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Rapid Communication

An Oral-Controlled Release Drug Delivery System for Liquid and Semisolid Drug Formulations

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Abstract. A novel oral drug delivery system for the controlled release of liquid drugs, drug solutions, and semisolid drug preparations is presented that is utilizing the constant vapor pressure of liquefied gas. The system is equipped with a capillary as an element determining the drug delivery rate and contains a liquefied propellant with a suitable boiling point below human body temperature. In the dissolution studies, polyacrylate gels of different viscosities containing paracetamol as model drug were used. Zero-order release kinetics was obtained. The release rates were dependent on the gel viscosity. Besides, by gel viscosity, the drug release rates could also be modified by changing the propellant type and the capillary parameters such as length or diameter. Accordingly, the new system enables a wide range of drug delivery kinetics which can be modified in a case-by-case basis in order to match the desired drug delivery characteristics.

KEY WORDS: controlled delivery of liquids; controlled release; extended release; oral drug delivery system.

INTRODUCTION

The achievement of stable drug plasma levels after oral application of controlled-release (CR) dosage forms is often clinically desired but is still a challenge in many cases. Especially, the development of CR dosage forms with constant drug delivery kinetics that are not affected by the wide variability of the mechanical and physicochemical conditions to which dosage forms are exposed during gastrointestinal (GI) transit is often a hurdle (1–4). Very successful drug delivery systems with proven constant release characteristics under *in vivo* conditions are oral osmotically driven systems in which the release of the active pharmaceutical ingredient is achieved by utilizing osmotic pressure or the swelling energy of polymers. However, the introduced systems are designed to deliver solid active pharmaceutical ingredients and to date only the L-OROS represents a technology for the controlled release of non-aqueous liquid and semisolid drug formulations (5).

The novel drug delivery system developed by our group is designed for the controlled release of aqueous and non-aqueous liquid and semisolid drug formulations as well as liquid drugs. The system is equipped with a capillary as a flow-controlling element. It contains a liquefied gas as a propellant that has a boiling point below the body temperature (37°C) like for example isopentane.

$$\Phi = \frac{\pi \times r^4 \times |\Delta p|}{8\eta \times l} \tag{1}$$

According to the Hagen–Poiseuille equation (Eq. 1), the capillary flow rate (Φ) of the system is determined by the radius (r), the length (l) of the capillary, the pressure gradient at the capillary ends (Δp), as well as the viscosity of the liquid formulation. The vapor pressure of liquefied propellant depends only on the temperature which is nearly constant (37°C) within the human GI tract. Thereby, by using a liquefied propellant, a constant pressure can be obtained that can act as the driving force for the capillary flow of a liquid formulation. The amount of propellant required for a reliable drug release should be very small. Theoretically, less than 10 μl of liquid isopentane are sufficient for a system with dimensions comparable to capsule size 000. The volume of the saturated vapor of isopentane at 37°C calculated according to Avogadro's law amounts to 2.17 mL and exceeds the fill volume of capsule size 000 which amounts to 1.37 mL. It should be considered that the amount of gas in the digestive tract is about 200 ml (115–1,000 ml) and carbohydrates (methane) produced by intraluminal bacteria present 0–56% of all amount (6,7). By an appropriate adjustment of the viscosity (η) of the drug formulation, it should be possible to obtain nearly constant capillary flow and consequently to achieve the desired zero-order drug delivery kinetics.

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MATERIALS AND METHODS

The corpus of the novel drug delivery system (Fig. 1) was manufactured from a nondegradable polymer Polymethylmethacrylate (Plexiglas®) and was composed of two parts. The lower part of the corpus was filled with the drug formulation. Paracetamol was used as the model drug. In the wall of this part, a spiral capillary (ø 0.5 mm, l=32 mm) was implemented as flow-controlling element. Fifty microliters of isopentane (boiling point 27.5°C, calculated vapor pressure at 37°C 1,000 mmHg) as the propellant were placed in the reservoir formed in the upper part of the corpus. Overall, the dimensions of the system corresponded to capsule size 000.

