Osmotic delivery systems for the β -adrenoceptor antagonists metoprolol and oxprenolol: design and evaluation of systems for once-daily administration

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- 1 The essential features and mode of action of oral osmotic drug delivery systems (Oros[®]) for metoprolol fumarate and oxprenolol succinate are described.
- 2 Critical aspects in the development of systems for once-daily administration of both drugs are discussed, and methods for evaluating *in vitro* release characteristics are presented.
- 3 *In vitro* testing confirmed that drug delivery corresponded closely to the theoretical release behaviour predicted from the physicochemical and membrane permeability characteristics for both oxprenolol and metoprolol systems.
- 4 *In vitro* release rates were also shown to be unaffected by pH, *in vitro* test procedures, dissolution media and long-term storage at different temperatures.

Keywords osmotic delivery systems metoprolol oxprenolol

Introduction

The β -adrenoceptor antagonists oxprenolol hydrochloride and metoprolol tartrate are recognised as safe and effective drugs in the treatment of angina and hypertension. Both are rapidly absorbed and have relatively short elimination half-lives (Mason & Winer, 1976; Bengtsson *et al.*, 1975). Treatment with rapid-release conventional tablets requires multiple daily administration with resulting inconvenience to the patient and the possibility of reduced compliance with prescribed therapy. This limitation has largely been overcome with the development of polymer-matrix slow-release formulations (Slow Trasicor[®] and Lopresor SR[®]) which are intended for once-daily use and have previously been shown to reduce peak plasma concentrations, delay the time to peak and maintain measurable drug concentrations for up to 24 h after dosing (West *et al.*, 1976; Kendall *et al.*, 1980). Their clinical efficacy has also been demonstrated in controlled trials, although recent studies have questioned their suitability for once-daily administration.

Petrie *et al.* (1980) in a study of hypertensive patients receiving Slow Trasicor reported a loss in blood pressure control during the 2-4 h preceding the next daily dose. Leahey *et al.* (1980) and Bobik *et al.* (1979) have also demonstrated in healthy volunteers that statistically significant levels of β -adrenoceptor blockade were not maintained throughout 24 h after single dosing with this formulation. Similar results have been reported for Lopresor SR following single (Quarterman *et al.*, 1979) and multiple dosing (Freestone *et al.*, 1982).

Polymer-matrix formulations, such as Slow Trasicor and Lopresor SR, release a substantial part of their total content in a relatively short period, thereby limiting the duration for which effective blood concentrations can be maintained. Drug dissolution from these dosage forms may also be influenced by physiological factors such as intestinal motility, pH of the gastric and intestinal fluid, and luminal content, all of which show considerable within- and between-subject variability.

Recent advances in the design of controlled-release dosage forms offer the possibility of considerably extending the duration of drug release and of maintaining blood concentrations within narrower limits for longer periods after dosing. In selecting improved dosage forms for oxprenolol and metoprolol, the following additional attributes were considered desirable: (1) drug delivery must not be influenced by the different physiological environments within the gut lumen; and (2) the release characteristics must be easily predictable from the known properties of the drug and the dosage form. These requirements were met by the Oros (oral osmotic) drug delivery system (Theeuwes, 1975) developed by the Alza Corporation, California, USA.

This paper outlines the mode of action of Oros systems and considers various aspects in the design of once-daily systems for metoprolol and oxprenolol. Procedures for evaluating *in vitro* release properties are also reported together with data on the influence of pH, dissolution media, *in vitro* test conditions and long-term storage at different temperatures on drug release.

Design and mode of action of Oros systems

Oros systems function in a radically different way from conventional slow-release formulations in that drug release is controlled by an osmotic process (Theeuwes & Eckenhoff, 1980). In appearance the Oros system resembles a conventional film-coated tablet. A typical system (represented diagrammatically in Figure 1), consists of an osmotically active core composed

Figure 1 Cross-section of typical osmotic drug delivery system (Oros®).

mainly of the drug substance surrounded by a semipermeable membrane through which a single small opening is drilled by means of a high-speed laser beam. The membrane is permeable to water but not to the drug or to other molecules present in gastric or intestinal fluid. When the device comes into contact with an aqueous medium, water permeates slowly into the system by osmosis and dissolves the drug on the surface of the core, producing a saturated solution. As more water enters, this solution is displaced through the opening and further drug is dissolved. While solid drug remains, the core solution will be saturated and a steady osmotic pressure will be maintained across the membrane. Under these conditions the influx of water will be constant and drug delivery from the system will be at a fixed zero-order rate. Once all the drug is dissolved—usually after 50 to 60% of the total content has been delivered—the core solution gradually dilutes, with a corresponding parabolic reduction in release rate.

