ELSEVIER

International Journal of Pharmaceutics 157 (1997) 43–52

international journal of pharmaceutics

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

Yihong Qiu *, Kolette Flood, Kennan Marsh, Sherry Carroll, Jay Trivedi, Stephen P. Arneric, Steven L. Krill

Pharmaceutical Products Division, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, IL 60064-3500, USA

Received 28 April 1997; received in revised form 27 June 1997; accepted 2 July 1997

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

* Corresponding author. Abbott Laboratories, Formulation Development Center, D-4P7/R1B, 1401 N. Sheridan Rd., North Chicago, IL 60064, USA. Tel: +1 847 9385220; fax: +1 847 9351997; e-mail: yihong.qiu@abbott.com

PII S0378-5173(97)00215-9

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.

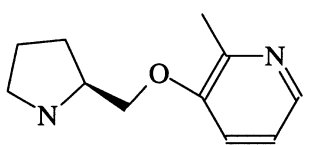
2.2. Formulations

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

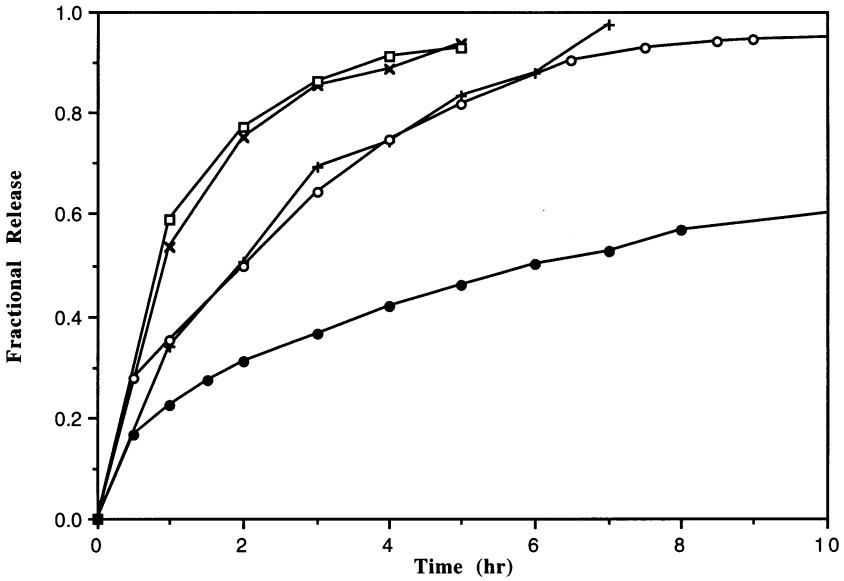


Fig. 2. In vitro release profiles of different types of hydrophilic matrices of ABT-089 containing [×] 26% Methocel K100M (H1); [□] 25% Polyox coagulant (H2); [+] 35% Methocel K100M with hydrophilic barrier layers (HHH) and [○] 35% Methocel K100M with hydrophobic barrier layers (WHW) compared with a 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 $\sim$ 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

