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# Time-controlled release pseudoephedrine tablets: bioavailability and *in vitro/in vivo* correlations

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In chronopharmacotherapy, circadian changes in disease symptoms are taken into account. Press-coated, time-controlled release tablets containing pseudoephedrine hydrochloride as a model drug have been formulated and the suitability of this highly soluble drug in relation to the new drug delivery system was evaluated. Hydroxypropylmethylcellulose was used in the coat of the tablet to adjust drug release. If such a formulation was administered in the evening it would have maximal effect in the early morning, and would be useful for the treatment of nocturnal symptoms. Two cross-over, single-dose bioavailability studies were carried out on eight healthy volunteers. A dissolution test method was developed to establish level A and level C *in vitro/in vivo* correlation for four formulations. With a low viscosity grade of polymer, peak concentrations were achieved after five hours. The drug was absorbed much more slowly from tablets containing a high viscosity grade polymer, with a plasma peak at ten hours. For further development of the drug delivery system described, a dissolution test method at pH 7.2 at a rotation speed of 150 $min^{-1}$ is recommended on the basis of level A *in vitro/in vivo* correlation.

## 1. Introduction

In recent years, development of time-controlled drug formulations has grown in importance as symptoms of diseases displaying circadian rhythms have increasingly been taken into consideration in drug treatment. Asthma, rheumatoid arthritis and cardiovascular diseases such as myocardial ischaemia are examples of conditions in which symptoms often occur early in the morning. A chronopharmacotherapeutic approach dictates that drug plasma levels should be highest when symptoms are most severe. If a formulation releasing most of the drug dose from 3:00 to 6:00 a.m. is administered the previous evening before bedtime (approximately 22:00 p.m.), its effectiveness in the treatment of diseases exhibiting early morning symptoms should be maximal.

A press-coated tablet formulation with such a property has been developed in our laboratory [1]. The core of this modified-release formulation is a conventional tablet containing all or most of the drug dose. The coat contains polymers such as hydroxypropylmethylcellulose (HPMC) to control drug release. Some drug can be included in the coat. In previous studies of such formulations we have used ibuprofen as a model drug [2, 3]. This sparingly soluble and highly permeable drug belongs to Group II of the Biopharmaceutics Classification System [4]. With ibuprofen it has proved possible to achieve peak drug plasma levels 4–12 h after administration. The viscosity grade of HPMC is an important variable controlling drug release. By combining different viscosity grades of HPMC plasma peak levels can be displaced to occur 6–8 h after administration. With ibuprofen formulations double plasma peaks have been achieved when the coat also contained drug. Food and timing of drug administration have also been found to affect plasma profiles after administration of a press-coated tablet formulation [5].

The first aim of the study reported here was to investigate whether a drug substance that is highly soluble at physiological pH values is suitable for use with the new drug delivery system for controlling $t_{max}$ values. Pseudoephedrine, in the form of its hydrochloride salt, was selected as a model drug. Pseudoephedrine is a sympathomimetic amine completely absorbed from the gastrointestinal tract with no presystemic metabolism [6]. It therefore belongs to Group I of the Biopharmaceutics Classification System. Peak plasma levels with immediate-release formulations are reached 0.5–2 h after administration. The predominant elimination route of pseudoephedrine is urinary excretion. Its elimination half-life is relatively short, approximately 6 h [7, 8].

Up to now dissolution tests have been considered useful mainly in process and quality control of drug products. Dissolution tests have also been routine in the pharmaceutical development of new drug formulations. However, *in vitro* tests are of practical value only if a correlation between *in vitro* and *in vivo* characteristics exists. Although *in vitro/in vivo* correlation serves primarily as a tool in quality control, it may also be applied as a surrogate for bioequivalence tests when minor changes are made to drug products [9]. A second objective of the study reported here was to develop a dissolution test method in order to establish in *vitro/in vivo* correlations related to four press-coated time-controlled formulations. Both level A and level C correlations were evaluated.

