J. Pharm. Pharmacol. 1992, 44: 623–625
Communicated October 10, 1991

An in-vitro comparison of controlled release aminophylline tablets: Phyllocontin Continus and Pecram

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Abstract—It has been suggested that two controlled release preparations containing aminophylline, Phyllocontin Continus and Pecram, are clinically equivalent and are therefore interchangeable. In this study, an in-vitro evaluation of the two preparations was completed using the British Pharmacopoeia dissolution apparatus, initially using water and then an acid/buffer medium to provide a similar pH environment to that within the gastrointestinal tract. Similar release profiles were found when water was used as the dissolution medium, with very little variation between tablets within each group. Good fits were obtained for dissolution-controlled release and diffusion-controlled release models. When the acid/buffer solution was used as the dissolution medium a reduction in the rate of release was observed with Phyllocontin. It was predicted that if this was repeated in-vivo then differences in the peak plasma levels between the two formulations would be seen, although these may be masked by the other variables encountered.

There has been recent controversy in the UK pharmaceutical press regarding the interchangeability of controlled release preparations containing aminophylline. It has been suggested from in-vivo studies that two preparations, Pecram and Phyllocontin Continus, are clinically equivalent and are therefore interchangeable (Crawford et al 1989). Thus an in-vitro study was performed to allow the comparison of these dosage forms under controlled experimental conditions that would permit the detection of dose dumping and any subtle formulation effects that may be masked in-vivo.

Materials and methods

Materials. Phyllocontin Continus tablets were from Napp Laboratories Ltd (Cambridge, UK) and Pecram was from Zyma (UK) Ltd (Cheshire, UK). Sodium phosphate dihydrate, tetrahydrofuran, acetic acid and HCl were obtained from BDH Chemicals Ltd, Poole, UK.

Methods. The rate of release of aminophylline into water was determined for 12 tablets each of Pecram and Phyllocontin in a dissolution apparatus (Model 6ST, Caleva Instruments Ltd, Ascot, UK) conforming to the standards laid down in the British Pharmacopoeia 1988, using paddles rotated at 75 rev min^{-1}. The concentration of drug in the dissolution medium was monitored every 10 min using a UV spectrophotometer (Ultrospec II, Pharmacia LKB Biochrom Ltd, Cambridge, UK) at a wavelength of 289 nm and the data collected and analysed using a computer programme supplied by Copley Instruments Ltd (Nottingham, UK). On completion of each experiment, HPLC analysis was performed to confirm that no other compounds released from the tablets during the dissolution experiments interfered with the spectrophotometric assay of aminophylline. A Waters 6000 HPLC pump with a Rheodyne 7125 valve loop injector and Waters 450 UV detector was used for the assay. Chromatography was on an ODS μBondapak column with a mobile phase of tetrahydrofuran, 0·6% acetic acid in water (flow rate 1·5 mL min^{-1}).

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In a similar procedure to that described by Li Wan Po et al (1990), appropriate drug release models were fitted to the data obtained over the first 3·5 h of the experiment. The 'goodness of fit' was expressed in terms of the correlation coefficient (r). Sheiner & Beal (1981) have argued that the mean square error provides a better measure of the goodness of fit, and this was also calculated in this study.

The rate of release from 6 tablets each of Phyllocontin and Pecram into solutions that more closely matched in-vivo pH conditions was investigated. One litre of 0·01 M HCl was used as the dissolution medium for the first hour (stomach pH), then 2·1 g of sodium phosphate dihydrate added to adjust the pH from 2 to 6 for the next 23 h (small intestine pH). A procedure for mathematically producing projected in-vivo data from in-vitro dissolution studies (Welling 1983; Buckton et al 1988) was used to illustrate the possible therapeutic consequences of differences in the drug release profiles in-vivo. The assumptions made in this mathematical model are that drug release rates in-vivo are similar to those in-vitro, drug release is the rate limiting step of drug absorption, all of the dose administered is absorbed and avoids first pass metabolism, the plasma half-life is 8 h, the volume of distribution is 0·5 L kg^{-1} and the subject is a healthy, nonsmoking, 70 kg male.

Results

Little difference was seen when water was used as the dissolution medium (Fig. 1). The variation in the release profiles between tablets within each group was small. The HPLC analysis confirmed that aminophylline and no other component of the formulation contributed to the UV absorbance. Although all the

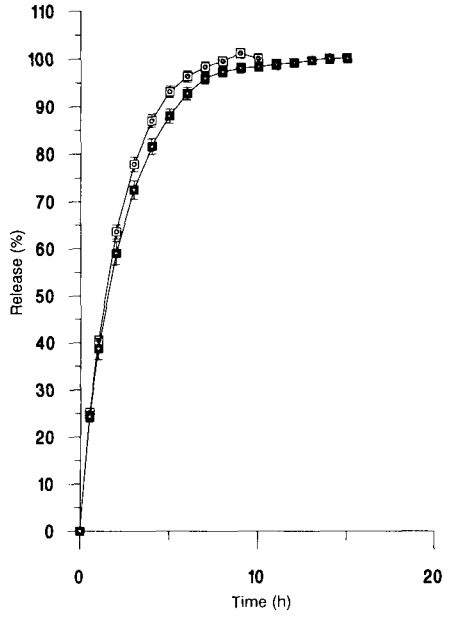

FIG. 1. Release of aminophylline into water (n = 12, bars represent s.d.). Pecram, □; Phyllocontin, ■.