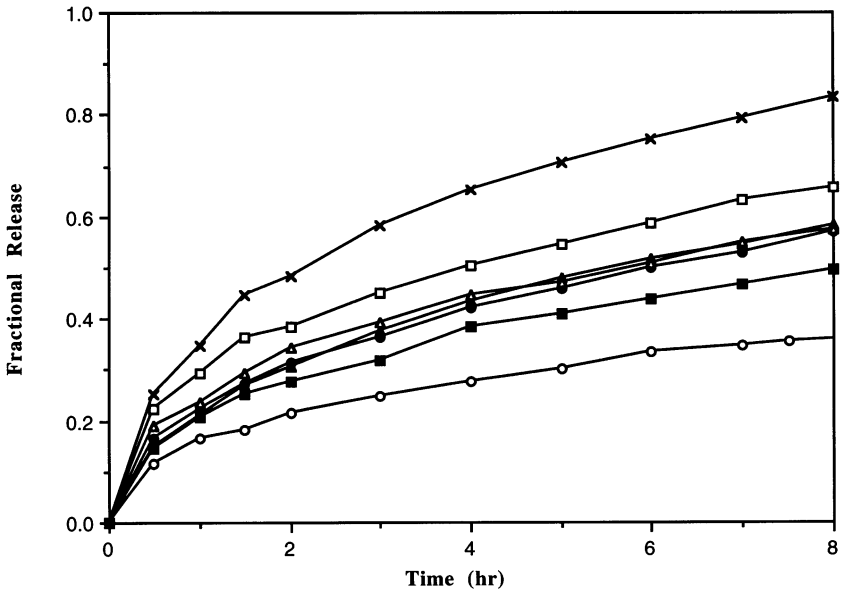


Fig. 3. Comparison of ABT-089 release profiles from hydrophobic matrices containing [△] 50% (W3); [●] 55% (W2); [■] 60% Carnauba wax (W1), and [×] 40% (W7); [□] 48% (W6); [▲] 51% (W5) and [○] 55% (W4) Sterotex K (24 h data not shown).

was rapid. Approximately 90% of the drug was released in the first 3–4 h. Rapid release was likely due to the high solubility as well as high diffusivity of ABT-089 since two matrices containing polymers of differing viscosities resulted in the same release rates at a relatively high polymer concentration.

3.1.2. Three-layer hydrophilic matrix system

Drug release rate is not only dependent on diffusion coefficient, diffusion path length and concentration gradient, but also on the surface area available for release. Hence, reduction of releasing area was used to modulate the dissolution rate of ABT-089. A hydrophilic matrix containing the drug was sandwiched with soluble/swellable barriers on both bases of the tablet by compression. In this system, the release of drug from the middle layer was effectively slowed by delaying or preventing drug diffusion from the two base surfaces. The early release of the drug occurred from the greatly reduced surface along the peripheral wall. Complete release can be achieved as a result of polymer dissolution over a prolonged period of time (e.g. 24 h). Fig. 2 indicates that the release rate of ABT-089 from the HHH system was significantly retarded. A different hydrophilic layered matrix, WHW, was prepared by applying hydrophobic insoluble barriers on both bases of the tablet. It was observed that the drug release rate of the system WHW was similar to that of HHH system. The fact that both insoluble and soluble barriers are equally effective in decreasing the release rate suggests that the middle layer hydrates and erodes more rapidly than the soluble barrier layers. Complete release was also obtained as the middle layer was completely hydrated and eroded by 24 h. The drug release from matrix WHW also followed a square-root of time relationship. Although decreased release rate had been obtained with the layered matrices, the overall drug release was still relatively fast, possibly a result of both high solubility and diffusivity of ABT-089. To further extend the release of ABT-089 from the dosage form, hydrophobic matrix systems were tested.

3.1.3. Hydrophobic matrix system

Hydrophobic inert matrix is one of the well developed matrix systems used for sustained drug delivery because of its effectiveness and low cost,

