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Controlled release of solid-reversed-micellar-solution (SRMS) suppositories containing metoclopramide-HCl

Axel Schneeweis, Christel C. Müller-Goymann *

Institut für Pharmazeutische Technologie, Technische Universität Braunschweig, Mendelssohnstr. 1, 38106 Braunschweig, Germany

Abstract

The investigated drug delivery system is a solid-reversed-micellar-solution (SRMS). The composition of this solution is 70% Witepsol W35 and 30% (w/w) lecithin. 1% (w/w) metoclopramide-HCl (MCP) was solubilizied in the SRMS. After melting and on contact with water or any physicological aqueous media the SRMS exihibits an application induced transformation into a semisolid system of liquid crystalline microstructure. The structure of the liquid crystal has been identified by polarized light microscopy as a lamellar mesophase. Due to a low coefficient of diffusion in this mesophase a controlled release of the drug may be possible. The release profiles of the in vitro experiments have shown zero order kinetics and a sustained release of the SRMS-suppositories (SRMS-supp.) in comparison with commercial suppositories (Gastrosil-supp.). To examine bioavailability an in vivo study with rabbits was carried out. Five SRMS-supp. (10 mg MCP) and five Gastrosil-supp. (10 mg MCP) were tested in a parallel-group study. These experiments have shown a five times longer mean residence time (parameter of sustained release) in comparison with Gastrosil-supp. In vitro and in vivo studies have shown that rectal application of SRMS-supp. provides an appropriate route for controlled release of MCP via application induced transformation into liquid crystals.

Keywords: Solid-reversed-micellar-solution; Suppositories; Metoclopramide-HCl

1. Introduction

Emesis is often described as a side effect of the analgesic therapy with opioids. To relieve this effect an almost constant plasma concentration of an antiemetic drug is desired.

The work deals with the antiemetic drug metoclopramide-HCl (MCP) in a solid-reversed-micellar-solution (SRMS) for controlled release. The investigated drug delivery system is developed from a liquid-reversed-micellar-solution (LRMS). The composition of this solution was 70% isopropylmyristate and 30% lecithin. On contact with water the LRMS exhibits an application induced transformation into a semi-solid system of liquid crystalline microstructure. The structure of the liquid crystal has been identified by polarized light microscopy as a lamellar mesophase.

Investigations of formulations, containing the amphiphilic drug diclofenac-Na (DS) have shown, that the apparent diffusion coefficient for DS in this system has decreased in comparison with an

* Corresponding author. Tel.: +49-531-391-5650; fax: +49-531-391-8108.

E-mail address: c.mueller-goymann@tu-bs.de (C.C. Müller-Goymann)

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oily or aqueous solution (Papantoniou and Müller-Goymann 1995). Furthermore, this LRMS, filled in soft gelatine capsules, is able to control drug release in vitro and in vivo (rabbits) after rectal application (Schneeweis and Müller-Goymann 1997).

A controlled release after peroral application of DS via a LRMS is not possible, because the endogenous substances in the upper intestine are able to disperse the lamellar mesophase which leads to an accelerated drug release (Schneeweis et al. 1997).

Suppositories are more common than soft gelatin capsules for rectal application. To achieve solid consistency of suppositories at room temperature the oily component isopropylmyristate has to be replaced by Witepsol W35. After melting and on contact with water this SRMS exhibits an application induced transformation into a semi-solid system of liquid crystalline microstructure.

The aim of the present work is the in vitro and in vivo investigations of drug release of a SRMS containing the hydrophilic drug MCP.

2. Materials and methods

2.1. Materials

MCP was supplied by Solvay (D-Hannover); Witepsol W35 was purchased from Contensio (D-Witten). The lecithin used was Phospholipon 90 G® (Rhone-Pourlec Rorer, D-Köln), which consisted of pure soya lecithin with a content of at least 90% phosphatidylcholine. The applied buffers were an isotonic phosphate buffer of pH 7.4 according to German Pharmacopoeia.

