaded emulsions for intravenous administration.

The technical requirements for an intravenous emulsion are highly constrained. The most widely studied formulation uses triglyceride oils and purified phospholipid surfactants from egg or soya bean. This system has proven to be biocompatible in relatively large doses and is widely used for intravenous feeding (Edgren and Wretlind, 1963; Wretlind, 1965) as well as for drug delivery (Benita, 1998). Rigorous control of droplet size is essential, as large droplets can cause pulmonary emboli. The limit for this risk is generally considered to be approximately 5 μm (United States Pharmacopeia, 2012). The emulsions are normally processed by high pressure homogenization in order to achieve a mean droplet size in the region of 200 nm, resulting in a highly stable product and good biocompatibility. Further detail concerning the formulation, stability and use of these materials can be found in previous publications (Singh and Raven, 1986; Washington, 1996). As an example, one of the best-known applications of this technology is the intravenous anaesthetic Diprivan® (AstraZeneca) which consists of the lipophilic active propofol formulated in the soya oil–lecithin system described above. A number of other drugs have been formulated using this technology (Benita, 1998).

In order for a drug to be active in this type of formulation, it must be released from the emulsion droplets after injection, so that it can reach the site of action. This is probably the least understood aspect of emulsion formulation behaviour, both in vivo and in vitro. We have always considered that drug release is a diffusion-controlled process, with the droplet oil–water interface posing an insignificant barrier. Consequently we would expect that, after dilution into the bloodstream, the drug re-establishes a partition-controlled equilibrium in a time that is comparable to the diffusion time of the drug across the droplet diameter. This time is of the order of milliseconds. However an experimental confirmation of this rate is difficult. Probably for this reason, dialysis methods are still frequently used to

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http://dx.doi.org/10.1016/j.ijpharm.2014.06.024
0378-5173/

measure drug release, obtaining release durations of the order of hours or longer (see, e.g. Wang et al., 2006) and erroneously concluding that sustained release formulations are technically feasible. We have previously discussed (Washington, 1989) the invalidity of these measurements for diluted (i.e. intravenous) systems. The reasons for this problem still seem to escape some workers so a few words of clarification may be useful.

An emulsion placed in a dialysis bag is actually a three-compartment system – the oil droplets, the aqueous phase inside the bag, and the release medium outside the bag. Diffusion across the dialysis membrane is driven by the concentration gradient across it, and this is only dependent on the drug concentration in the inner aqueous compartment – i.e. the emulsion aqueous phase. However this is not the drug concentration in the emulsion. It is set by the partition coefficient of the drug between the oil phase and the inner aqueous phase, and consequently may be very low indeed. Thus, the rate at which the drug appears in the outer release medium is limited largely by the membrane transfer rate and the drug partition coefficient, and is not dependent on the microscopic release rate of the drug from the oil droplets. Alternatively, if the emulsion is directly diluted, then the drug content in the emulsion aqueous phase is reduced – we now have a 2-compartment system – and the release will be controlled by diffusion from the oil droplets. In this context, it is relevant to note that intravenous propofol emulsions induce anaesthesia within seconds of administration, which is consistent with free diffusional release of the active molecule. We justifiably assume that drug-loaded oil droplets do not readily cross the blood–brain barrier.

We previously described an electrochemical pH-based technique for drug release (Washington and Evans, 1995) that had a time resolution of the order of seconds, although our suspicion was that this method was still insufficiently fast to properly characterize drug release. In the present work we describe a continuous-flow technique for estimating the release rate of a moderately hydrophobic model drug (tetracaine base, CLog $P_{oct-water}$ = 3.65) from a parenteral emulsion formulation. We have improved the time resolution of the method to the millisecond timescale, and our results confirm that drug release is rapid and occurs on a timescale comparable to that of unhindered diffusion from the emulsion droplet.

2. Materials and methods

Medium chain triglyceride (MCT) oil and lecithin (Lipoid S75) were obtained from Lipoid AG (Steinhausen, Switzerland). Tetracaine and all remaining reagents were from Sigma–Aldrich. The emulsions all contained 10% w/v MCT oil, 0.5% tetracaine base (i.e. 5% tetracaine predissolved in the oil phase) and 1.2% lecithin with the remainder being water. No tonicity-adjusting agents (e.g. glycerol) were included.

Emulsions (of identical composition) were prepared using three different process conditions to achieve different droplet size distributions. In all cases the tetracaine base was dissolved in the oil, the lecithin was dispersed in the water, and the oil phase mixed with the aqueous phase prior to homogenization.