For simple osmotic systems the initial zero-order mass delivery rate $(dm/dt)_z$ is given by the expression:

$$\left(\frac{dm}{dt}\right)_z = \frac{A}{h} \cdot k (\Pi_f - \Pi_e) S_d \quad (1)$$

where S_d is the drug concentration within the system (= aqueous solubility of the drug), Π_f the osmotic pressure of the drug formulation, Π_e the osmotic pressure of the environment (7.7 atm. for isotonic saline at 37°C), k the membrane permeability to water, A the area and h the thickness of the membrane. The rate of drug delivery during the terminal parabolic phase $(dm/dt)_p$ is given by the expression:

$$\left(\frac{dm}{dt}\right)_p = \frac{Z}{1 + \frac{Z}{S_d V} (t - t_z)}^2 \quad (2)$$

where Z is the mass delivery rate defined in equation 1, V the internal volume of the system and t_z the duration of the initial zero-order phase.

It can be seen from equation 1 that the initial zero-order release rate from Oros systems can be manipulated by altering the physical dimensions of the system, the permeability characteristics of the membrane, or the solubility of the drug. The most appropriate drug solubilities for extended zero-order delivery lie between 10 and 50% (weight/volume). In some instances an osmotic driving agent may also need to be included in the core to achieve the desired release profile.

The semipermeable membrane surrounding the core consists mainly of inert cellulose derivatives (cellulose acetates) which are stable in gastrointestinal fluids. The rate-controlling membrane is a unique feature of the Oros system in that it permits only the passage of water into the unit thus effectively isolating the dissolution process from the environment within the gut. The *in vivo* release rate of the system should therefore be independent of its position in the gastrointestinal tract and unaffected by extraneous factors such as pH, luminal content and intestinal motility. For systems with defined physical dimensions, membrane permeabilities, drug solubilities and osmotic pressures, release rates will depend only on the osmolarity and temperature of the luminal environment, both of which show little physiological variation. Since factors determining drug release can be simply measured it is possible to predict accurately the release characteristics for individual Oros systems.

The opening in the semipermeable membrane is drilled by means of a high-speed laser beam to the desired diameter of between 300 and 500 microns; the strength of the beam is adjusted to ensure penetration of the membrane but to leave the core unaffected. Trials under manufacturing conditions have demonstrated the reliability of the drilling procedure, the estimated failure rate being less than one in a million.

Spent Oros systems are excreted harmlessly in the faeces and are of similar appearance to loaded systems despite the fact that most of the drug content is released.

Oros dosage forms are characterized in terms of their initial zero-order release rate and total content; thus a 16/260 Oros system contains 260 mg of drug which is released initially at a rate of 16 mg/h. The total duration of release, however, is not given by division of these numbers, since the release process is not constant but decreases non-linearly over the final phase.

Systems development

The essential aspects to be considered in designing an Oros system include: (1) selection of a suitably soluble form of the drug; (2) permeability requirements for the membrane; (3) the need for an osmotic driving agent; and (4) the conditions for laser drilling. In addition, pharmaceutical methods need to be developed and validated to assess *in vitro* drug release from prototype and final dosage forms. The *in vitro* test conditions should also reflect those encountered in the gut lumen to ensure that the

in vitro result is an accurate predictor of the *in vivo* delivery rate. Some aspects of system design and evaluation are considered in the following sections, with particular reference to the development of metoprolol and oxprenolol Oros systems.

Methods

Solubilities and osmotic pressures

Saturated aqueous solutions of drug with and without osmotic driving agents were prepared in closed containers at 37°C. Excess amounts of each material were added to ensure saturation, and solutions were equilibrated for 24 h. The saturated solutions were filtered at 37°C through pre-heated 0.2 µm millipore filters attached to syringes, and their concentrations determined by u.v. analysis after appropriate dilution.

Osmotic pressures were determined at 37°C for the filtered saturated solutions using a vapour pressure osmometer (Hewlett-Packard Model 302B).

Manufacture

Tablet cores were obtained by granulating and tableting on a rotary press using standard concave (IPT) tooling. The average weight, volume, density, and surface area of the cores were determined by standard methods. Tablet cores were coated with semipermeable cellulosic rate-controlling membranes developed by Alza.

