ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 53 (2002) 29–35

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejphabio

Research paper

Pharmacokinetics of verapamil and norverapamil from controlled release floating pellets in humans

Wiesław Sawicki*

Department of Pharmaceutical Technology, Medical University of Gdańsk, Gdańsk, Poland

Received 5 October 2000; accepted in revised form 12 July 2001

Abstract

Pharmacokinetics of verapamil (V) in a dose of 40 mg and its metabolite norverapamil (N) from the new oral drug formulation in a form of capsule filled with floating pellets was determined. Conventional 40-mg tablets used in a medical practice served as a reference. Bioavailability studies were carried out in 12 healthy volunteers including six men and six women. In an in vitro test the pellets floated on the surface of the extraction fluid for 6 h. Mean value of maximum plasma concentration (C_{max}) of V for floating pellets was 28.27 ng ml^{-1} and t_{max} 3.75 h. The value of the area under the concentrations versus time, $AUC_{0-\infty}$ was calculated as 364.65 ng ml^{-1} h, biological half-lives of the absorption and elimination ($t_{0.5el}$) phase were 0.5 h and 10.68 h, respectively. For the reference conventional tablets those values were 33.07 ng ml^{-1}, 1.21 h, 224.22 ng ml^{-1} h, 0.36 h and 6.17 h, respectively. The average concentration of N in plasma was similar to that of V.

Keywords: Verapamil; Norverapamil; First-pass effect; Floating pellet; Controlled release; Oral bioavailability; Pharmacokinetics

1. Introduction

The fact that absorption and residence of the drug in particular sections of the gastrointestinal tract may be correlated must be taken into account while developing oral dosage drug forms, especially slow release formulations [1]. Hence, attempts are made to work out such drug forms whose slow release takes place in a specific section of the gastrointestinal tract only (for example in the stomach, small intestine or colon) [2,3].

Verapamil (V) belongs to the group of calcium channel antagonists. In medical practice it is mostly used in a conventional tablet form a minimal dose of 40 mg and a maximal dose of 180 mg, and in a slow release from in doses of 120 to 240 mg. Only 10–20% out of the 90% of the dose absorbed from the digestive tract penetrates to the circulatory system in an unchanged form [4]. The remaining part of V dose undergoes a first-pass effect, mainly in the liver [5]. In humans V is metabolized to six and, according to some authors, to 12 metabolites excreted mainly in urine [6]. Norverapamil (N) is the most important of them. Its pharmacological activity attains about 20% of activity of V [7].

Studies on preparation of drug forms which are capable of ensuring a more effective release and absorption of V were performed in our department. They included novel buccal drug form consisting of a thin elastic disc made of two layers [8,9].

An observation that solubility of V in the stomach is several times higher than in the small intestine [10] was a base of the concept of the present work. It was confirmed that solubility of V in hydrochloric acid (0.1 mol/l) and phosphate buffer, pH 6.8 was 360 and 54 mg/ml, respectively [11].

The aim of this paper is to determine pharmacokinetics V and its metabolite N from a form of a capsule filled with floating pellets of V. It was assumed that this form should reside in the stomach floating for several hours and gradually releasing the drug in a controlled way. This should result in an increased absorption rate of V and a more favorable pharmacokinetics as compared to the conventional tablets currently in use. A dose of 40 mg of V in a capsule was delivered.

2. Materials and methods

2.1. Materials

Verapamil (Sigma Chemical Co., St. Louis, MO, USA),

* Department of Pharmaceutical Technology, Medical University of Gdańsk, ul. Hallera 107, 80-416 Gdańsk, Poland. Tel.: +48-58-349-3185; fax: +48-58-349-3190.

E-mail address: wsawicki@farmacja.amg.gda.pl (W. Sawicki).