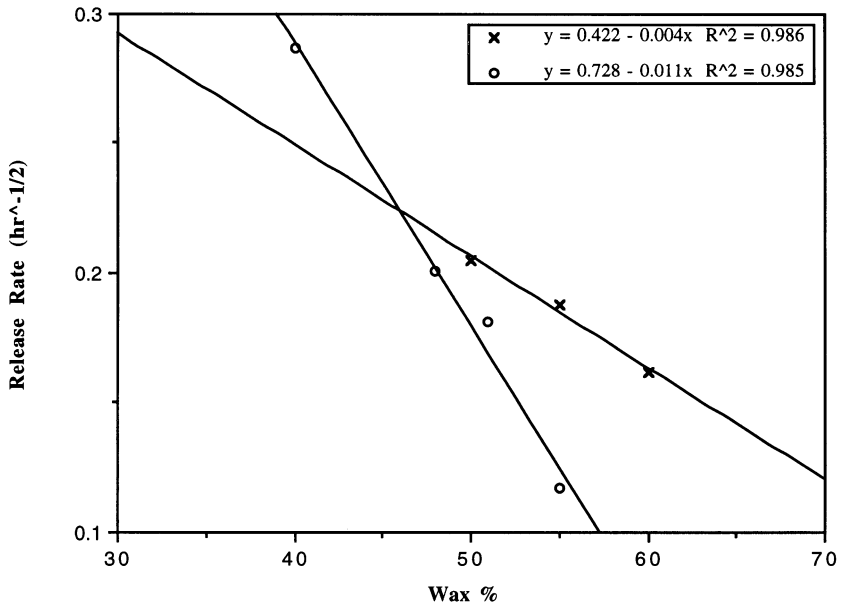


Fig. 4. Release rates versus percent wax of different hydrophobic matrices ([×]: Carnauba wax; [○]: Sterotex K).

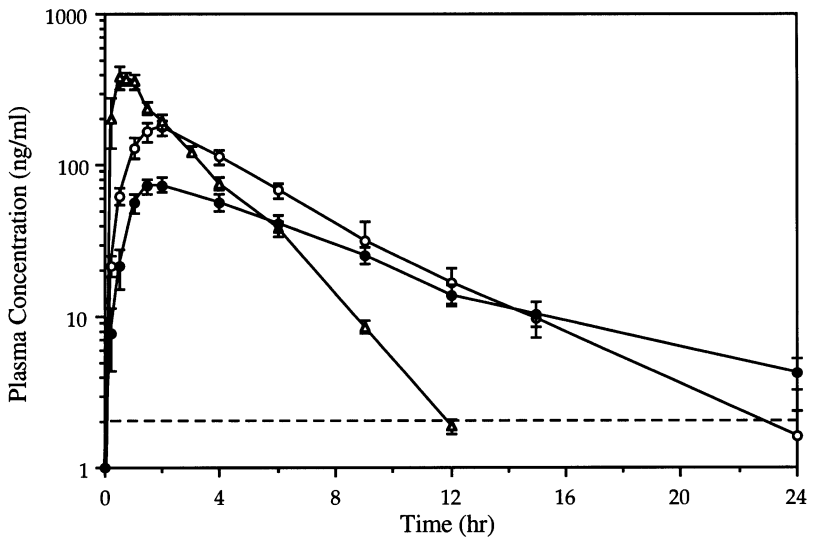


Fig. 5. Plasma concentration–time profiles of ABT-089 in dogs after a single oral dose of [△] an immediate-release (IR) capsule, [○] a layered hydrophilic matrix containing 35% Methocel K100M (HHH) and [●] a hydrophobic matrix containing 55% carnauba wax (W2) in the fasted state; [—] MEC (mean ± S.E., Dose = 3.0 mg/kg).

especially for highly water-soluble compounds. There have been many studies concerning the matrix system and its variations with modified release kinetics (Higuchi, 1963; Desai et al., 1965; Foster and Parrott, 1990; Scott and Hollenbeck, 1991; Lee, 1992; Otsuka and Matsuda, 1994, 1995; Hildgen and McMullen, 1995). Compared with other delivery systems, this type of matrix is relatively insensitive to changes in release environment because diffusion from the noneroding ma-