Gastrosil® 10 and 20 mg suppositories for comparative purposes were purchased in a retail pharmacy.

2.2. Preperation of the reversed-micellar-solution

While being stirred with a teflon coated magnet, 30% lecithin was dissolved in 70% Witepsol W35 at a temperature of 60°C. After 1 h a yellowish solution was obtained.

The MCP was dissolved in equal parts of bidistilled water (w/w). After uniting of both solutions the water was vaporized at 60°C for about 24 hours. The water content of the final solutions was less than 0.7%.

2.3. In vitro drug release

The dissolution apparatus consisted of a water-bath (37°C) containing a beaker. The acceptor medium in the beaker (800 ml of isotonic phosphate buffer adjusted to a pH of 7.4) was stirred by a KMO_2 magnetic stirrer (Janke und Kunkel, D-Staufen) at 750 rpm. Either the RMS or a suppository was inserted together with 1.0 ml isotonic buffer into a dialysis membrane tubing of 7 cm length (Spectra Por® Membrane (MWCO 6–8000), Spectrum Medical Industries, Los Angeles, USA), siliconized by a 2% (w/w) solution of silicon oil in diethylether to make the membrane hydrophobic. After closing in air-free packaging with clips the tube was placed into the beaker. Aliquots of 5 ml were removed from the acceptor medium during 6 h and replaced by fresh buffer. Drug concentration was measured by UV detection using a photometer (Shimadzu, D-Duisburg) at a wavelength of 275 nm.

2.4. In vivo bioavailibility

The bioavailability after rectal application was tested in rabbits.

Either a SRMS-suppository (SRMS-supp.) or an Gastrosil® 10 mg suppository was applied to female chinchilla bastard rabbits.

To guarantee the contact between the formulation and the rectal mucosa during the whole absorption time, the anus was manually kept shut over this period.

Five SRMS-supp. and five Gastrosil-suppositories (Gastrosil-supp.) were tested in a parallel-group study.

After drug application, blood samples (2.0 ml) were taken from marginal ear vein catheter at 10, 20, 30, 60, 90, 120, 180, 240, 300, 360 min (SRMS-supp.) or 5, 10, 15, 20, 25, 30, 60, 90, 180, 240 min (Gastrosil-supp.). The specimens were centrifuged immediately at 2000 rpm with a UJ3s

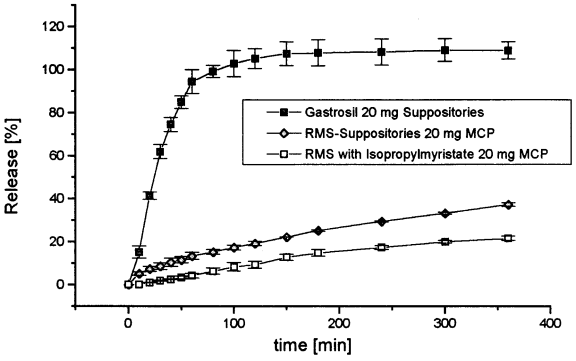

Fig. 1. In vitro drug release of metoclopramide-HCl (MCP)-formulations.

