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Controlled delivery of metoclopramide using an injectable semi-solid poly(ortho ester) for veterinary application

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Abstract

In animal health care, current therapeutic regimens for gastrointestinal disorders require repeated oral or parenteral dosage forms of anti-emetic agents. However, fluctuations of plasma concentrations produce severe side effects. The aim of this work is to develop a subcutaneous and biodegradable controlled release system containing metoclopramide (MTC). Semi-solid poly(ortho ester)s (POE) prepared by a transesterification reaction between trimethyl orthoacetate and 1,2,6,-hexanetriol were investigated as injectable bioerodible polymers for the controlled release of MTC. MTC is present in the polymeric matrix as a solubilised form and it is released rapidly from the POE by erosion and diffusion because of its acidic character and its high hydrosolubility. If a manual injection is desired, only low molecular weight can be used. However, low molecular weight POEs release the drug rapidly. In order to extend polymer lifetime and decrease drug release rate, a sparingly water-soluble base $Mg(OH)_2$ was incorporated to the formulation. It was possible to produce low molecular weight POE that can be manually injected and releasing MTC over a period of several days.

Keywords: Poly(ortho ester); Bioerodible polymer; Controlled release; Metoclopramide; Veterinary medicine

1. Introduction

Metoclopramide (MTC) is a commonly prescribed drug used for the management of gastrointestinal disorders such as gastric stasis, gastroesophageal reflux and for the prevention of cancer chemotherapy-induced emesis (El-Sayed et al., 1995). It has a pronounced effect upon gastrointestinal motility and improves the coordination of the gastropyloric small intestinal motor function. Hence, MTC is a useful agent in treating and preventing various types of vomiting (Beckett et al., 1987). The drug has a short biological half-life (3–4 h) and is usually administered in a dose of 10–15 mg given up to four times daily in order to maintain effective concentration throughout the day (El-Sayed et al., 1995). In long

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term therapy, fluctuation in the plasma concentrations, with high concentration peaks and troughs are common for drugs with rapid absorption and elimination. These fluctuations produce adverse reactions in many subjects, such as restlessness, somnolence, nervousness, confusion, dystonic reactions and feelings of unreality. Awareness of these factors has encouraged the use of controlled release MTC dosages forms which allow for extended dosing intervals with more steady plasma drug concentrations. Moreover, peak plasma concentrations of MTC occur about 1–2 h after an oral dose. However, it undergoes hepatic first-pass metabolism, which varies considerably between subjects, and hence the absolute bio-availability and the plasma concentrations are subject to wide inter-individual variation. Although, there are some sustained formulations administered twice daily on the market (Madej et al., 1988; Bruera et al., 1994; Harrison et al., 1994), the approach of using an oral dosage form for such medication is controversial, especially in the veterinarian field. A controlled release formulation administered subcutaneously or intra-muscularly and releasing MTC over 3–5 days would be advantageous.

During the last 9 years, semi-solid poly(ortho ester)s (POE) have being extensively studied in the ophthalmic field as adjunctive treatment after glaucoma filtering surgery by a controlled delivery of 5-fluorouracil and dexamethasone (Merkli et al., 1995; Einmahl et al., 1999) and in the periodontal field as adjunctive treatment of periodontitis using a controlled delivery of tetracycline (Roskos et al., 1995). These viscous polymers provide unique advantages such as the ability of incorporating active ingredients by simple mixing procedures without the use of organic solvents or elevated temperature and also the possibility of administering low molecular weight polymer containing the drug by manual injection using conventional syringe. Moreover these semi-solid POE show an excellent biocompatibility even in particularly sensitive region such as the eye (Zignani et al., 1998; Einmahl et al., 2000).

Synthesis, physicochemical and structural characterisation, stability and degradation study of these polymers have been evaluated and published (Heller, 1993; Merkli et al., 1993).

The present investigation describes the physicochemical and thermal properties of POE of different molecular weights, the syringeability of these polymers and also the in vitro release of MTC monohydrochloride (MTC_{HCl}) from POE.

A preliminary in vivo evaluation of POE/MTC formulations on dogs is also reported.

2. Materials and methods

2.1. Materials

Materials were purchased as follows: trimethyl orthoacetate and 1,2,6-hexanetriol from Aldrich Chemie (Steinheim, Germany), MTC hydrochloride from Sigma® Chemie AG (Buchs, Switzerland). All other chemicals and solvents were purchased from Fluka®-Chemie AG (Buchs, Switzerland).

