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In vitro dissolution testing of parenteral aqueous solutions and oily suspensions of paracetamol and prednisolone

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ABSTRACT

The number of intramuscularly applied dosage forms has been continuously increasing during the last decades. However, up to date no in vitro dissolution test method for parenteral dosage forms has been described in the Ph. Eur. or USP. It was the aim of this study to investigate dissolution test setups based on the compendial flow-through cell and the reciprocating holder for this purpose. Both apparatuses were equipped with dialysis membranes to accommodate the drug formulation. The suitability of the dissolution method was evaluated by comparing release profiles with blood level curves that were obtained previously in an in vivo study in rats by our group. Aqueous solutions and oily suspensions of paracetamol and prednisolone were tested in vitro that were also applied in the in vivo study. In the case of the aqueous solutions in which no formal dissolution occurs, transport from the applied depot across a dialysis membrane was investigated. While the drug transport across the dialysis membrane of both drugs in aqueous solution was similar in all applied test methods, differences in the release behavior of paracetamol and prednisolone as an oily suspension were observed. This was mainly due to sedimentation of the particles within the oily depot.

1. Introduction

The number of newly developed formulations for intramuscular application is increasing continuously. Various compendial and non-compendial dissolution test methods have been investigated for in vitro dissolution testing of these dosage forms, including rotating dialysis cell (Dibbern and Wirbitzki, 1983; Larsen et al., 2000a), dialysis sac (Chidambaram and Burgess, 1999; D'Souza and DeLuca, 2005; Nippe et al., 2013), flow-through cell (Zolnik and Burgess, 2008) as well as combination of flow-through cell and dialysis sac (Bhardwaj and Burgess, 2010) or sample and separate method (Hyun et al., 2007). However, no in vitro dissolution test method is described in the Ph. Eur. or USP for parenterally administered formulations. The urgent need for standardized in vitro dissolution tests for parenteral dosage forms is widely discussed, making suggestions to use test setups based on compendial methods and indicating an attempt to compile a monograph in the USP (Burgess et al., 2004; Martinez et al., 2008; Rathbone, 2009; Seidlitz and Weitschies, 2012; Shah et al., 2015). Furthermore, there is a lack of biorelevant dissolution test methods that are needed in the phase of development of new formulations in order to predict in vivo behavior. One reason for this may be the lack of data describing the parameters affecting the absorption behavior of intramuscularly applied dosage forms in vivo. Therefore an in vivo study in rats was performed previously, with the aim of defining the impact of certain physiological parameters (Probst et al., 2016). The focus was set on the investigation of volumes and surface areas of the injected depots (oily suspensions or aqueous solutions) within the muscle tissue at certain time points by means of magnetic resonance imaging (MRI) and subsequent blood sampling. It was the aim of the study presented here to transfer the obtained data to in vitro dissolution test setups by simulating the volumes and surface areas of these aqueous and oily depots. In the case of the aqueous solutions in which no formal dissolution occurs, drug transport from the depot applied inside a dialysis membrane into the surrounding medium was investigated. Therefore the formulations that were used in the in vivo study also had to be applied in the in vitro dissolution investigations. Consequently, aqueous solutions and oily suspensions of paracetamol and prednisolone were tested.

Abbreviations: c_{max}, maximal blood concentration; dpm, dips per minute; HPLC, High Performance Liquid Chromatography; MCT, medium-chain triglycerides; MRI, Magnetic Resonance Imaging; MV, mean value; MWCO, Molecular Weight Cut Off; PBS, phosphate buffer saline; Ph. Eur., European Pharmacopoeia; RC, regenerated cellulose; SD, standard deviation; t_{max}, time point of maximal blood concentration; USP, United States Pharmacopeia; UV/VIS, Ultraviolet/Visual

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2. Materials and methods

2.1. Materials

Raw materials were obtained from the following sources and were used as received unless otherwise described: paracetamol, prednsiolone and sodium hydroxide (all Caesar & Loretz GmbH, Germany), prednisolone-21-hemisuccinate sodium salt (Sigma-Aldrich Chemie, Germany) potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate (all Merck KGaA, Germany), medium-chain triglycerides (Miglyol® 812 N), polyethylengylcol 400 (both Fagron GmbH & Co.KG, Germany).

2.2. Formulations

All formulations were freshly prepared in order to avoid problems of instability and aggregation as previously described (Probst et al., 2016).

Aqueous solutions: The aqueous solvent for the paracetamol solutions consisted of 90% purified water and 10% polyethylenglycol 400 as a cosolvent. The pH was adjusted to 7.4 ± 0.2 by the addition of potassium hydrogen phosphate and sodium hydroxide. The osmolality of the solution was 459 ± 16 mosmol/kg.

Due to solubility problems the hemisuccinate sodium salt had to be used in the aqueous formulations of prednisolone. It was not necessary to add a cosolvent to the purified water. The pH was adjusted to 7.4 ± 0.2 by the addition of disodium hydrogen phosphate dihydrate and potassium hydrogen phosphate. The osmolality of the solution was adjusted to 270 ± 5 mosmol/kg by adding sodium chloride.

Paracetamol or prednisolone hemisuccinate sodium were added to the particular solvents shortly before the experiment started. Drug concentrations were 15 mg/mL for paracetamol and 25 mg/mL for prednisolone. 100 µL of the formulations were added to 400 µL PBS pH 7.4 and used for the dissolution experiment.