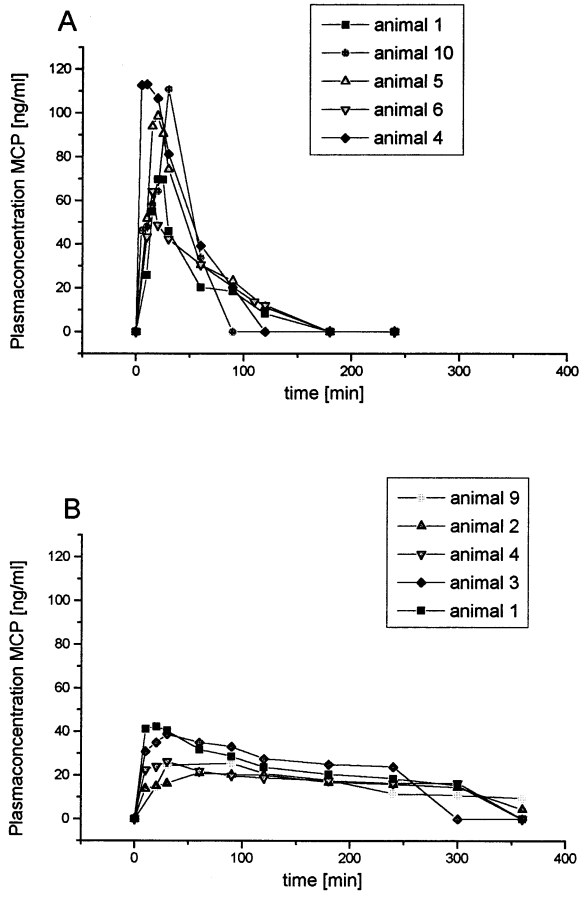

Fig. 2. Plasma concentration–time curves. (A) Gastrosil-suppositories (Gastrosil-supp.); (B) solid-reversed-micellar-solution (SRMS)-suppositories (SRMS-supp.).

centrifuge (Heraeus, D-Osterode) for 30 min. The plasma was transferred into polyethylene tubes and stored at $-18°$ until analysed. Plasma concentration of the drug was measured by HPLC using the method of Buss et al. (1990).

3. Results and discussion

3.1. In vitro drug release

In vitro drug release was carried out with a LRMS and a SRMS of MCP and compared to the drug release of Gastrosil-supp. Each formulation contained 20 mg MCP. Fig. 1 shows the percentage of MCP released versus time in minutes for the in vitro simulation of rectal application. The release of the reversed micellar solutions is slower than that from Gastrosil-supp. The release from the reversed micellar solutions follows nearly zero order kinetics. About 15% of the drug was released from the liquid reversed micellar system during 6 h. From the solid reversed micellar system during the same time 30% of MCP was released. Gastrosil-supp. released about 18% within 10 min.

The in vitro investigations shows that the liquid and the SRMS slow down drug release after transformation into a system of lamellar liquid crystals on contact with water.

3.2. In vivo bioavailibility

Bioavailibilty studies with the SRMS were done to show if a controlled release is possible in vivo.

Fig. 2 shows the plasma concentration in ng/ml versus time in min for the MCP release from the SRMS-supp. and Gastrosil-supp. after rectal application in rabbits. Differences in terms of c-max and t-max between both formulations could be observed. C-max of the SRMS-supp. is lower than c-max of the Gastrosil-supp. whereas the t-max time is longer.

The bioaquivalence was investigated further by comparing the AUCs. No significant differences

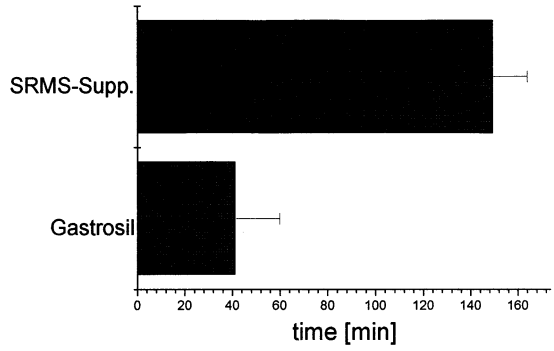

Fig. 3. Mean residence time (MRT) of Gastrosil-suppositories (Gastrosil-supp.) and solid-reversed-micellar-solution (SRMS)-suppositories (SRMS-supp.).

between the 95% confidence levels of the AUCs of both formulations have been detected.

Next the mean residence time (MRT) was determined for each application as a parameter for sustained release. The MRT is the quotient of the ABC and the AUC.

Fig. 3 shows the mean values of the MRT of both formulations. The MRT of the SRMS-supp. is significantly higher than that of the Gastrosil-supp. The MRT of the Gastrosil-supp. is about 40 min whereas the SRMS-supp. has a four times higher MRT (150 min).

The significant elongation of the MRT by SRMS-supp. ensures a sustained release after rectal application.

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