2.2. Synthesis and characterisation of the polymer

The semi-solid POE was synthesised by a transesterification reaction between 1,2,6-hexanetriol and trimethyl orthoacetate under anhydrous conditions and characterised as described earlier (Fig. 1; Merkli et al., 1993). To eliminate residual monomers and impurities, the polymer was purified by precipitation into methanol. POE was produced aseptically by drying the polymer under high vacuum at 40 °C to eliminate residual

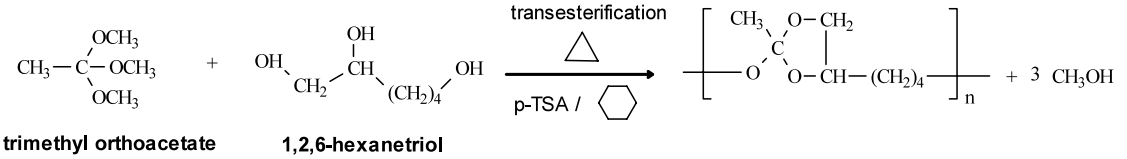

Fig. 1. The chemical structure of a semi-solid poly(ortho ester) obtained from 1,2,6-hexanetriol and trimethyl ortho acetate.

solvents and eventually by breaking the vacuum with argon to avoid contact with air. Low molecular weight polymers were produced by changing stoichiometry. Different polymer molecular weights were obtained by varying the ratio of 1,2,6-hexanetriol to trimethyl orthoacetate. The polymers synthesised were stored under argon at 4 °C.

Analytical high pressure size exclusion chromatography (HPSEC) was performed using a Waters® 600 E equipment using a series of four Styrogel HR® 1–4 columns as the stationary phase, an autosampler Waters® 717 plus and a refractometer Waters® 410. The mobile phase was stabilised THF (Romil Chemical, Leics, UK). Calibration was carried out using polystyrene standards (Tosoh Corporation, Tokyo, Japan) covering the 500–96 400 Da range.

Differential scanning calorimetry (DSC) studies were performed using a DSC 200 C microcalorimeter (Seiko, Tokyo, Japan). Glass transition temperatures, T_g's, were obtained from half-heights of the heat capacity discontinuity. Heating rate was 6 °C/min.

The manual syringeability of the polymer was evaluated by using a tensile tester (Schenk-Trebel RM 50, CH-Nänikon), fitted with force and displacement transducers (Types U1 and W5TK) and driven by a control unit, as illustrated in Fig. 2. An analog-to-digital converter which interfaced the latter unit to a microcomputer and a data acquisition software package facilitated data collection.

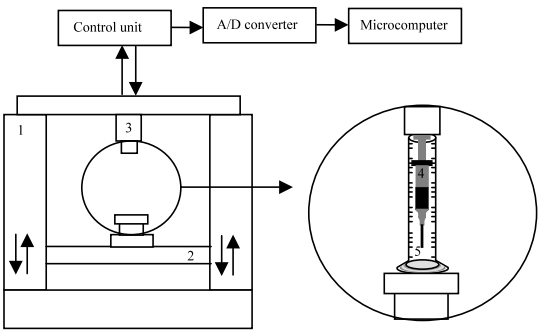

Fig. 2. Experimental set-up for the measurement of the syringeability force developed during polymer injection. 1, frameload; 2, crosshead; 3, force transducer; 4, syringe filled with the viscous POE; 5, Plexiglas® cylinder.

2.3. In vitro drug release

Drug–polymer formulations were prepared by simple mixing of POE and MTC_{HCl}. In vitro drug release studies were conducted in a previously described thermostated flow through cell containing 100 mg of drug product (Merkli et al., 1993). The drug product was placed into the cells, and phosphate buffer pH 7.4 (0.15 M) was circulated through at a rate of 3.3 ml/h, and collected every 6 h using an automatic fraction collector 2111 Multirac (LKB®, Bromma, Sweden). The cell temperature was maintained at 37 °C. All experiments were carried out in triplicate. For determination of the amount of released MTC_{HCl}, UV–visible spectrophotometric analysis at 308 nm was performed. At this wavelength, no interference between polymer degradation products and MTC_{HCl} was observed.

2.4. In vivo pharmacokinetics

Six healthy beagle dogs, weighing between 10 and 20 kg were used in the present study. Three dogs received MTC solution and three dogs received low molecular weight POE #3 (Table 1) loaded MTC 10 wt.% at the same dose of 0.5 mg/kg of drug. Formulations were administered subcutaneously in the neck using conventional syringe and an 18 Gauge needle. The dogs were fasted for about 18 h prior to drug administration and 3 h after administration, but had free access to water throughout the experiment. Multiple blood samples (3 ml) were collected from the cephalic vein in heparinised glass tubes before ($t = 0$ h) and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 32, 48, 56 and 72 h. Plasma was then separated after centrifugation and stored frozen at −20 °C for HPLC analysis (Vétoquinol procedure).