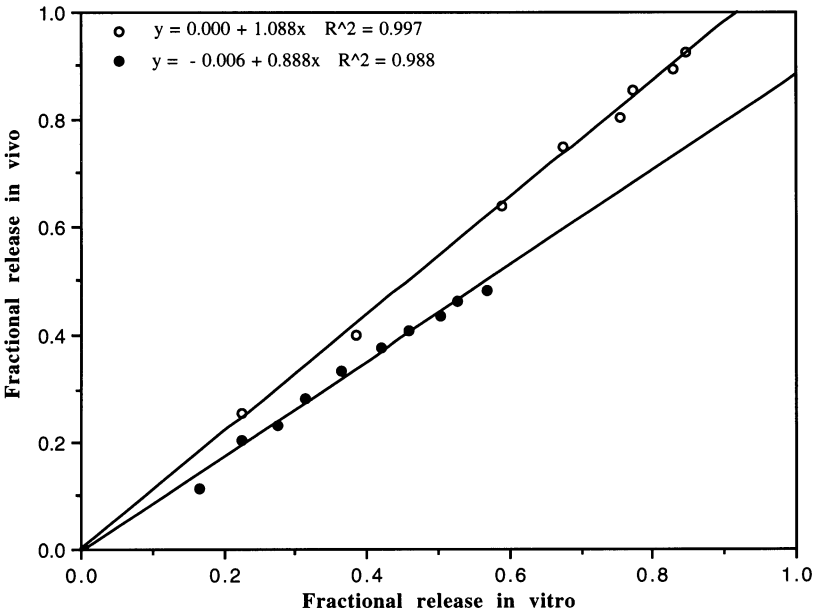


Fig. 6. Correlations between in vitro and in vivo release of ABT-089 from [○] a layered hydrophilic matrix containing 35% Methocel K100M (HHH) and [●] a hydrophobic matrix containing 55% carnauba wax (W2).

trix is the rate controlling factor (Desai et al., 1965). The release mechanism of a heterogeneous matrix is diffusion through aqueous channels formed by dissolution of the drug and soluble excipients in the formulation. Based on sink conditions and pseudo-steady-state approximation (drug loading per unit volume, A, $\gg$ solubility, Cs), Higuchi (1963) developed an approximate analytical solution for a rigid planar matrix, i.e.

$$\frac{M_t}{M_\infty} = \frac{1}{M_\infty}\left[\epsilon Cs(2A - \epsilon Cs)\frac{D}{\tau}t\right]^{\frac{1}{2}} \quad (2)$$

where M_t and M_∞ are the amounts released per unit area at t and infinity, respectively. D is the diffusion coefficient of the drug in the medium, ϵ is porosity and τ is tortuosity of the matrix.

In the present study, the use of a hydrophobic carnauba wax matrix significantly decreased release rates of ABT-089 as demonstrated in Fig. 3. The release mechanism from the non-swellable matrix system followed typical Fickian diffusion that can be described by Eq. (2) (Table 3).

Carnauba wax was found to be effective in controlling the release of ABT-089. However, the formulation suffered from rapid hardening and sticking which caused difficulty in cleaning equipment. In order to overcome this problem, partially hydrogenated cottonseed oil (Sterotex K), with a melting point similar to carnauba wax, was evaluated as a hydrophobic rate controlling material. Drug release profiles comparing hydrophobic matrix formulations containing different percentages of carnauba wax (W1–W3) and Sterotex K (W4–W7) are shown in Fig. 3. The release rates of Formulations W1–W7 were determined by fitting the in vitro release data to Eq. (2) (Table 3). It was found that approximately linear relationships between drug release rate and percent wax in the formulations were obtained for carnauba wax as well as Sterotex K formulations (Fig. 4). As can be seen, the formulations containing carnauba wax resulted in a comparatively higher release rate than those containing Sterotex K at the concentrations above approximately 46%. The rate of drug release also changed more rapidly with wax concentration for formulations containing Sterotex K. This observation may be attributed, at least in part, to the difference in hydrophobicity between the two wax materials. More hydrophobic trigylerides (Sterotex K) might

be more effective in preventing the penetration of water and/or interaction with water than esters of hydroxylated unsaturated fatty acid (Carnauba wax).

3.2. In vivo absorption

Fig. 5 shows the plasma concentration–time profiles of ABT-089 following single oral administration of the two matrix formulations in dogs as compared with an immediate-release capsule formulation. Prolonged absorption was achieved with both sustained-release formulations, providing plasma levels of ABT-089 above the minimum effective concentration (Arneric et al., 1996) of 2 ng/ml for over 22 h. Qualitative comparison of the two formulations relative to the reference suggested that the sustained effects were in the same rank order as the in vitro drug release. Preformulation and animal studies had indicated that ABT-089 is stable at intestinal pH and efficiently absorbed throughout the whole intestinal tract (unpublished data). This was indirectly supported in the current study by the fact that complete absorption relative to an ABT-089 solution was achieved with the hydrophilic matrix (HHH) and that absorption of a compound having a very short half-life was extended beyond the time frame of small intestine transit in dogs.