Table 1. The goodness of fit for models for the release of aminophylline from Phyllocontin Continus tablets into water.

Model	Equation	r	MSE
Zero order	$Mt/M_\infty = kt$	0·966	1·139
1st order	$Ln(1-M_t/M_\infty) = -kt$	0·941	1·153
Higuchi	$(1-M_t/M_\infty)^2 = -kt$	0·997	1·253
Roseman & Higuchi (1970)	$M_t/M_\infty + (1-M_t/M_\infty \ln(1-M_t/M_\infty) = kt$	0·996	1·129
Hixson & Crowell (1931)	$(1-M_t/M_\infty)^{1/3} = -kt$	0·992	1·068

MSE, mean square error.

Table 2. The goodness of fit for models for the release of aminophylline from Pecram tablets into water.

Model	Equation	r	MSE
Zero order	$M_t/M_\infty = kt$	0·968	1·136
1st order	$Ln(1-M_t/M_\infty) = -kt$	0·938	1·149
Higuchi	$(1-M_t/M_\infty)^2 = -kt$	0·996	1·251
Roseman & Higuchi (1970)	$M_t/M_\infty + (1-M_t/M_\infty \ln(1-M_t/M_\infty) = kt$	0·995	1·121
Hixson & Crowell (1931)	$(1-M_t/M_\infty)^{1/3} = -kt$	0·996	1·121

MSE, mean square error.

models provided reasonable fits to the data, the most appropriate models for aminophylline release from both Phyllocontin Continus and Pecram tablets were the Roseman & Higuchi (1970) and Hixson & Crowell (1931) models (Tables 1, 2). A plot of residuals obtained from regression analysis against time did not suggest that either of these two models provided a superior fit to the data. The residuals plot also indicated that the large mean square error obtained with the Higuchi model of drug release was due to an abnormally large error at time zero in both cases.

A more pronounced difference was observed in the release profiles when the simulated in-vivo system was used (Fig. 2). The rate of release from Phyllocontin tablets was significantly reduced under these conditions (Table 3).

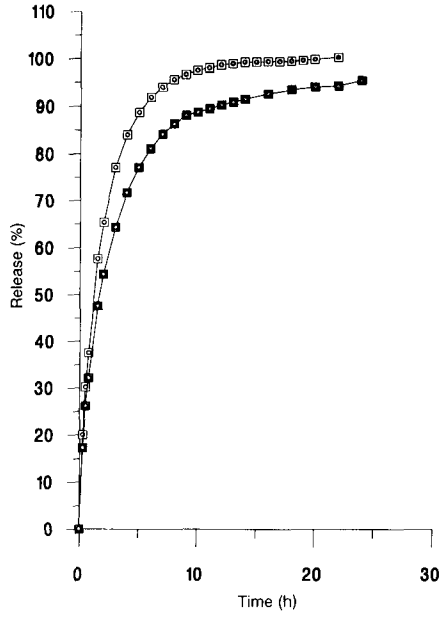

FIG. 2. Release of aminophylline into an acid/buffer solution (n = 6). Pecram, □; Phyllocontin, ■.

Table 3. The time required for 50% (T50) and 75% (T75) aminophylline to be released from tablets of Phyllocontin and Pecram.

Formulation	Dissolution medium	T50 (min) (s.d.)	T75 (min) (s.d.)
Phyllocontin (n = 12)	Water	79 (7·6)	176 (11·2)
Pecram (n = 12)	Water	81 (3·1)	165 (7·2)
Phyllocontin (n = 6)	Acid/buffer	99 (3·7)	285 (6·3)
Pecram (n = 6)	Acid/buffer	74 (0·7)	169 (2·7)

Discussion

Both preparations exhibit similar release profiles into water and the data obtained provide good fits for mathematical models designed for diffusion controlled drug release from non-erodible cylindrical matrices under sink conditions (Roseman & Higuchi 1970) and for dissolution controlled drug release for systems that do not dramatically change in shape (Hixson & Crowell 1931). Phyllocontin Continus tablets consist of pellets of the drug and a hydroxyalkylcellulose, incorporated into a matrix of a higher aliphatic alcohol. Pecram consists of primary granules containing the active ingredient in a secondary matrix consisting of a water soluble/dispersible slow release wax. The relative complexity of these formulations may explain why no single model appears wholly appropriate for these formulations, as drug release is controlled by more than one process. From the similarity of the goodness of fit data and the release profiles into water, there appears to be little indication of differences between the rate and mechanism of drug release from these two preparations. However, the reduced rate of drug release from the Phyllocontin tablets into the simulated in-vivo solution suggests that this formulation may be pH sensitive. These differences and their potential therapeutic consequences are illustrated by pharmacokinetic modelling (Fig. 3).