0939-6411/02/$ - see front matter
PII: S0939-6411(01)00189-8

sodium hydrocarbonate (POCh S.A., Gliwice, Poland), microcrystalline cellulose- Avicel PH 101 (FMC Europe N.V., Brussels, Belgium), lactose (Merck, Darmstadt, Germany), Povidone K-30 (Fluka Chemie AG, Buchs, Switzerland), Eudragit NE 30D and Eudragit L30D 55 (Röhm Pharma, Darmstadt, Germany), triethyl citrate (Morflex, Greensboro, USA), talcum Polish Pharmacopoeia V (FP V) grade.

2.2. Drug form preparation

Floating drug formulation (F) is a gelatin capsule filled with tens of granules pellets with V in a dose of 40 mg, coated with a control release film. Pellets were prepared by wet granulation of a powder mixture, spheronization of the granulated mass and coating of the cores with a sustained release film.

Pellet core contents (%):

Verapamil hydrochloride	20.0
Sodium hydrocarbonate	20.4
Microcrystalline cellulose	43.72
Lactose	12.08
Povidone K-30	3.80

150 g of a powder mixture was moistened with 95 g of 40% ethanol solution. The resulting mass was extruded through a metal sieve (Retsch, Haan, Germany), 1.2 mm mesh diameter. The granulate was partly dried for 5 min in a blow dryer (Laborgerate, Berlin, Germany) at 40°C. Spheronization process was conducted in a Caleva Model 120 apparatus (Caleva Ltd., Dorset, UK). The granulate (humidity of 60% approximately) was introduced to the spheronizer cylinder in 20-g portions. The following parameters of the device operation were determined: the pressure of air incoming to the path steering cylinder 0.5 bar; spheronizer shield rotation speed measured by means of tachometer (Caleva) 1200–1300 rpm; spheronization time of a 20-g portion of granulate 4 min. Wet cores were dried in a blow-dryer at 40°C for 12 h and then separated into fractions of 0.8–1.25, 1.25–1.6 and 1.6–2.0 mm by means of a sieve set. Pellets of 1.25–1.6 mm in diameter constituted the biggest fraction (60% approximately) in the given conditions of spheronization. This fraction was designated for the coating process. The contents of the coating mixture was as follows (%): Eudragit NE 30D 27.40; Eudragit L-30D 55 27.36; triethyl citrate 1.36; talcum 2.92; distilled water 40.96. Talcum was added at the and after rubbing through a sieve (mesh diameter-0.08 mm).

Core coating (200 g) was done in an Uni-Glatt apparatus (Glatt GmbH, Systemtechnik, Dresden, Germany). The following parameters of the device operation were considered most favorable: incoming air temperature 40°C, outgoing air temperature 30°C; incoming air pressure 6 bar; air pressure in spray nozzle 2 bar; peristaltic pump feeding rate 0.2 (position according to the device scale). After each consumption of 50 ml of the coating mixture, a 10-g coated pellet sample was taken. Then they were dried in a blow-dryer at 40°C for 30 h precisely.

The thickness of the coating film was measured under a microscope after taking it off the pellet surface, cross-sectioning. In order to determine proper film thickness, ten pellet samples were analyzed. In the in vitro dissolution test thickness film of 75–85 μm was acknowledged to be most favorable.

Contents of a 75–85 μm thick film (%):

Eudragit NE	39.7
Eudragit L	39.6
Triethyl citrate	6.6
Talcum	14.1

Pellets of 1.25 mm–1.6 mm grain size, enclosed in gelatin capsules no. 00 were selected for testing the bioavailability in humans. Average mass of single capsule is 0.358 g ± (1.5%) and the contents of V is 0.041 g ± (8.5%), which conforms to FP V norm.

Conventional tablets, Staveran 40 mg (S) (Polpharma S.A., Starogard Gdanski, Poland) comprised the reference drug.

2.3. In vitro drug release test

The measurement of release rate of V from F and S was performed using the Ph Eur paddle apparatus, Pharma Test Model PTWS-3 (Pharma Test, Hainburg, Germany). At the temperature of 37 ± 0.5°C vessels were filled with 250 ml of hydrochloric acid (0.1 mol/l). The concentration of V in the samples was determined spectrophotometrically at 278 nm [12]. For a given pellet formulation, in vitro drug release test was repeated five times.