## 2. Investigations, results and discussion

### *2.1. Tablet formulations*

Each of the press-coated tablet formulations studied consisted of a core and a coat. Pseudoephedrine hydrochloride was used as model drug. The total amount of drug in

**Table 1: Compositions of press-coated tablets**

| Formulation | A | B | C | D |
|---|---|---|---|---|
| Core | | | | |
| Pseudoephedrine hydrochloride (mg) | 80 | 80 | 100 | 100 |
| Lactose (mg) | 60 | 60 | 60 | 60 |
| Magnesium stearate (%) | 1 | 1 | 1 | 1 |
| Talc (%) | 2 | 2 | 2 | 2 |
| Coat | | | | |
| Pseudoephedrine hydrochloride (mg) | 20 | 20 | – | – |
| HPMC K4M (mg) | 180 | – | 180 | – |
| HPMC K100 (mg) | – | 180 | – | 180 |
| Magnesium stearate (%) | 1 | 1 | 1 | 1 |
| Talc (%) | 2 | 2 | 2 | 2 |

the tablet was 100 mg. Either all of the drug was placed in the core, or 80 mg were placed in the core and the rest in the coat. Two viscosity grades of HPMC, K100 and K4M, were used in the tablet coat to control drug release. The compositions of the tablets are shown in Table 1.

### *2.2. In vitro dissolution studies*

Three media of different pH were used to evaluate the effect of pH on drug release from the press-coated tablets. At pH 5.8 drug dissolution did not differ significantly from dissolution profiles at pH 7.2, at 50 $min^{-1}$ agitation rate. Further studies with agitation rates of 100 and 150 $min^{-1}$ were conducted at pH 7.2 and 1.2. For 2–6 h, release was independent of pH. Subsequently, release rate was the highest at pH 1.2, especially in the case of formulation C (Fig. 1). Release from tablets containing the low viscosity HPMC K100 varied greatly. The differences between results at pH 7.2 and 1.2 are not significantly different although rank order correlation exists. It has been suggested that HPMC K100 does not swell homogeneously [10]. This could explain substantial variation. Lack of homogeneity of the HPMC K100 grade is proposed being responsible for a manifestation of rapid gel-layer dissolution and higher drug release rate.

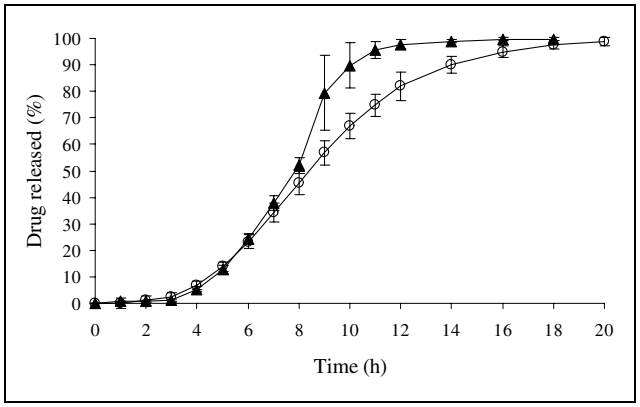


Fig. 1: Release of pseudoephedrine hydrochloride from formulation C at pH 1.2 (▲) and pH 7.2 (○), mean ± S.D., n = 6

The explanation of the differences in release profiles at the levels of pH studied may be that a stable HPMC gel is formed over a pH range 3–11 in aqueous solutions [11]. Low pH levels result in formation of a more degradable gel surrounding the tablet. The formulation is beginning to lose its integrity at a certain point e.g. in the case of formulation C at 6–8 h (Fig. 1). An HPMC gel formed at pH 7.2 would therefore be more stable than one formed at pH 1.2.

The effect of the rotation speed of the paddles at pH 7.2 in relation to the tablets is shown in Fig. 2. The effect varied according to the viscosity grade of the polymer used. In formulations A and C, in particular, a speed of 100 $min^{-1}$ had no significantly different effect from a speed of 50 $min^{-1}$. At 150 $min^{-1}$ drug release was slightly increased. These results reflect the rigidity of the gel layer formed around the tablet containing HPMC K4M. The results in the study reported here are in accordance with those in a previous study, from which it was concluded that the rate of erosional drug release is independent of agitation conditions up to 100 $min^{-1}$ for HPMC K4M [12].