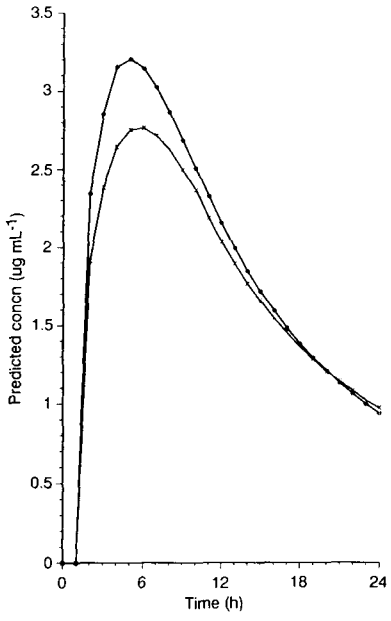

FIG. 3. Simulated plasma concentration obtained using rate of release data for Pecram (O) and Phyllocontin (×) into an acid buffer solution.

In the light of the assumptions made with this mathematical model, these extrapolations have to be treated with caution (the conditions within a British Pharmacopoeia dissolution test vessel are clearly very different to those experienced by a dosage form within the gastrointestinal tract). However, it is suggested from this work that on single dosing Pecram would obtain a higher peak plasma level at a slightly faster rate than Phyllocontin.

It may be concluded from this investigation that differences between the two formulations were detected in-vitro which may result in differing performances in-vivo. However, these differences are small and could be masked by other, larger, sources of variation experienced on in-vivo evaluation.

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J. Pharm. Pharmacol. 1992, 44: 625–626

Book Review

Power and Dependence: Social Audit on the Safety of Medicines
By Charles Medawar
Edited by Elaine Rassaby and Brian Guthrie
Published 1992 Social Audit Ltd, London
283 pages
ISBN 0 946448 04 3 £10.00 paperback

If you are a pharmaceutical scientist or a member of a health profession, this is an important book to read. It will not be an easy read because you will find on most pages statements or assertions which you will believe to be untrue, distorted or simple exaggerations. Consequently, the immediate temptation will be to discard the book, determined not to waste more of your time with it. That would be a mistake.

You will ignore this book at your peril. It expresses the other man's point of view. This particular author is persuasive, his book tells us how other people see the pharmaceutical industry, what others think of the regulations governing the introduction and periodic review of medicines. Eventually the book will need answering, either through better public relations or, preferably, through a more open approach by industry and the regulatory authorities.

Social Audit is an independent 'watch-dog' organization first set up in 1971, and this book comes out of a project funded for the Public Interest Research Centre by the Rowntree Charitable Trust. Charles Medawar is also a member of the advisory council of the Drug & Therapeutics Bulletin; and has been associated with patients involved in litigation with the manufacturers of the non-steroidal anti-inflammatory drug, Opren, with patients infected with HIV through contaminated blood products, and more recently the developing benzodiazepine litigation. Medawar's attitude to the pharmaceutical industry, some of its products and the various regulatory committees and procedures, is thus a consistent one.

The book comprises 15 chapters, but they are more a collection of essays than a coherent developing story. Although liberally referenced, the source material has been quoted fairly selectively, as has the interpretation placed on many of the chosen statements. Each chapter returns to the problems of sedatives, hypnotics and anxiolytics, eventually focussing on some aspect of drug-induced dependence or the benzodiazepines. It is not a scholarly treatise, its impact is almost pure journalism.

The book has important interwoven themes, and each is given some prominence. Thus, drugs cause avoidable clinical adverse effects and a substantial number of hospital beds are occupied wholly through iatrogenic disease. Too much of the information given to prescribers and other health professionals about these products is provided by the drug companies themselves, with too little data on the likely adverse effects. The pharmaceutical industry's processes of self-regulation, for example on questions of publicity and public relations, do not work; and the various regulatory committees created under the 1968 Medicines Act are clothed in secrecy. Whilst the Author identifies what he sees to be wrong, there is no real attempt to bring together a package of new regulations or procedures which would solve these problems. Perhaps the structure of the book prevents a 'chapter on strategies', but such suggestions would then possibly leave the Author open to charges of naivety. The Author's motive is