In the fasted state, estimates of bioavailability relative to oral solution were $103.6 \pm 6.2\%$ and $59.9 \pm 14.0\%$ for the hydrophilic (HHH) and the hydrophobic (W3) matrix, respectively. The hydrophobic matrix provided a smaller fluctuation ratio ($C_{max}/C_{24\,h}$) of the plasma levels. The more prolonged absorption corresponding to the lower extent of absorption was not unexpected as formulations with slower release rates could be expelled from the body prior to the completion of the drug release. It is known that the average transit time in the entire gastrointestinal tract in fasted dogs is about 13 h (Davies and Morris, 1993).

The in vivo release of the drug from matrices was estimated by deconvolution of plasma profiles based on linear system analysis (Cutler, 1978). Plasma concentration data for each dog following administration of the oral solution were fitted to polyexponentials and used as unit impulse response $C_\delta(t)$. Drug plasma data of the tablet formulations from the same dog, $C(t)$, were deconvoluted with $C_\delta(t)$ to obtain in vivo drug release from the matrix formulations. The cumulative percent of the dose released in the GI tract, i.e. 'GI bioavailability' (Gillespie and Veng-Pedersen, 1985) of both matrices were estimated by the plateau values from respective in vivo release profiles at 24 h. The bioavailability estimates were $105.7 \pm 6.5\%$ for the hydrophilic system and $61.7 \pm 13.8\%$ for the hydrophobic system, respectively. The results closely match the relative bioavailability data calculated based on AUC, suggesting formulation release-controlled apparent absorption.

3.3. In vitro/in vivo correlation

The establishment of a relationship between the in vivo input rate and in vitro drug release from the dosage form is an important part in the formulation development process. A validated relationship between in vitro and in vivo release can be useful in setting up a meaningful in vitro quality control procedure that is predictive of product performance and can justify a change in formulation (Skelly et al., 1990).

The preliminary in vitro/in vivo correlations for ABT-089 sustained-release tablets were explored by comparing the in vitro release data with in vivo drug release obtained from deconvolution. The results in Fig. 6 demonstrate linear correlations between in vivo and in vitro release for both matrix systems. A slope of 1.09 with an intercept of zero was obtained for the hydrophilic matrix, indicating a near 1:1 relationship. A slope of 0.89 along with a near zero intercept also shows a good linear relationship between in vitro and in vivo release for the hydrophobic matrix. Overall, the in vivo drug release rate was slightly slower compared with the in vitro drug release. It has been well recognized that separate in vitro/in vivo correlations are generally obtained for different types of products of the same drug (Skelly et al., 1990).

4. Conclusions

In summary, the present study demonstrated that prolonged oral delivery of ABT-089 with reduced fluctuation of plasma levels can be achieved using matrix systems. However, it is difficult to obtain sustained delivery over a longer period of time with hydrophilic matrix systems for a compound having extremely high solubility and diffusivity, such as ABT-089. Hydrophobic matrix is more effective in extending the release of this type of compound. Therefore, use of either insoluble heterogenous matrix or reservoir system may be necessary in order to develop an once-daily formulation of ABT-089 for humans.

Acknowledgements

Technical assistance from Lisa Ruiz is appreciated. The authors also would like to thank Drs P.K. Gupta and S. Silvestri for helpful discussions, Dr W. Gillespie for providing the PCDCON program.

References

Arneric, S.P., Bannon, A.W., Briggs, C.A., Brioni, J.D., Buccafusco, J.J., Decker, M.W., Gopalakrishnan, M., Holladay, M.W., Kyncl, J., Lin, N.H., Marsh, K.G., Qiu, Y., Radek, R., Donnelly-Roberts, D.L., Sullivan, J.P., Williams, M., 1996. ABT-089: an orally active cholinergic channel modulator (ChCM) with cognitive enhancing and neuroprotective activity. In: Becker, R., Giacobini, E., Robert, P. (Eds.), Alzheimer's Disease: From Molecular Biology to Therapy. Birkhäuser, Boston.