With formulations B and D a significant difference was seen only between rates of 50 and 150 $min^{-1}$. When the viscosity of the gel layer formed around the tablet is low, (HPMC K100), the layer is more susceptible to erosion and higher rates of agitation are associated with a greater

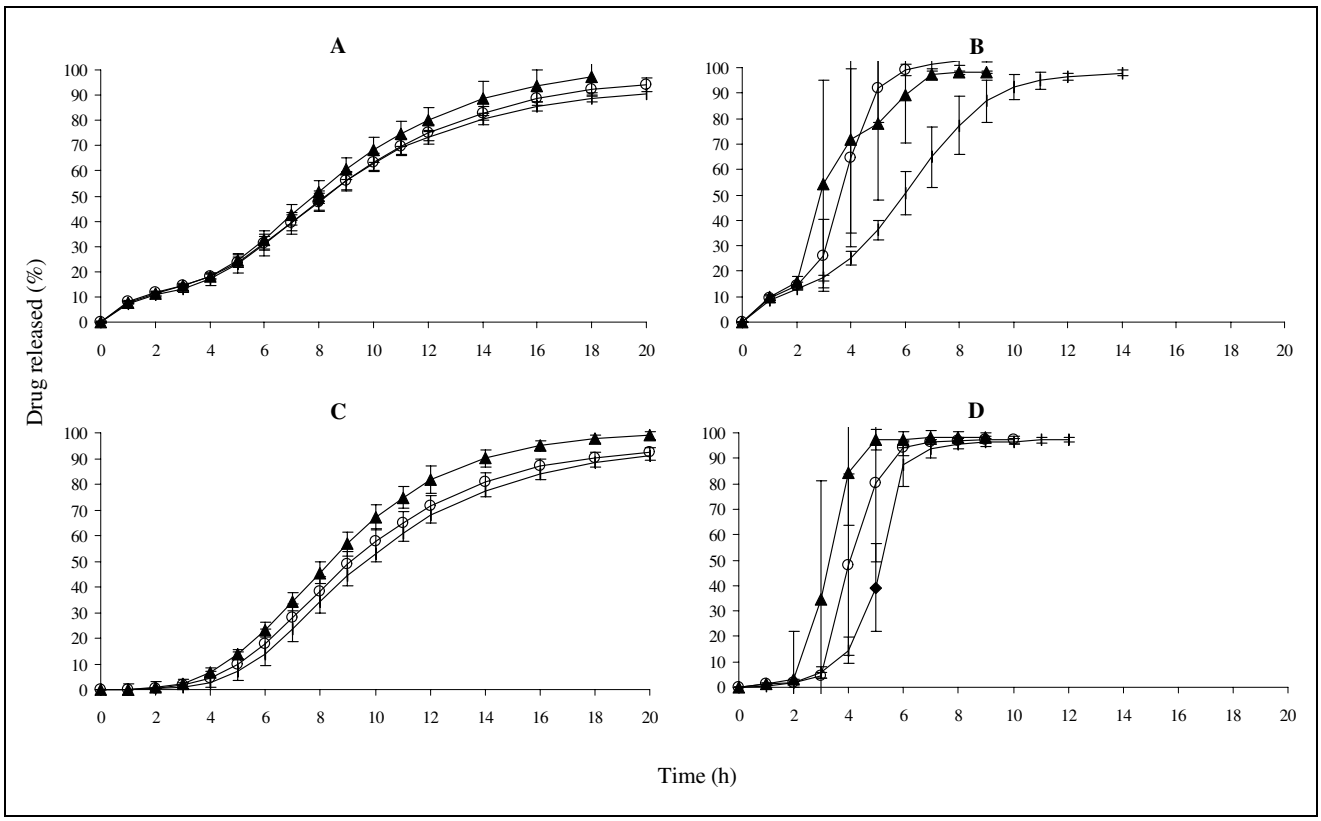


Fig. 2: Release of pseudoephedrine hydrochloride from press-coated tablets A, B, C and D at agitation speed of 50 $min^{-1}$ (◆), 100 $min^{-1}$ (○) and 150 $min^{-1}$ (▲) at pH 7.2, mean ± S.D., n = 6