Oily suspensions: The dispersion agent for the oily suspensions were medium-chain triglycerides (MCT, Miglyol® 812 N). Paracetamol was micronized for 2 min in a ball mill (Narva Vibrator GM 9458, Germany) before it was suspended in MCT and placed in an ultrasonic bath (USR18H Merck eurolab N. V., Belgium) for 30 min. Prednisolone, which was already purchased micronized, was dispersed in MCT in the ultrasonic bath for 1 min.

The amount of drug in the oily suspension was the same compared to the aqueous solutions (1.5 mg paracetamol und 2.5 mg prednisolone) but the volume was set to 250 µL by dilution of the formulation with 150 µL MCT. Particle sizes (means ± standard deviation) for the used drug suspensions were 13.05 ± 1.89 µm for paracetamol and 4.34 ± 0.09 µm for prednisolone. Both drugs were practically insoluble in the used medium-chain triglycerides.

2.3. In vitro dissolution test setups

Membrane Adapter: An in vitro dissolution test setup was employed based on a model of Bhardwaj and Burgess, which combines the dialysis sac method and the flow-through cell (Bhardwaj and Burgess, 2010). The dimensions of the model were adjusted to the experimental requirements in order to simulate volumes and surface areas of aqueous and oily depots being determined after intramuscular injection in rats (Probst et al., 2016) (Fig. 1). The volume of the aqueous depots in the in vivo study was about 500 µL and of the oily suspensions 250 µL. The surface areas of the depots in vivo were about 700 and 480 mm^2 in mean. In vitro the shape and dimensions of the depots were predefined by a dialysis tube consisting of regenerated cellulose with a MWCO (molecular weight cut off) of 50 kDa. The dialysis membrane was washed in unionized water and saturated in PBS pH 7.4 (phosphate buffer saline) for at least 12 h. Then the membrane was mounted on an adapter consisting of two teflon pieces that were connected via two metal strives. The endings of the dialysis tube were sealed by silicon oil and O-rings that were applied on the upper and lower part of the adapter. In the upper teflon piece a screw thread was incorporated allowing the injection of a formulation into the mounted dialysis tube. Subsequently the injection channel was sealed by a teflon screw. By adjusting the length of the metal strives and the dialysis tube the surface area and volume of the simulated depots were variable. The prepared adapter (Fig. 1A) was then placed in a holder (Fig. 1B) which was in turn placed in a flow-through cell (Fig. 1C). The holder should ensure a stable position of the adapter within the flow-through cell. The dimensions of the cell differed from the ones being described in Ph. Eur. and USP (see Fig. 1C). The conical part was filled with 2 mm glass beads. The whole test setup was placed in a water bath at 37 ± 0.5 °C. Consequently, the flow-through cell was operated in closed system. This means that release medium (PBS pH 7.4, 500 mL, 37 °C) was pumped out of the vessel through the flow-through cell from bottom to top and back into the vessel where the medium was stirred at 250 rpm. During the whole experiment sink-conditions, defined as a maximum concentration of 10% of the saturation concentration, were maintained in the circulating media. At predetermined time points aliquots of the release medium were taken from the vessel and drug concentration was determined by HPLC-measurements. Besides volumes and surface areas of the depots, flow rates and positions (vertical or horizontal) of the adapter were varied. The influence of different flow rates and the influence of the position of the adapter on the release behavior of the drugs from the depot into the release medium were investigated. Furthermore, the membrane adapter was tested with respect to the possibility of discriminating between the aqueous and oily formulations of paracetamol and prednisolone.

Reciprocating holder (USP apparatus 7): In vitro dissolution tests were also performed in the reciprocating holder (Agilent 400-DS, Agilent Technologies, USA). Therefore, an adapter was employed that enabled clamping the dialysis tube (Externbrink and Klein, 2014) (Fig. 2). The lower ending of the tube was fixed between a clamp consisting of two screwed plates. Afterwards the formulations were injected into the dialysis tube, air bubbles were removed from the membrane and the upper ending of the tube was sealed in the same manner as the lower ending. Both clamps were adjustable along a wire via a screw thread. The dialysis tubes were identical to the ones being used in the membrane adapter. The membrane clamped in the holder was placed in the release cell, which was filled with 10 mL PBS pH 7.4. Consequently, the holder was moved vertically together with the membrane within the release cell at a frequency of 10 or 40 dpm. At predetermined time points aliquots were taken by an autosampler and drug concentrations were determined via HPLC-measurements. After each sampling point the residual medium in the release cell was removed and replaced by fresh medium. The release medium was tempered to 37 ± 0.5 °C throughout the whole experiment. Sampling time points were chosen with respect to the maintenance of sink-conditions.

2.4. HPLC-method

The samples of paracetamol and prednisolone in PBS pH 7.4 were mixed with 15% acetonitrile. Via an autosampler (Shimadzu SIL-20A, Shimadzu, Japan) aliquots of 10 µL of the paracetamol probes and 20 µL of the prednisolone probes were injected into the HPLC-system (Shimadzu CBM201, Shimadzu, Japan). The mobile phase consisted of 85% sodium acetate buffer pH 4.0 and 15% acetonitrile in case of paracetamol and a mixture of the same components in a ration of 60%/40% in case of prednisolone samples. The composition of the acetate buffer was 0.164% sodium acetate, 0.525% acetic acid (100%) and 99.311% millipore-water. The flow rate was set at 1 mL/min. Reversed phase chromatography was performed using a RP-18 column (LiChrospher® 100 RP-18 (5 µm), LiChroCART® 125-4, Merck, Germany for paracetamol and ODS Hypersil™ 250 × 4 mm (5 µm), Thermo Electron Corporation, Great Britain for prednisolone) and isocratic elution was carried out over a time span of 5 min (paracetamol) or

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