In vitro dissolution methods

Differential release rates were determined by placing each system in a nylon netting mesh bag attached to a plastic rod, which was clamped to a vertically reciprocating platform. Stroke distance and cycle were 6.4 cm and 2 s, respectively. The dissolution medium was contained in rows of tubes positioned in a 37°C water bath. Systems were immersed for a predetermined interval (usually 1 or 2 h) before being transferred to tubes containing fresh solution. Mixing was achieved through the vertical motion of the plastic rod and mesh bag. Differential release rates (i.e. the amounts of drug released per hour) were estimated by dividing the drug content in each tube by the immersion time in hours. This method was used to compare different dissolution media, including: (1) distilled water; (2) isotonic saline; and (3) simulated gastric fluid for 2 h followed by simulated intestinal fluid without enzymes for the remainder of the experiment.

Cumulative release profiles were determined by using the USP Dissolution Apparatus I and II. Simulated gastric fluid (without enzymes) and normal saline were used as dissolution media, and different stirring rates were examined. In all tests, appropriate volumes of solution were removed periodically and replaced with fresh solution equilibrated to 37°C. Samples were diluted if necessary and analysed using a u.v. spectrophotometer at an appropriate wavelength. The amount of drug released at each point was calculated and summed to give the cumulative amount.

Separate determinations of differential and cumulative release rates were made using the column flow-through method described by Langenbucher & Rettig (1977). The dissolution media used were stimulated gastric fluid (without enzymes) for 2 h, followed by normal saline or simulated intestinal fluid (without enzymes) for the remainder of the test. Experiments were conducted without flow pulsation, since this more closely mirrors conditions encountered in the gut. Pulsation at the normal rate of 130 pulses/min exerted a mechanical pumping action on the Oros system increasing its delivery rate in an unpredictable manner. Systems were positioned in the flow chamber on top of glass beads to achieve laminar (non-turbulent) conditions. The dissolution fluid was not recycled.

Results

System design

The existing pharmacokinetic and pharmacodynamic data for oxprenolol and metoprolol (e.g. Bengtsson *et al.*, 1975; Mason & Winer, 1976) indicated that acceptable levels of β -adrenoceptor blockade can be maintained over 24 h if plasma concentrations remain above 50 ng/ml; statistically significant effects, however, can be achieved at lower concentrations. Since both drugs (oxprenolol in particular) have short plasma elimination half-lives, the goal of the development programme was to produce systems with extended zero-order delivery and total release times exceeding 20 h. Prototype systems were designed to release 90% of their drug content within 20–24 h.

Systems with different total contents and release rates were developed for both drugs, and included 16/260, 10/170, 16/170 and 8/130 oxprenolol Oros, and 19/285, 19/190 and 14/190 metoprolol Oros dosage forms.

The hydrochloride salt used in commercial formulations of oxprenolol was found to be too soluble in water (70% w/v) to maintain ex-

tended zero-order delivery from Oros systems and was replaced by the succinate salt. The 260 and 130 mg amounts of succinate contained in the Oros preparations corresponded to approximately 240 and 120 mg of the hydrochloride salt. It was also found that sodium bicarbonate needed to be added to the core as an osmotic driving agent to achieve the required release profile. An inner microporous film was also inserted around the oxprenolol core to minimize deformation of the semipermeable membrane due to the peristaltic movements of the gut.

Metoprolol fumarate was selected as the sole drug and osmotic driving agent for the metoprolol systems. The 190 and 285 mg quantities of fumarate were approximately equivalent to 200 and 300 mg, respectively, of the tartrate salt in the commercial tablet.

Some properties of the core formulations for oxprenolol and metoprolol systems are listed in Table 1. All values were measured experimentally except for the fraction of drug released at zero order, which was calculated (Theeuwes, 1975).