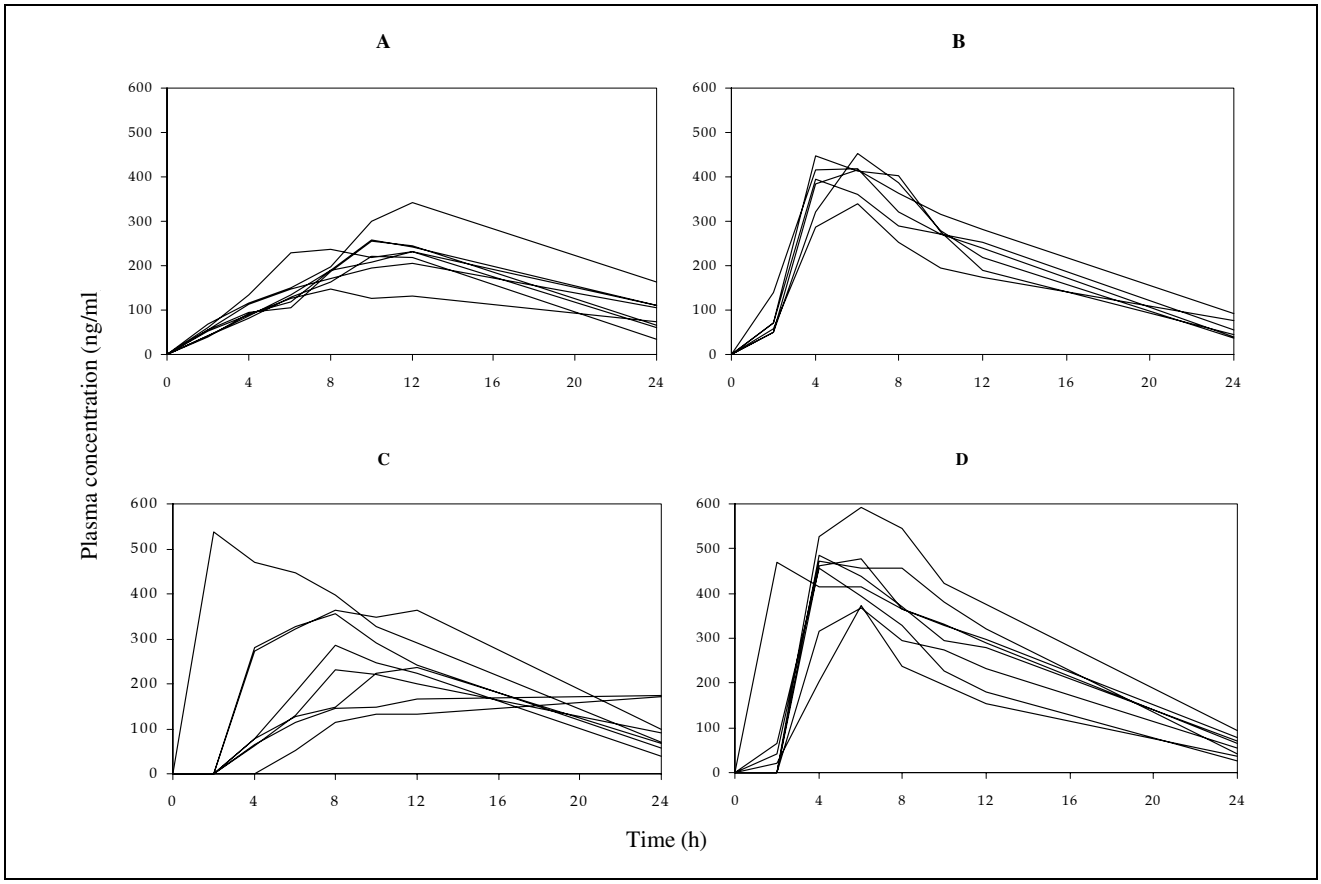


Fig. 3: Individual plasma concentration curves of pseudoephedrine after administration of press-coated tablets

variation in dissolution curves. Formulations A and B, containing 20 mg of the drug in the coat, exhibited a burst effect at the beginning of the dissolution test. A similar profile has been observed with a corresponding ibuprofen formulation [3]. In conclusion, dissolution lag time is independent of the solubility of drug used in the press-coated formulation.

### *2.3. Bioavailability studies*

Two randomized cross-over single-dose studies were carried out on healthy humans. Individual plasma curves are shown in Fig. 3. Fig. 4 shows mean plasma concentration curves for pseudoephedrine hydrochloride. Pharmacokinetic parameters and statistically significant differences relating to the formulations are recorded in Table 2.