Table 1
Physicochemical characteristics of the different POEs synthesised

POE	Monomer ratio[a]	M_w	M_n	Polydispersity $I=(M_w/M_n)$	T_g (°C)
1	1/1	10 900	8100	1.34	−30.5
2	1/0.95	9400	6800	1.40	−33.4
3	1/0.90	5200	4300	1.19	−39.8

[a] Ratio 1,2,6-hexanetriol/trimethyl orthoacetate.

3. Results and discussion

3.1. POE and POE/MTC characterisation

By varying the ratio of 1,2,6-hexanetriol to trimethyl orthoacetate, it was possible to produce a family of POE having different molecular weights and physicochemical properties. If this ratio is increased or decreased, lower molecular weights are obtained (Table 1). Glass transition temperature (T_g) values and weight average molecular weights of POE are linearly dependent on 1,2,6-hexanetriol percent in the range of 100–90 mol% (Fig. 3).

Fig. 4 shows DSC curves of MTC, pure POE and MTC loaded POE. MTC presents an exothermic peak due to decomposition at 89.8 °C with a melting enthalpy of 187.9 mJ/mg. This peak is also kept for MTC loaded POE but with a lower melting enthalpy of 28 mJ/mg. The decrease of enthalpy of melting can be explained by the presence of the drug predominantly in its solubilised form than dispersed crystals in the polymeric matrix. Moreover, POE alone presents a T_g of −39.6 °C and the POE/MTC a lower T_g at −40.2 °C. The T_g value decrease can be explained by the plasticising effect of POE by the drug molecules.

The force exerted on the syringe to manually inject the viscous POE was evaluated by a tensile tester. The principle consists of applying a given displacement rate of the piston of the syringe filled with the polymer and measuring the force (N) developed by the viscous product. Three different molecular weight POEs were evaluated by using 0.9 and 1.6 mm diameter needles with various displacement rate (5 and 10 mm/min). Results are summarised on Table 2. The lower the polymer molecular weight, the lower the viscosity and the better the syringeability. To be selected for the present study the polymer must develop a manual injection force at 5 mm/min lower than 50 N.

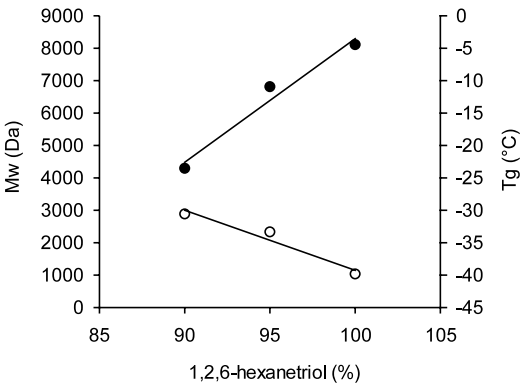

Fig. 3. Glass transition temperature of POEs (T_g) (○) and POE number average molecular weights (●) as a function of mol% 1,2,6-hexanetriol.

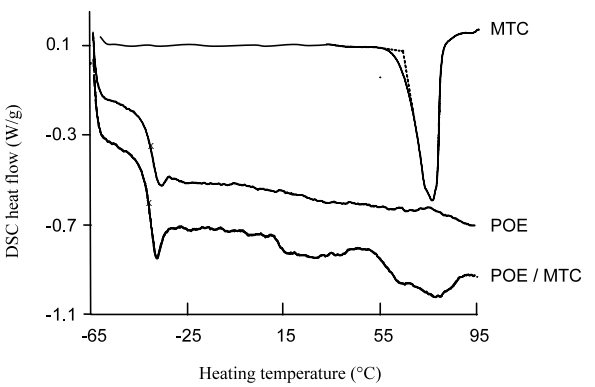

Fig. 4. DSC thermograms during heating of MTC hydrochloride (MTC), pure polymer (POE) and MTC loaded polymer (POE/MTC).

Table 2
Force (N) developed by viscous POE formulation during manual injection through 0.9 and 1.6 mm diameter needles

$\varnothing_{ext}$ (mm)	Displacement rate (mm/min)	POE #1	POE #2	POE #3
0.9	10	ND	ND	237
	5	> 300	240	143
1.6	10	ND	ND	45
	5	150	72	23

3.2. In vitro drug release study

Fig. 5 shows in vitro MTC release from POE of different molecular weights and loaded with 5% (w/w) MTC. The data show that MTC is released from the POE within 3 days for the lowest molecular weight polymer and in about 9 days for the highest molecular weight polymer. The same results were obtained in a previous study with 5-fluorouracil (Merkli et al., 1994). The burst effect observed at 1 day decreased by increasing polymer molecular weight. The most interesting release profiles were obtained with high molecular weight polymers that are hardly injected.

