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Design of sustained-release matrix systems for a highly water-soluble compound, ABT-089

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Abstract

ABT-089 is a potent cholinergic channel modulator under investigation for treatment of cognitive disorders. It is a highly water soluble compound with a short elimination half-life of 1.7 h in dogs. Hydrophilic and hydrophobic matrix systems were designed to investigate the feasibility of prolonged oral delivery of ABT-089 and to explore the preliminary in vitro and in vivo correlations. The sustained-release single and layered matrix tablets were prepared by compression. In vitro release testing using a USP apparatus II was performed for formulation screening. The release rates were modulated by varying concentrations of different types of rate controlling materials and by restricting surface area available for drug release. The transport mechanism of the compound from different types of systems typically followed Fickian diffusion. Based on the in vitro release characteristics, two types of prototype matrix systems were evaluated in beagle dogs. Both formulations provided prolonged plasma levels of ABT-089 above the minimum effective concentration for over 22 h with reduced fluctuation of plasma levels. In vivo drug release from the tablet matrix estimated by deconvolution correlated well with drug release in vitro. In conclusion, prolonged oral delivery of highly soluble ABT-089 was achieved using diffusion controlled matrix systems. The hydrophobic matrix was found to be more effective than hydrophilic matrix in extending the release of the compound. Linear relationships between in vitro and in vivo drug release indicated by the initial results for both types of systems can provide useful information for further formulation development. © 1997 Elsevier Science B.V.

Keywords: Cholinergic channel modulator; Sustained-release; Matrix system; In vitro release; Deconvolution; In vitro/in vivo correlation

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1. Introduction

ABT-089, [2-methyl-3-(2-(*S*)-pyrrolidinylmethoxy)pyridine], is a potent and selective cholinergic channel modulator which is under investigation for treatment of cognitive disorders (Williams and Arneric, 1996) (Fig. 1). Unlike (-)-nicotine, ABT-089 is substantially orally available and has a reduced activation of human ganglionic nicotinic receptors. Hence, it has a reduced propensity to elicit cardiac arrhythmias at high doses (Arneric et al., 1996). The compound is crystalline and thermally stable both in solution and in the solid state. ABT-089 is very soluble in aqueous media at pH values between 1–14 (> 6 g/ml). However, it is eliminated rapidly in vivo with a $t_{1/2}$ of 1.7 h in dogs (Arneric et al., submitted). Multiple dosing is necessary to maintain plasma concentrations above minimum effective concentration (MEC) of 2 ng/ml (Arneric et al., 1996). In addition, preliminary studies have shown that prolonged exposure to ABT-089 with a reduced peak-to-trough ratio is therapeutically beneficial in selected animal models. Therefore, a sustained-release formulation which could be given once daily should be advantageous.

In the present study, various matrix systems of ABT-089 were designed and tested for sustained release of ABT-089. The objectives of the study were (1) to investigate the feasibility of prolonged oral delivery of ABT-089, (2) to evaluate the performance of hydrophilic and hydrophobic matrix systems in retarding the release of this highly soluble compound, (3) to explore the preliminary relationship between in vitro and in vivo drug release from the matrix systems to facilitate further formulation development.

2. Experimental section

2.1. Materials and equipment

The following materials were used in the study: ABT-089·2 HCl (Pharmaceutical Products Division, Abbott Laboratories) (Lin et al., 1997); Hydroxypropyl methylcellulose, Methocel K100M (Dow Chemical Co.); Poly(ethyleneoxide), Polyox® coagulant (Union Carbide Co.); Carnauba wax (J.W. Hanson Co., Inc.); Partially hydrogenated cottonseed oil, Stereotex K (Abitec Co.). All other chemicals and reagents were either AR or HPLC grades and used as received. A Vanderkamp® 600 dissolution tester and a HP8452A UV–VIS diode array spectrophotometer were used to determine the in vitro drug release. An HPLC system consisted of an Applied Biosystems 400 isocratic pump, an ABI 491 high-pressure dynamic mixer, a Hitachi 655A-40 autosampler and a Shimadzu RE-551 fluorescence detector with a Beckman PeakPro data collection system.

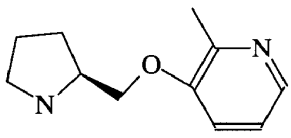
2.2. Formulations

2.2.1. Hydrophilic matrix system

High viscosity grade hydroxypropyl methylcellulose (HPMC) and poly(ethyleneoxide) were used to prepare single and/or layered matrix tablets by direct compression using a Carver hydraulic press. Their compositions are described in Table 1.

2.2.1.1. Single tablet. ABT-089·2 HCl was dry mixed with the polymer and other excipients. The blend was directly compressed into a 300-mg tablet using a concave punch at 4000 lb with a dwell time of 5 s.