The plasma curves display minor interindividual variation, indicating consistency of tablet compression. However, dose dumping clearly occurred in one subject (Fig. 3, left lower panel). Error in the compression coating procedure of the tablet administered to this subject could have caused this. Dose dumping could also have occurred if the tablet had been chewed during drug administration. Plasma data for formulation C for this subject were excluded from calculations of mean concentrations and parameters in Fig. 4 and Table 2.

$C_{max}$, $t_{max}$ and AUC values clearly show that rates and extents of bioavailability were highest from tablets B and D (Table 2). The rate parameters MRT and $C_{max}$/AUC confirm this. In addition, $t_{lag}$ was shorter for formulations B and D than for formulations A and C. When no drug was included in the coat $t_{lag}$ values were the longest. Formulations B and D differed from each other only in respect of $C_{max}$ and $t_{lag}$. The absorption patterns for formulations A and C were also fairly similar. The only differences relate to $t_{lag}$ values. Overall, including part of

**Table 2: Pharmacokinetic parameters of pseudoephedrine hydrochloride (single dose 100 mg) from press-coated tablets**

| Parameter | Formulation | | | |
|---|---|---|---|---|
| | A** | B** | C* | D** |
| $C_{max}$ (ng ml$^{-1}$) | 237 ± 55 | 385 ± 62[b] | 260 ± 78.8[b] | 461 ± 70[cdf] |
| $t_{max}$ (h) | 10.3 ± 1.7 | 5.0 ± 1.1[b] | 13.1 ± 7.6[c] | 4.8 ± 1.5[ce] |
| $t_{1/2}$ (h) | 11.1 ± 4.1 | 5.5 ± 2.4[a] | 18.9 ± 22.1 | 6.0 ± 1.2[e] |
| $t_{lag}$ (h) | 0.74 ± 0.26 | 0.52 ± 0.11[a] | 2.42 ± 0.71[cd] | 1.21 ± 0.88[ad] |
| MRT (h) | 15.0 ± 5.7 | 8.5 ± 2.5[a] | 27.5 ± 33.9 | 8.5 ± 1.4[e] |
| $AUC_{0-24\,h}$ (ng ml$^{-1}$ h) | 3561 ± 734 | 4562 ± 830[a] | 3689 ± 1087 | 5425 ± 1300[ae] |
| $C_{max}/AUC_{0-24\,h}$ (h$^{-1}$) | 0.066 ± 0.005 | 0.085 ± 0.011[b] | 0.071 ± 0.010[a] | 0.087 ± 0.014[ae] |

* n = 7 mean ± S.D.; **n = 8
[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.01$, comparison with previous column
[d] $p < 0.05$, comparison with B
[e] $p < 0.01$, [f] $p < 0.001$, comparison with A

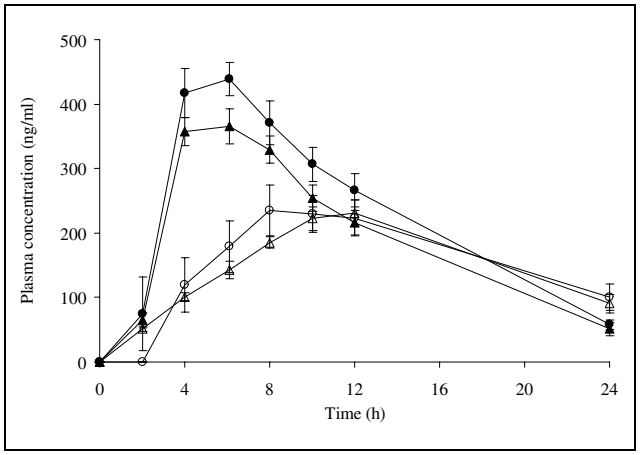


Fig. 4: Mean plasma concentrations of pseudoephedrine after administration of press-coated tablets A (△), B (▲), C (○) and D (●). The bars represent S.E.M.

the drug dose in the coat had little effect on drug absorption profiles but HPMC viscosity grade greatly affected bioavailability of pseudoephedrine. Both rate and extent of bioavailability were lowest when the higher viscosity was used.