For application in glaucoma filtering surgery, periodontal disease or subcutaneously for veterinary applications, a relatively low viscosity of POE is essential. Ideally, the viscosity should be such that the drug loaded POE can be manually injected by using a hypodermic syringe. As shown in Fig. 5, the low molecular weight polymer characterised by a low viscosity leads to a fast drug release. In order to achieve a drug release from POE over an extended period of time, basic excipients such as $Mg(OH)_2$ have been studied in order to stabilise the polymeric matrix preventing hydrolysis and concomitant drug release (Merkli et al., 1995; Einmahl et al., 1999). Another factor that influences the hydrophobic/hydrophilic balance of a polymer-drug system is the amount of drug incorporated into the matrix. In previous investigations with the same semi-solid POE, we have found that the higher the drug loading of the water-soluble 5-FU in POE, the faster the release rate (Merkli et al., 1995). Fig. 6 shows the effect of varying the concentration of MTC incorporated in a low molecular weight POE and also the effect of magnesium hydroxide on drug release. This study shows clearly that the higher the drug loading the faster the release rate. Since MTC hydrochloride is an acidic and water soluble drug, it promotes water penetration into the polymeric matrix accelerating thus the rate of polymer degradation and

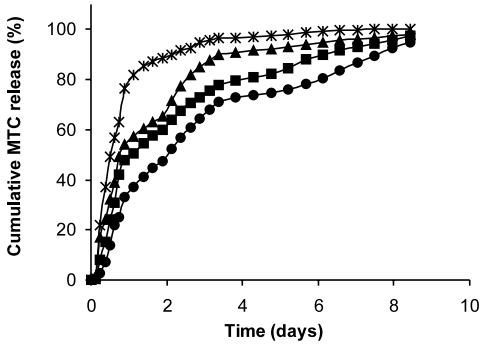

Fig. 5. Cumulative MTC release from POEs of different molecular weights loaded with MTC 5 wt.%. (●) POE 14 100 Da, (■) POE 11 600 Da, (▲) POE 9400 Da, (★) POE 5200 Da. (Phosphate buffer, pH 7.4 at 37 °C, $n = 3$, sdm smaller than symbols).

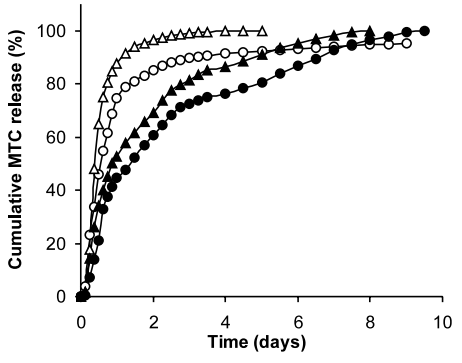

Fig. 6. Influence of drug loading and magnesium hydroxide on the in vitro release of MTC from POE 5200 Da in phosphate buffer pH 7.4 at 37 °C ($n = 3$, sdm smaller than symbols). (○) 5 wt.% MTC, (●) 5 wt.% MTC+1 wt.% $Mg(OH)_2$; (△) 10 wt.% MTC, (▲) 10 wt.% MTC+1 wt.% $Mg(OH)_2$.

the rate of drug release. Fig. 6 shows also the stabilising effect of $Mg(OH)_2$ on polymer hydrolysis.

3.3. In vivo pharmacokinetics

Preliminary pharmacokinetics results on dogs are shown in Fig. 7. Sustained plasma concentrations for up to 30 h were obtained with the delivery system POE/MTC. However, in the case of MTC solution a short half-life was obtained.

4. Conclusion

In this investigation, we have evaluated the potential of semi-solid POE for the delivery of MTC hydrochloride. We have shown that polymers with low viscosity and low molecular weight can be easily injected by using a conventional syringe. However, MTC release rate from such polymers have to be prolonged by using either a basic excipient such as magnesium hydroxide or by using a low drug loading when the drug is water soluble and acidic. The drug was released from the POE by an erosion process concomitant with diffusion. According to the preliminary results obtained in this study, the formulation containing MTC 10 wt.% and stabilised by magnesium hydroxide can be considered as a promising new controlled release system for animal health care.

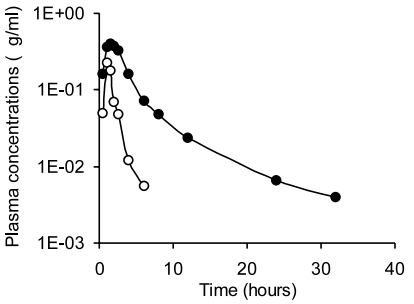

Fig. 7. Mean plasma concentration vs. time values in dogs treated with MTC solution (○) or POE/MTC delivery system (●) ($n = 3$).

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