2.2.1.2. Layered tablet. Two types of layered tablets were designed, i.e. the hydrophilic matrix containing the drug is coated with hydrophilic barriers on both faces of the tablet by compression (HHH) and the hydrophilic matrix containing the drug is coated with hydrophobic barriers on both faces of the tablet by compression (WHW). Ingredients of the middle and barrier



$C_{11}H_{16}N_2O$, MW = 192.28

Fig. 1. Chemical structure of ABT-089.

Table 1
Hydrophilic matrix system components

Dosage form	Single tablet		Layered tablet					
Label	H1	H2	HHH			WHW		
			Top layer[a]	Middle layer	Bottom layer[a]	Top layer[b]	Middle layer	Bottom layer[b]
ABT-089·2 HCl (%)	10	10	—	51.8	—	—	51.8	—
Methocel® K100M (%)	26	—	54.5	35.0	54.5	10	35.0	10
Polyox® coagulant (%)	—	25	—	—	—	—	—	—
Carnauba wax (%)	—	—	—	—	—	90	—	90
Lactose anhydrous (%)	64	65	45.5	13.2	45.5	—	13.2	—
Total (mg)	300	300	110	80	110	110	80	110

[a]Hydrophilic barrier layer.
[b]Hydrophobic barrier layer.

layers were blended separately. Layered matrix tablets were prepared by compressing the barrier layer at 300 lb followed by middle layer at 300 lb and another barrier layer at 4500 lb using a flat-faced punch with a dwell time of 5 s.

2.2.2. Hydrophobic matrix system

Carnauba wax (W1–W3) and partially hydrogenated cottonseed oil (W4–W7) were used as the rate controlling materials to prepare hydrophobic matrix tablets by compression using a Carver press. The formulations of the matrices are listed in Table 2. Drug and other excipients were blended and slowly added to molten wax at ~95°C and mixed thoroughly. The mixture was allowed to congeal at room temperature while mixing. The congealed solids were milled and passed through a 30 mesh screen. The tablets were prepared with a concave punch by compressing at 4500 lb with a dwell time of 5 s. The chemical stability of ABT-089 (m.p., 210°C) in the formulation was confirmed by potency assay.

2.3. In vitro release

The in vitro release tests were performed using the USP apparatus II (paddle method). The dissolution medium was 900 ml of distilled water maintained at 37 ± 0.5°C. The paddle rotation speed was kept at 100 rev./min. Water was used as the initial dissolution medium because of extremely high solubility of ABT-089 at different pH. In all

Table 2
Hydrophobic matrix system components

Formulation	W1	W2	W3	W4	W5	W6	W7
ABT-089·2 HCl (%)	13.8	13.8	13.8	13.8	13.8	13.8	13.8
Carnauba wax (%)	60	55	50	—	—	—	—
Sterotex K wax (%)	—	—	—	55	51	48	40
Lactose anhydrous (%)	26.2	31.2	36.2	31.2	35.2	38.2	46.2
Total (mg)	300	300	300	300	300	300	300

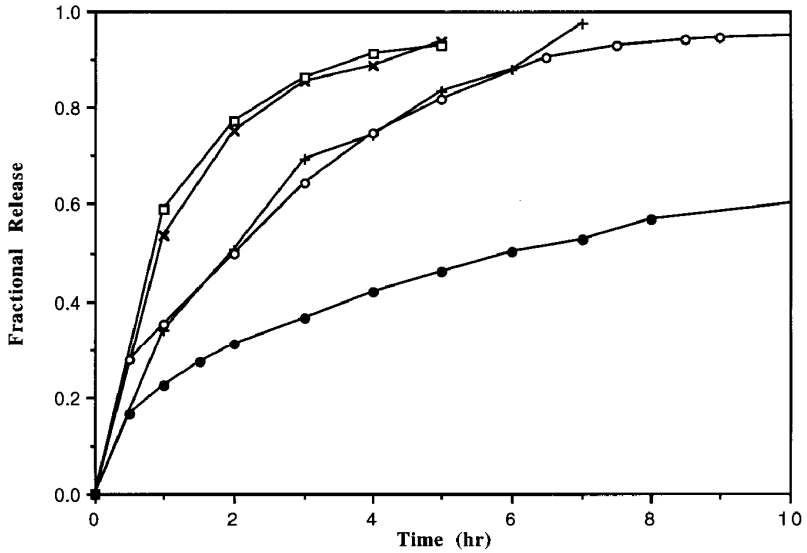


Fig. 2. In vitro release profiles of different types of hydrophilic matrices of ABT-089 containing [×] 26% Methocel K100M (H1); [□] 25% Polyox coagulant (H2); [+] 35% Methocel K100M with hydrophilic barrier layers (HHH) and [○] 35% Methocel K100M with hydrophobic barrier layers (WHW) compared with a hydrophobic matrix containing [●] 55% Carnauba wax (W2) (24 h data not shown).

experiments, 3.0 ml dissolution samples were withdrawn at predetermined time intervals for up to 24 h, and replaced with equal volumes of the fresh medium to maintain the total volume constant. Samples were filtered through a filter (4.5 μm) and assayed by UV spectrophotometry at 276 nm.