In a study on press-coated ibuprofen tablets corresponding to formulation A, plasma curves were bimodal for each subject. For most subjects the first peak occurred at 4–6 h, the second at 10–12 h [2]. Pseudoephedrine formulation A exhibited only one peak, at 8–12 h (Fig. 3, left upper panel). Pseudoephedrine formulation B and the corresponding ibuprofen formulation exhibited $t_{max}$ values at 10–12 h. The difference between these studies can be explained by the differences relating to administration of the formulations. In the ibuprofen study three tablets ($3 \times 100$ mg) were administered, but in the pseudoephedrine study one tablet (100 mg) was given. Non-disintegrating solid particles can leave the stomach gradually during 4 h in fasted state [13] which could have happened with ibuprofen formulations [2].

We conclude that readily soluble drugs as well as slightly soluble drugs can be used in the kind of time-controlled release formulations studied. If $t_{max}$ at 6–8 h is desirable some higher viscosity polymer (e.g. 10%) could be included in formulations containing HPMC K100. Such a formulation would be suitable for administration at 22.00 p.m. to allow maximal effect to occur in the early morning hours. A night-time absorption study is however needed to evaluate the effects of circadian variation on plasma levels of pseudoephedrine with the press-coated formulation. Such a study has been carried out with ibuprofen [5]. The chronopharmacokinetic behaviour was found to be a property of the press-coated formulation, not just a property of the drug substance, ibuprofen.

### *2.4. In vitro/in vivo correlation*

Six *in vitro* dissolution methods were used in determining level A and level C correlations. Level C correlation was evaluated by the relationships between *in vitro* dissolution parameters and mean pharmacokinetic parameters. Single-point level C correlations are recorded in Table 3. The data indicate that a good correlation was obtained throughout between $t_{50\%}$ and $t_{max}$ values. The best correlation of all was obtained at pH 7.2 and agitation of 50 $min^{-1}$. A correlation exists between $D_{6h}$ and $t_{max}$ values. The results of linear regression analysis were the best at rotation speeds of 100 $min^{-1}$ and 150 $min^{-1}$. AUC and $C_{max}$ values correlated poorly with both *in vitro* parameters.

To establish level A correlation the relationship between drug absorbed *in vivo* and drug released *in vitro* was evaluated. There was no satisfactory level A correlation under any dissolution conditions when all four formulations were included. The relationship between *in vitro* dissolution and *in vivo* performance in the case of formulation C was different from the relationships for formulations A, B and D. Formulations C clearly is that with the lowest release rate and was therefore excluded [9]. With formulation C excluded correlation was better. A linear plot of drug release *in vitro* against drug absorbed *in vivo* is

**Table 3: Level C correlations for four press-coated tablet formulations under different dissolution conditions, as evaluated using linear regression analysis ($y = kx + b$)**

| pH | | 7.2 | | | 1.2 | | |
|---|---|---|---|---|---|---|---|
| $min^{-1}$ | | 50 | 100 | 150 | 50 | 100 | 150 |
| $D_{6h}$ vs $C_{max}$ | k | 3.114 | 2.304 | 2.665 | 3.360 | 2.200 | 2.472 |
| | b | 193.4 | 196.4 | 174.1 | 169.5 | 201.0 | 175.2 |
| | $R^2$ | 0.8699 | 0.8390 | 0.9214 | 0.8605 | 0.8720 | 0.8668 |
| $D_{6h}$ vs $t_{max}$ | k | −0.1151 | −0.0962 | −0.1056 | −0.1265 | −0.0901 | −0.1018 |
| | b | 13.57 | 14.13 | 14.72 | 14.57 | 13.83 | 14.923 |
| | $R^2$ | 0.7892 | 0.9714 | 0.9616 | 0.8107 | 0.9715 | 0.9767 |
| $D_{6h}$ vs AUC | k | 26.14 | 17.69 | 20.92 | 28.14 | 17.03 | 19.15 |
| | b | 3102 | 3227 | 3029 | 2905 | 3255 | 3054 |
| | $R^2$ | 0.9222 | 0.7440 | 0.8538 | 0.9078 | 0.7853 | 0.7821 |
| $t_{50\%}$ vs $C_{max}$ | k | −47.69 | −34.02 | −33.57 | −50.58 | −33.56 | −35.92 |
| | b | 682.4 | 549.2 | 523.9 | 667.6 | 533.8 | 518.1 |
| | $R^2$ | 0.8482 | 0.8339 | 0.8505 | 0.8088 | 0.8635 | 0.8591 |
| $t_{50\%}$ vs $t_{max}$ | k | 1.993 | 1.422 | 1.378 | 2.103 | 1.378 | 1.484 |
| | b | −6.176 | −0.6118 | 0.5854 | −5.488 | 0.1814 | 0.7766 |
| | $R^2$ | 0.9842 | 0.9676 | 0.9523 | 0.9288 | 0.9669 | 0.9745 |
| $t_{50\%}$ vs AUC | k | −380.3 | −260.6 | −257.0 | −413.2 | −258.7 | −277.4 |
| | b | 7062 | 5933 | 5738 | 7009 | 8524 | 5706 |
| | $R^2$ | 0.8112 | 0.7360 | 0.7496 | 0.8119 | 0.7718 | 0.7705 |