To evaluate the drug delivery behavior of the system, the lower part of the system and the capillary were filled with polyacrylate gels (Carbopol 980 NF) of different concentrations: 0.05%, 0.1%, 0.2%, and 0.3% (*w*/*w*) each containing 12.5 mg/ml acetaminophen. The dynamic viscosity (η) of the gels were characterized using a cone-plate rotational viscometer (CP 25–1, gap d=0.052) at 37°C and shear rates of 0.001–10/s. The results are presented in Fig. 2.

The release properties of the novel delivery system were carried out in the USP apparatus 2 at 37±0.5°C applying a stirring speed of 50 rpm and using 1,000 ml USP phosphate buffer pH 6.8 as the dissolution medium. The amount of the drug dissolved was determined in 5-min intervals at a wavelength of λ=243 nm using an online UV-Vis spectroscopy system (Shimadzu 1650). The system was equipped with quartz flow through cuvette with a light patch of 1 cm, peristaltic pump (Ismatec IPC 16), Tygon® tubing, and operated in a closed-loop configuration. The dissolution media was withdrawn from the vessels through a filter (poroplast 0.1 μm pore size) by the peristaltic pump operating at a flow rate of 10 mL/min, in a pump interval of 5 min (4 min pumping time, 1 min pause for measurement).

RESULTS AND DISCUSSION

As expected, rheological measurements clearly indicate that the flow behavior is dependent on the polyacrylate concentration. With increasing concentrations of this gelling agent, an increase in the dynamic viscosity can be observed (Fig. 2). The results from the drug release experiments (Fig. 3) are in good agreement with these observations. From all gel formulations, acetaminophen was released with an almost constant rate that was close to zero-order kinetics (Table I). The release rate was strongly dependent on the concentration of the gelling agent and consequently on the gel viscosity. In the case of low viscous gels obtained for polyacrylate concentrations of 0.05% and 0.1%, drug delivery was completed within 30 and 60 min, respectively. In contrast, gels with higher polyacrylate concentrations showed incomplete drug release within the test duration of 8 h, i.e., 80% of the dose was released from the gel containing 0.15% of gelling agent and only about 20% of the dose from the gel containing 0.30% of polyacrylate. In this work, the capillary was prefilled with the gel prior the dissolution and so no lag time in the delivery profiles was observed. However, if the capillary will not be prefilled, it is possible to achieve lag times depending on the gel viscosity. The lack of dose dumping is related to system robustness and usage of uniformly drug-loaded gels which viscosity remained constant during the delivery time. In the present setup, the system is activated by the temperature increase above BP of isopentane. However, by sealing the capillary with polymers of desired properties, it become likely that besides the temperature the water contact or pH could trigger the delivery process.

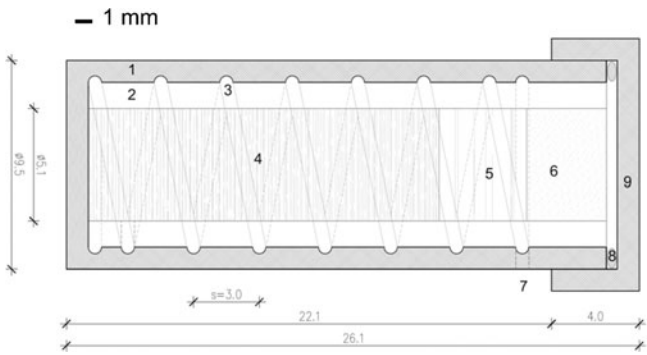

Fig. 1. Schematic representation of the liquid gas based drug delivery system. *1* external wall, *2* internal wall, *3* capillary, *4* drug formulation, *5* hydrogel plunger, *6* liquefied gas, *7* output gap, *8* gasket, *9* cap. All dimensions are given in millimeters