Arneric, S.P., Campbell, J.E., Holladay, M.W., Johnson, P., Lin, N.H., Marsh, K.G., Petersen, B., Qiu, Y., Roberts, E.M., Rodrigues, A.D., Sullivan, J.P., Trivedi, J., Williams, M., submitted. ABT-089 [3-(2-(*S*)-pyrrolidinylmethoxy)-2-methyl-pyridine]: III. An orally effective cholinergic channel modulator with potential once-a-day dosing and cardiovascular safety. Drug Development Research, in press.

Cutler, D., 1978. Linear system analysis in pharmacokinetics. Journal of Pharmacokinetics and Biopharmaceutics 6, 265–282.

Davies, B., Morris, T., 1993. Physiological parameters in laboratory animals and humans. Pharmaceutical Research 10, 1093–1095.

Desai, S.J., Simonelli, A.P., Higuchi, W.I., 1965. Investigation of factors influencing release of solid drug dispersed in inert matrices. Journal of Pharmaceutical Sciences 54, 1459–1464.

Foster, T.P., Parrott, E.L., 1990. Release of highly water-soluble medicinal compounds from inert, heterogeneous matrixes. I: Physical mixture. Journal of Pharmaceutical Sciences 79, 806–810.

Gillespie, W., Veng-Pedersen, P., 1985. A polyexponential deconvolution method. Evaluation of the 'gastrointestinal bioavailability' and mean in vivo dissolution time of some ibuprofen dosage forms. Journal of Pharmacokinetics and Biopharmaceutics 13, 289–307.

Higuchi, T., 1963. Mechanism of sustained-action medication. Journal of Pharmaceutical Sciences 52, 1145–1150.

Hildgen, P., McMullen, J.N., 1995. A new gradient matrix formulation and characterization. Journal of Controlled Release 34, 263–271.

Hogan, J.E., 1989. Hydroxypropylmethylcellulose sustained release technology. Drug Development and Industrial Pharmacy 15, 975–999.

Hui, Y., Marsh, K.C., 1995. Sensitive detection of selected cholinergic channel activators derived with 7-fluoro-4-nitrobenzo-2-oxa-1,3-diazole. Journal of Pharmaceutical and Biomedical Analyses 14, 131–142.

Lee, L., 1992. In: Kydonieus, A. (Ed.), Treatise on Controlled Drug Delivery: Diffusion-Controlled Matrix Systems. Marcel Dekker, New York, pp. 155–198.

Lin, N.H., Gunn, D.E., Ryther, K.B., Garvey, D.S., Donnelly-Roberts, D.L., Decker, M.W., Brioni, J.D., Buckley, M.J., Rodrigues, A.D., Marsh, K.G., Anerson, D.J., Sullivan, J.P., Williams, M., Arneric, S.P., Holladay, M.W., 1997. Structure-activity studies on ABT-089: an orally bioavailable 3-pyridyl ether cholinergic channel moderator with cognitive enhancing properties. Journal of Medicinal Chemistry 40, 385–390.

Otsuka, M., Matsuda, Y., 1994. Controlled drug release of highly water-soluble pentoxifylline from time-limit disintegration-type wax matrix tablets. Pharmaceutical Research 11, 351–354.

Otsuka, M., Matsuda, Y., 1995. Programmable drug release of highly water-soluble pentoxifylline from dry-coated wax matrix tablets. Journal of Pharmaceutical Sciences 84, 443–447.

Scott, D.C., Hollenbeck, R.G., 1991. Design and manufacture of a zero-order sustained-release pellet dosage form through nonuniform drug distribution in a diffusional matrix. Pharmaceutical Research 8, 156–161.

Skelly, J.P., et al., 1990. In vitro and in vivo testing and correlation for oral controlled/modified-release dosage forms. Pharmaceutical Research 7, 975–982.

Williams, M., Arneric, S.P., 1996. Alzheimer's disease: Prospects for treatment in the next decades. In: Brioni, J.D., Decker, M.W. (Eds.), Alzheimer's Disease. Wiley-Liss, New York, 1996.