*In vitro* amount of drug released at 6 h or time point at which 50% of drug had dissolved plotted against a mean pharmacokinetic parameter

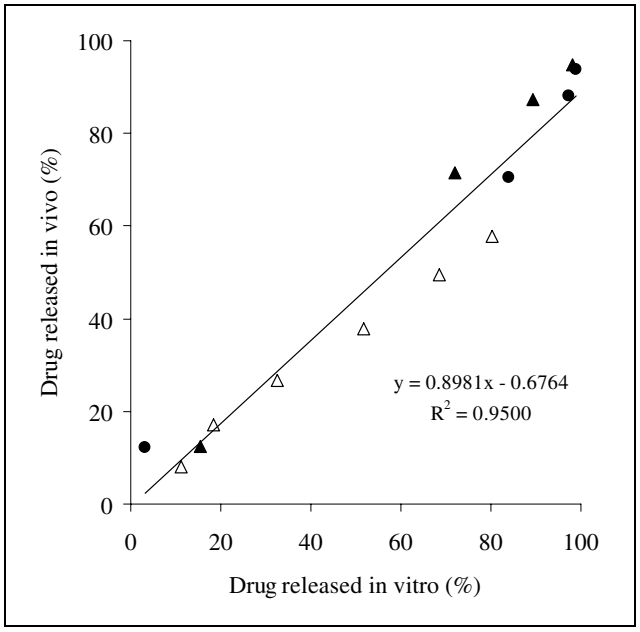


Fig. 5: Level A in *vitro/in vivo* correlations for press-coated tablet formulations A (△), B (▲) and D (●) at rotation speed of 150 $min^{-1}$ at pH 7.2. The regression line and the corresponding equation are shown for the dissolution method giving the best fit

shown in Fig. 5. Because of to the lack of data points in the early stage of the absorption study (the first sample was taken at 2 h) only three or four points exist for formulations B and D. Correlations are less satisfactory in these cases.

For further development of the drug delivery system described a dissolution test method at pH 7.2 and a rotation speed of 150 $min^{-1}$ can be recommended. Only if the viscosity grade of the polymer used in the coat is lower than 4000 cps (HPMC K4M) and all of the drug dose is contained in the core no direct conclusions regarding *in vivo* properties can be predicted from *in vitro* results. It would be useful if conclusions regarding $t_{max}$ values could be drawn from dissolution parameters (e.g. $t_{50\%}$). There would be a need to conduct less bioavailability tests on healthy volunteers, especially if the objective is to adjust time to peak concentrations.

## 3. Experimental

### *3.1. Preparation of press-coated tablets*

Pseudoephedrine hydrochloride (BP) and lactose (Pharmatose DCL 21, DMV, The Netherlands) were mixed in a Turbula mixer (W. A. Bachofen, Switzerland) for 15 min. Magnesium stearate (Ph. Eur.) and talc (Ph. Eur.) were added and mixed for 2 min. HPMC Methocel K4M (4000 cps in 2% aqueous solution) or K100 (100 cps in 2% aqueous solution, Colorcon Ltd., U.K.) and pseudoephedrine hydrochloride were mixed for 10 min in preparing the coat batches. Magnesium stearate and talc were mixed into the batches for a further 2 min.

Cores were compressed using concave punches (7 mm in diameter) in an instrumented Korsch EK-O single-punch press (Erweka Apparatebau GmbH, Germany). The compression force (12 kN) was controlled by computer software (PuuMan Oy, Finland). One half of the coat mass for a single tablet was weighed into the die. The core was centred on top of the powder bed. The other half of the coat mass was added to fill the die. The tablet was then compressed (12 kN) using concave punches (11 mm in diameter).