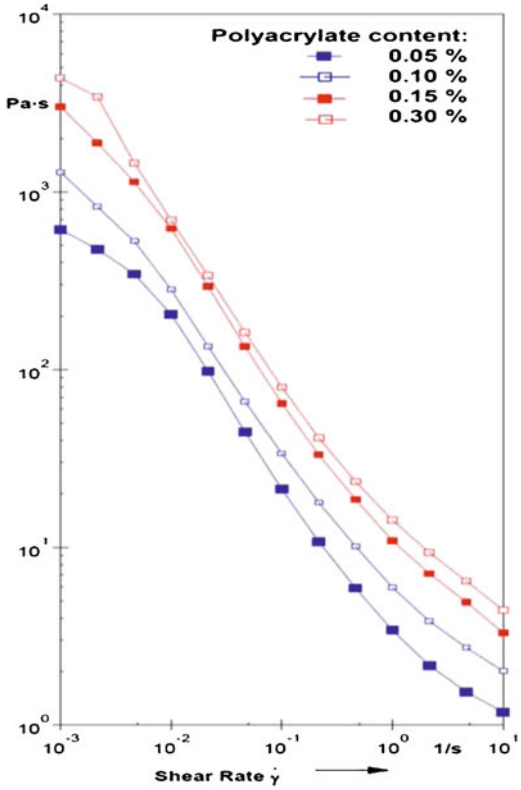

Fig. 2. Dynamic viscosity (η) of polyacrylate gels at various shear rates measured with cone plate viscometer at 37°C. Presented are means of n=3

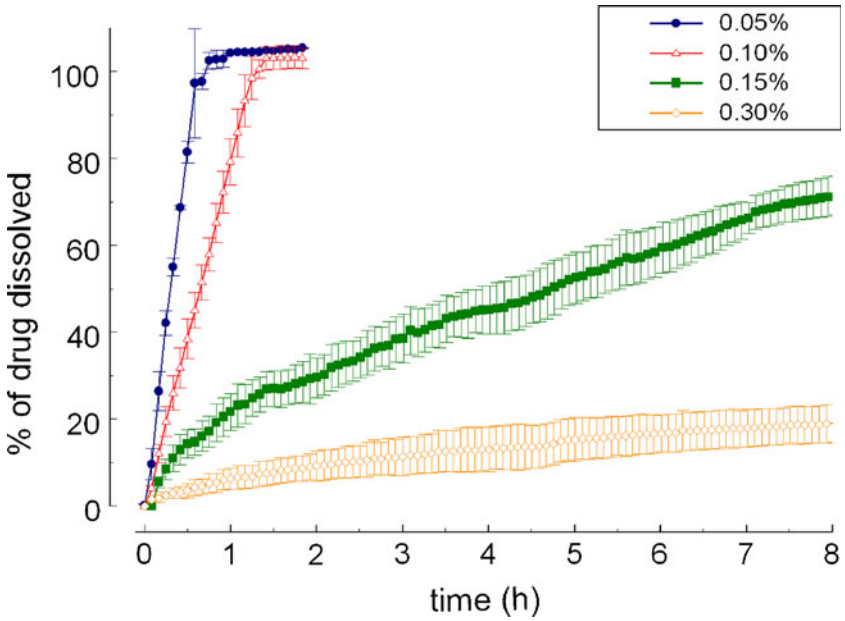

Fig. 3. Mean drug release profiles of the novel drug delivery system loaded with gels containing different concentrations of polyacrylate (USP apparatus 2, 50 rpm, 1,000 ml USP phosphate buffer pH 6.8, 37°C, means of $n=6\pm$SD)

The results indicate that by using liquefied gas-based drug delivery systems, it is possible to achieve zero-order release kinetics over highly variable time spans for liquid or semisolid drug formulations. Further changes of the drug delivery characteristic can be achieved by the modification of capillary parameters (length, radius) as well as by use of propellants with different vapor pressures.

CONCLUSION

The novel gas-based drug delivery system is a suitable device for the controlled delivery of liquid drugs, drug solutions, and semisolid formulations. The drug delivery kinetics of the system can be adjusted by selection of appropriate flow properties of the drug containing vehicles, vapor pressure of the propellant, and the dimensions of the system capillary as the flow controlling element. The new system therefore enables to achieve a wide range of drug delivery kinetics which can be modified in order to achieve clinically desired drug delivery rates.

Table I. Slopes of the Dissolution Profiles and the Corresponding Regression Coefficients

Concentration of the gelling agent	Slope of the dissolution profile (R^2)
0.05	16.447 (0.9975)
0.10	7.847 (0.999)
0.15[a]	0.573 (0.9749)
0.30[a]	0.134 (0.9708)

[a] Calculated after 180 min

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