2.4. In vivo studies

Based on the in vitro release, a layered hydrophilic matrix (HHH) and a simple hydrophobic matrix (W2) with significantly differing in vitro release rates were assessed in a series of studies in a group of six beagle dogs. Animals were handled according to protocols approved by Abbott's Institutional Animal Care and Use Committee. Each study was carried out at least 1 week apart. An oral aqueous solution of ABT-089 and an immediate-release capsule were used as references.

The preliminary evaluation of the matrix formulations HHH was carried out in a sub-group of three animals. The animals were fasted overnight prior to dosing but were permitted water ad libitum. Each animal received a single tablet containing 30 mg of ABT-089 followed by ~10 ml of water. Under this fasting dosing regimen, food was returned to each animal 12 h after dosing.

A second study evaluated the matrix formulation W2 with the release rate slower than matrix HHH. The formulation was orally administered to a group of six fasting animals using the same protocol as described above.

Sequential blood samples were obtained from each animal prior to dosing and at selected time points post dosing interval in each of the studies outlined above. The blood sampling schemes were 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 9.0, 12.0 h for the immediate-release formulations and 0, 0.25, 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 9.0, 12.0, 15.0 and 24.0 h for the sustained-release tablets, respectively. Plasma was separated by centrifugation (2500 rev./min × 10 min, 4°C) and frozen (− 30°C) until analyzed. The plasma concentrations of ABT-089 were determined by a validated method of reverse phase HPLC following pre-column fluorescent derivatization (Hui and Marsh, 1995).

Table 3
Results of linear regression of fractional release (F) vs square-root-of-time ($t^{1/2}$) for hydrophilic and hydrophobic sustained-release matrices of ABT-089

Matrix system	Release rate constant ($h^{-1/2}$)	Intercept	Coefficient of Determination (R^2)
H1	0.449	0.105	0.9983
HHH	0.424	−0.082	0.9752
WHW	0.355	0.015	0.9947
W1	0.162	0.043	0.9952
W2	0.188	0.039	0.9985
W3	0.205	0.013	0.9967
W4	0.115	0.045	0.9928
W5	0.181	0.071	0.9940
W6	0.201	0.098	0.9952
W7	0.287	0.071	0.9906

2.5. Data analysis

The area under the plasma concentration–time curve from time zero to the last sampling time point t (AUC_t) was calculated by the trapezoidal rule. The AUC values were normalized on the basis of dog weights. Deconvolution was performed in order to evaluate the rate of drug release/absorption. Plasma concentration data following oral administration of the solution were fitted to polyexponentials (PROC NLIN of SAS, version 6.09, of SAS Institute, Cary, NC and RSTRIP of Micromath®, Salt Lake City, UT) and used as the unit impulse response, $C_\delta(t)$. Drug plasma data from tablet formulations $C(t)$ were fitted to a smoothing cubic spline function and then deconvoluted with $C_\delta(t)$ using program PCDCON (W.R. Gillespie, FDA) to estimate in vivo drug release from the matrix formulations.

3. Results and discussion

Physicochemical properties of a compound are important to drug absorption as well as the design of the delivery system. Due to extremely high aqueous solubility of ABT-089, hydrophobic and hydrophilic matrix systems with or without restricted release area were tested to control the drug release.

3.1. In vitro release kinetics

Fig. 2 compares drug release profiles of different types of matrix formulations. Each curve typically represents the mean of three replicates. Overall, low variability was observed in the release profiles (CV < 5%).

3.1.1. Hydrophilic matrix system

The release of a dispersed drug from a non-crosslinked hydrophilic polymer matrix system can be related to time according to Eq. (1) (Hogan, 1989):

$$F = kt^n \quad (1)$$

where F is the fraction released at time t, k is a constant incorporating characteristics of the macromolecular network system and the drug, and n is an exponent characteristic of the transport mechanism. Eq. (1) is a generalized semi-empirical equation that describes two apparently independent mechanisms of drug transport from a matrix system, i.e. a Fickian and a non-Fickian mechanism. ABT-089 was homogeneously dispersed throughout the hydrophilic polymer matrix. Because of its high solubility, Fickian diffusion is expected to be a predominant release mechanism. Thus, an approximately linear relationship between fractional release and the square root of time was obtained for this system (Table 3). The drug release from the single layer matrices

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