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Research paper

Pharmacokinetics of an immediate release, a controlled release and a two pulse dosage form in dogs

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Abstract

Clinical studies have shown that circadian patterns influence the pharmacokinetics of certain drugs used in the treatment of different diseases. For such drugs, the bioavailability is influenced by the time of administration. The objective of this study was to investigate differences in the pharmacokinetic patterns between a pulsatile drug delivery system using a pulsatile capsule, an immediate release tablet and a controlled release tablet. Metoprolol was chosen as a model drug because of its high solubility and high permeability pattern throughout the GI tract. The dosage forms were administered to four dogs and the plasma levels were measured using LC-MS/MS. Pharmacokinetic parameters were determined for each dosage form. Fluctuations in the plasma time curves over the observation period indicated that physiological factors like motility have an influence on the drug absorption. The comparison of the plasma time curves of the dosage forms showed that each dosage form caused significant differences in the drug plasma levels. The pulsatile drug delivery capsule caused two defined C_{max} values for each dose between 1–1.75 and 2.5–3.5 h. Implications for the use of a pulsatile drug delivery device for chronopharmacotherapy are discussed. Pulsatile drug delivery offers a promising way for chronopharmacotherapy if the time of administration and pulse time are adjusted to the circadian pattern.

Keywords: Metoprolol; LC-MS/MS; Pulsatile drug delivery; Chronopharmacotherapy; Pharmacokinetics; Beta blocker; Dog study; In vivo study; Immediate release; Controlled release; Sustained release; Pulsatile release

1. Introduction

The oral route is the most common route of drug administration. Modern drug delivery strategies try to improve oral drug delivery. The most common way to prolong drug delivery is to use sustained or extended release dosage forms [1]. The aim of such strategies is to increase the availability of the drug at the site of drug action over a prolonged time period [2]. A controlled drug delivery may result in a lower but constant pharmacological availability which might reduce toxic side effects. In many cases, this overcomes compliance problems with patients by reducing the dosing frequency to one dose per day. Other controlled drug delivery strategies utilize the pH change within the GI passage to control the drug release [3]. This can be used for drugs which are easily decomposed in the acidic environment of the stomach e.g. peptides, or to protect the stomach from drug side effects e.g. aspirin. Such systems are also promising for a local therapy in the lower parts of the intestine e.g. colon targeting to treat diseases like ulcerative colitis [4].

However, constant drug release is not desirable for all drugs; some drugs require repeated drug administration during a day. This might be due to factors such as high metabolism, short half life or a limited absorption window as shown for levodopa [5]. If such drugs are delivered using a sustained release formulation, their bioavailability might decrease due to the mentioned factors [6,7]. Another reason

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for repeated dosing might be the development of receptor tolerances. A prolonged stimulus of nitrates, for example, decreases the drug efficacy [8]. For such drugs constant drug plasma concentrations can cause a failure of the therapeutic intervention.

Different biopharmaceutical and pharmacodynamic reasons point out that there are certain circumstances in which a repeated dosing is advantageous compared to sustained release dosage forms. However, a patient's compliance might be lower if a drug has to be taken more than once a day. If drug absorption throughout the gastrointestinal tract is not limited, then pulstile drug delivery might be a suitable alternative to repeated dosing. This might be especially useful if peak plasma levels are desirable in the night time or the early morning hours.

The pulsatile capsule used in this study was designed to release two drug doses at different time points [9]. The first dose was immediately released after administration, while the second dose was released after a predetermined time due to the composition of the osmotic system (Fig. 1). The osmotic system presses a plug out of the non-soluble capsule body and initiates the second drug release. The second dose can be released as an immediate or a controlled release dosage.

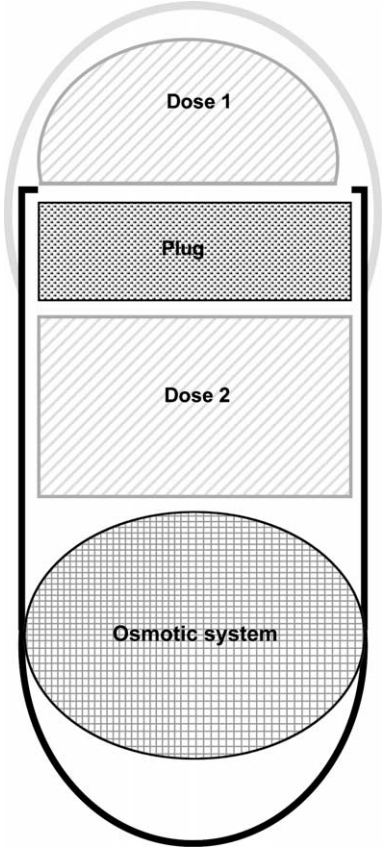

Fig. 1. The pulsatile capsule is designed for two drug doses. The first is placed into the capsule cap while the second dose is released from an insoluble capsule body. The pulse time is determined by an osmotic system which presses an insoluble plug out of the capsule body.

The objective of this study was to investigate differences in the pharmacokinetic pattern between a pulsatile drug delivery system delivering two times (50 mg) metoprolol, an immediate release tablet (50 mg) and a controlled release tablet (50 mg). Metoprolol was chosen as the model drug because of its high solubility and high permeability pattern throughout the GI tract. The dosage forms were administered to dogs and the plasma levels were measured. Pharmacokinetic parameters were calculated using non-compartmental. Implications for the use of a pulsatile drug delivery device for chronopharmacotherapy are discussed.

2. Material and methods

2.1. Preparation of the pulsatile capsule

Metoprolol tartrate (MT) was purchased from Sigma (St Louis), the pulsatile capsule (PC) was supplied by Port Systems (Ann Arbor), and contained two doses of metoprolol tartrate each 50 mg the pulse time was adjusted to 2 h. Metoprolol tartrate Tablets USP (Geneva Pharmaceuticals INC, Broomfield CO) and a controlled release dosage form (Beloc Duriles, Astra Promed, Germany) were used for the study. All other chemicals were of analytical grade.

2.2. Dissolution test

The in vitro dissolution of the PC was tested in a USP XXIII apparatus 2 at 75 rpm. The dissolution medium was 500 ml Simulated Gastric Fluid USP XXIII without enzyme (SGF) for the first hour. The SGF was changed to Simulated Intestinal Fluid USP XXIII (SIF) by adding 400 ml of a 37 °C heated phosphate buffer containing 2.72 g monobasic potassium phosphate and 1.25 g sodium hydroxide. The pH was adjusted to pH 6.8. The samples were analyzed by a HPLC assay using a LiChrospher 60 RP-select B column (E. Merck, Darmstadt, Germany), and a Thermo Quest HPLC system (San Jose, CA) equipped with an UV detector at a wavelength of 230 nm. An 80:20 mixture of a 25 mmol phosphate buffer, pH 6.5 and acetonitrile was used as a mobile phase at a flow rate of 1 ml per minute. A five point calibration curve was prepared with a regression coefficient >0.999, ranging from 5 to 150% of the maximum expected drug content per capsule.

2.3. Animal study

The University Committee on Use and Care of Animals (UCUCA) approved the animal protocol 6879A and the dogs were under the care of the Unit for Laboratory Animal Medicine (ULAM).

Two male and two female mongrel dogs were used for the study. Each dog was fasted over night before