Table 1 Core properties for oxprenolol succinate and metoprolol fumarate systems

Attribute	Oxprenolol Oros	Metoprolol Oros
Core diameter (mm)	9.5 (16/260)	7.9 (19/190)
Core surface area (cm ²)	2.2 (16/260)	1.65 (19/190)
Core volume (cm ³)	0.23 (16/260)	0.16 (19/190)
Solubility (mg/cm ³)	496*	435
Osmotic pressure of saturated solution (atm)	57*	32.5
Core density (g/cm ³)	1.23	1.25
Fraction of drug released at zero order rate	0.60	0.62

*Oxprenolol succinate + sodium bicarbonate

In vitro release rates

Cumulative release profiles measured by the column flow-through method for the existing commercial slow-release and Oros dosage forms of oxprenolol and metoprolol are shown in Figures 2 and 3, respectively. For both preparations, the Oros systems delivered drug in a more zero-order fashion for a significantly longer period than the commercial slow-release forms. The total durations of release were also significantly extended, and in the case of the 10/170 oxprenolol and 19/285 metoprolol Oros systems exceeded 24 h. With both polymer matrix slow-release forms, a significant part of the total content was rapidly delivered; for Slow Trasicor (Figure 2) 40 to 50% was released

Figure 2 Comparison of the cumulative amount of oxprenolol released *in vitro*, measured by the column flow-through method and expressed as a % of the total content, from a slow-release tablet (■) and from 16/170 (▲) and 10/170 (●) oxprenolol Oros systems.

Figure 3 Comparison of the cumulative amount of metoprolol released *in vitro*, measured by the flow-through method and expressed as % of the total content, from a slow-release tablet (●) and from 19/190 (▲) and 19/285 (■) metoprolol Oros systems.

within the first 2 h of the 12–14 h total delivery period.

A more detailed analysis of the release behaviour of the 16/260 oxprenolol system is presented in Figure 4. This shows that the actual release, measured by the differential method, corresponded closely to the theoretical release behaviour obtained by substituting appropriate values from Table 1 into equations 1 and 2, together with a specific membrane resistance of 3.2×10^3 h.atm/cm. The agreement between actual and theoretical rates for other oxprenolol and metoprolol systems was as good as that for 16/260 oxprenolol Oros.

Comparison of profiles in simulated gastric and intestinal fluids without enzymes, and in normal saline indicated that release rate was independent of the pH of the dissolution medium. This result is illustrated for 16/260 Oros in Figure 4 but was obtained for all systems which were tested.

Release rates obtained by different methods were also similar. Comparisons of the average release rates over 2–12 h estimated by the USP and differential release method (Figure 5) show that *in vitro* drug release was independent of the test apparatus. Release rates in normal saline or simulated gastric fluid obtained with the USP apparatus were also shown to be unaffected by changes in stirrer speed, provided that an upper limit of 100 rev/min was not exceeded. At high speeds, some erratic behaviour in release rate was observed.

During the course of system development the same formulations were tested in different laboratories; no significant differences in results were obtained.

Stability results

Stability studies were undertaken to demonstrate that only minimal and clinically insignificant changes in *in vitro* drug release occurred during storage of the Oros systems. The repro-

Figure 4 Cumulative release and differential release rate profile for 16/260 oxprenolol Oros in normal saline (●), artificial gastric (▲) and intestinal fluid (■) compared to the release rate predicted from the theoretical model (—).

Figure 5 Average release rates for a single batch of 16/260 oxprenolol Oros determined in USP dissolution (■) and differential release apparatus (●) under different test conditions.

ducibility of the release rate profile was assessed under different storage conditions for variable lengths of time. In all experiments, systems were stored in closed amber glass bottles. The profiles presented in Figure 6 for 16/260 oxprenolol Oros illustrates the typical response obtained for both oxprenolol and metoprolol

systems. There was no indication of any significant deterioration in performance after storage for 2 years at 23°C. The results presented in Figure 7 for systems stored at 37 and 51°C for 1 year support the observation that no changes occur in these systems after long-term storage, even under stressed conditions.

Figure 6 Average release rate profiles for a single 16/260 oxprenolol Oros batch stored at 23°C for 0 (●), 12 (■), and 24 (▲) months. The vertical bars are standard deviations of the mean.

Figure 7 Average release rates for a single 16/260 oxprenolol Oros batch stored for 1 year at 23 (●), 37 (■), and 51 (▲) °C. The vertical bars represent standard deviations of the means.

In conclusion, the results presented here demonstrate that Oros systems with the required release characteristics can be produced both for metoprolol and oxprenolol. The systems have the required physicochemical and membrane permeability characteristics to produce substantial drug delivery (~60%) at zero-order rates, and total durations of release sufficiently

long to permit once-daily administration while maintaining an acceptable level of pharmacological response over 24 h. The manufacturing and control methods have also been successfully transferred from research to development laboratories and the stability of the final systems shown to be satisfactory on long-term storage.

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