### *3.2. In vitro dissolution studies*

Drug dissolution from the press-coated tablets was performed using the USP 23 paddle method apparatus 2. The dissolution media (USP 23) used were: phosphate buffers pH 7.2 and pH 5.8, and hydrochloric acid buffer pH 1.2 (500 ml at 37 ± 0.5 °C). Dissolution of 100 mg of pseudoephedrine hydrochloride alone was found to be independent of pH. The rotation speed was 50, 100 or 150 $min^{-1}$. The dissolution apparatus (Sotax AT7, Sotax Ag, Switzerland) was connected to a spectrophotometer with 10 mm cells (Ultrospec III, LKB Biochrom Ltd., U.K.) via a peristaltic pump (Watson-Marlow 202U, Smith and Nephew, U.K.). Measurement of absorbance from six parallel samples was controlled by tablet dissolution software for 20 h (TDS™, LKB Biochrom Ltd., U.K.).

### *3.3. In vivo studies*

#### *3.3.1. Bioavailability studies on humans*

Two groups of eight healthy volunteers participated in two randomized cross-over single-dose studies. In the first study formulations A and B were administered to one group and in the second study formulations C and D to a second group. Between the administration of formulations there was a wash-out period of one week. The ages of the volunteers varied from 21 to 37 years and their weights from 43 to 87 kg. All were non-smokers. They were each subjected to physical examination, routine laboratory tests and an ECG. The volunteers were informed of possible risks and side effects of the drug, and written consent was obtained from each. The study was carried out in accordance with the recommendations of the Declaration of Helsinki (World Medical Assembly 1964) as revised in Tokyo in 1975. The study protocol had been approved by the Ethical Committee of the University of Tartu.

Each formulation was administered with 200 ml of water following a fast of at least 10 h. A standard lunch was provided 3 h after drug administration. Blood samples were collected into heparinized tubes just prior to drug administration and 2, 4, 6, 8, 10, 12 and 24 h thereafter. Plasma was separated and stored at −20 °C until analysed.

#### *3.3.2. Plasma assay*

Pseudoephedrine plasma concentrations were determined by means of HPLC using the method described by Dowse et al. [14] with slight modifications. The HPLC system used has been described in a previous paper [3]. Determinations were carried out on three samples in parallel.

The standard curve was found to be linear ($R^2 > 0.999$) over the concentration range of 35–800 ng $ml^{-1}$ used. The accuracy and precision of the method were investigated as recommended by Shah et al. [15] by analysing six plasma samples spiked with pseudoephedrine hydrochloride. Mean values at the extremes of the concentration range were 35.9 ng $ml^{-1}$ (CV% 8.6%) and 798.8 ng $ml^{-1}$ (CV% 2.7%). There were no interfering peaks in the plasma blanks.

#### *3.3.3. Pharmacokinetic analysis*

Maximum concentration ($C_{max}$) and time to peak concentration ($t_{max}$) were determined directly from individual time versus plasma concentration curves. Pharmacokinetic parameters calculated using the Sipha™ program (Simed, France) were apparent elimination half-life ($t_{1/2}$), lag time for absorption ($t_{lag}$), mean residence time (MRT) and area under the curve ($AUC_{0-24\,h}$). AUC values were calculated according to the trapezoidal method. Rate of absorption was also evaluated by means of the ratio $C_{max}$/AUC. Statistical analyses were carried out using Student's paired t-test, the Mann-Whitney non-parametric U-test and Wilcoxon's matched-pairs rank test.

### *3.4. In vitro/in vivo data analysis*

The *in vitro* parameters were the time point at which 50% of the drug has been dissolved ($t_{50\%}$) and the amount dissolved in 6 h ($D_{6h}$). The pharmacokinetic parameters were $C_{max}$, $t_{max}$ and AUC. Each *in vivo* parameter was plotted against an *in vitro* parameter and linear regressions were calculated.

To establish level A correlation the *in vivo* plasma data was transformed to fraction of drug absorbed by using the Wagner-Nelson method [16] in the Sipha™ program. Mean elimination half-life of 6 h was used in calculations. The relationship between drug absorbed *in vivo* and drug released *in vitro* was evaluated by means of linear regression.

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