"Coarse" emulsion was manufactured using an UltraTurrax T25 homogenizer (Janke and Kunkel, Germany) operating at its top speed of ~22,000 rpm, for 10 min at 60–70 °C. The formulation was placed on a hotplate during homogenization to maintain the temperature.

"Medium" emulsion was prepared using a Model 110 Microfluidiser (Microfluidics Inc., Newton, MA, USA) at 2000–2500 psi liquid pressure, which was the lowest at which the formulation could reliably be processed. The sample was homogenized for six cycles at ambient temperature, which resulted in a liquid stream at 35–40 °C.

"Fine" emulsion was also prepared by microfluidisation in the same equipment, but for six cycles at 8500–9000 psi. Prior to homogenization, the premixed sample was heated to 60 °C, and during homogenization the process temperature was 65–70 °C.

The drug release apparatus is illustrated in Fig. 1. The emulsion was mixed with a suitable release buffer at the entry point to a continuous flow thin cylindrical glass tube (a 3 mm × 200 mm NMR tube, 2.7 mm I.D., Wilmad, Vineland, NJ, USA from which the closed base had been removed by grinding). The buffer was injected with a constant flow rate of 67.5 ml min^{-1} in all the experiments reported here. The emulsion was injected into the tube from a 21 g × 120 mm syringe needle (B. Braun) and immediately flowed, together with the buffer, through a 0.5 mm dia. × 5 mm long cylindrical PTFE venturi orifice. The objective of this structure was to achieve rapid turbulent mixing of emulsion and release buffer within the orifice. A fluid dynamics simulation (Ansys Fluent v 14.0) was run to confirm efficient mixing. The calculated average cross-sectional area velocity of the flow in the constriction was 5.7 ms^{-1}, corresponding to a Reynolds number of 2865. The transitional value for Re in pipe plows is 2100, and the calculated concentration profiles confirmed complete mixing of the fluids prior to exit from the constriction. The average transit (mixing) time through the constriction was 0.9 ms. Both the buffer flow and the emulsion flow were driven by syringe pumps (Harvard Instruments). The injection rate of the emulsion was varied from 0.2 ml min^{-1} to 0.8 ml min^{-1} to generate a series of release curves at different dilution ratios. Under the flow conditions used, these injection rates corresponded to emulsion dilution factors of approximately 60–250.

The mixed emulsion – buffer mixture then flowed down the tube under laminar flow conditions. The buffer mixture contained a suitable indicator so that the pH of the mixture could be determined at any particular point from the colour of the liquid. In the present experiment the buffer was 0.2 mM sodium dihydrogen phosphate, adjusted to pH 5.7 with a small quantity of 0.1 M hydrochloric acid. The indicator was bromothymol blue (0.02% w/v). The flow tube was enclosed in a water-filled gap between glass plates so that it could be photographed clearly. A set of accurately adjusted buffered indicator samples (pH 5–8) were positioned so that they could be photographed in the same frame, and the whole illuminated by diffuse daylight with a white background. Photographs were taken with a 105 mm macro lens (Sigma) on a tripod-mounted Pentax K5 camera with an exposure time of 0.5 s at F9 and a sensitivity of ISO200. White balance was set to diffuse daylight (not auto) and images were stored as full-resolution JPEG files. A typical image is shown in Fig. 2; the horizontal calibration scale is in centimetres.

Images were analysed using the open-source package Gimp (www.gimp.org). For each image, the colour of the indicator was quantified using the HSL (hue–saturation–level) model, the colour being extracted as the hue angle. This was measured in the centre of each pH calibration tube and at 2 cm intervals down the centre of the flow tube. The colour-sampling area was set to slightly less than the width of the tube to achieve a degree of colour noise averaging. As the basic drug was released from the emulsion, the

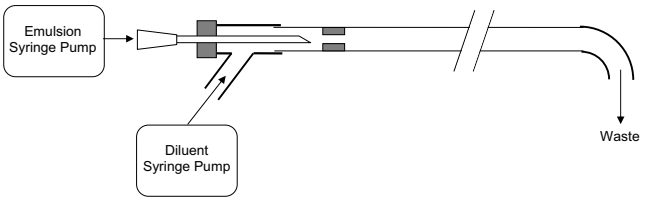

Fig. 1. Schematic diagram of drug release equipment.