The results obtained are presented in Fig.1.

2.4. In vivo study

The bioavailability studies were carried out in a group of 12 Caucasian volunteers, six men and six women, aged 20–38 (26.2 ± 5.82) years, weighing from 50 to 94 kg (70.67 ± 13.57 kg), and height ranging from 155 to 185 cm (171.75 ± 0.16 cm). The study had the approval of the Ethics Committee of the Medical University of Gdansk. The volunteers were admitted to the study after detailed medical

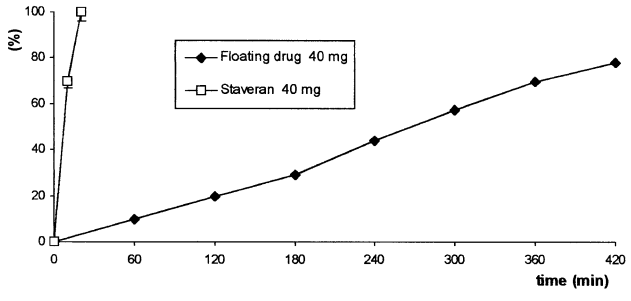

Fig. 1. In vitro verapamil release from flotation drug formulation 40 mg and Staveran tablet 40 mg ($n = 5$).

and laboratory examinations (morphology, ionogram, ALAT, AspAT, creatinine, general examination of urine). The main inclusion criteria were the absence of heart, liver, renal and digestive tract diseases. All of the women were in the first half of their menstrual cycle and had negative results of pregnancy test (Clearview test, Unipath, Bedford, UK). None of the volunteers took other drugs during the previous 4 weeks nor took part in other clinical tests during 3 months before the study. The volunteers were given written information about the aim of the study and informed consent was obtained from each of them. They started the study after an overnight fast. The crossover test was conducted 7 days after administering a single dose of F 40 mg or S 40 mg. During all the stages of the tests the volunteers stayed for 24 h in the Clinical Pharmacology Unit of the Child Health Center Monument Institute in Warsaw, Poland. They were examined by a cardiologist. They got their first meal (standardized breakfast) 2 h after the beginning of the experiment. Blood was taken for analysis from the elbow vein before drugs administration and then 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after the administration of the drugs tested. Plasma was separated within 0.5 h after collection and stored at −20°C until analysis. Plasma levels of V and N were determined employing the high-performance liquid chromatography method with fluorescence detection [13]. Limit of detection was calculated as three standard deviations (SD) and limit of determination as ten SD observed after injection of standards at concentration 1 and 4 ng/ml for V and N, respectively. Recovery was 92.12% (variability index, CV = 3.03%) and 89.58% (CV = 1.62%) for V and N, respectively. Stability in the whole range of the calibration curve was found. Internal standard (propranolol hydrochloride) was extracted with an average 82.5% yield (CV = 3.72% for $n = 34$).

The limits of detection and limit of determination for V and N were determined by using 1 ng of standard V and 4 ng of standard N dissolved in 1 ml of solution comprising 50 ng of internal standard. For V, the limit of detection was 0.92 ng/ml and the limit of determination was 3.08 ng/ml. That corresponds to 1.23 ng/ml of V in the plasma sample. For N, the limit of detection was 0.03 ng/ml and the limit of determination was 1 ng/ml, which corresponds to 0.4 ng/ml of N in plasma sample.

2.5. Pharmacokinetic and statistical analysis

Calculation of pharmacokinetic parameters was done provided employing Topfit version 2.0 (Fisher Verlag, Stuttgart, Germany, 1993). Statistical analysis was conducted by means of the Statgraphics Plus software, Rockville, USA, 1998. Biagent analysis of analysis of variance (ANOVA) variation for the Latin square after logarithmic transformation was conducted for parameters AUC and C_{max}. The value of t_{max} was analyzed by means of the Kruskal–Wallis nonparametrical test (Statgraphics Plus software, Rockville, USA, 1998)

3. Results and discussion

In order to improve pharmacokinetics of V, in comparison with a conventional tablet, an alternative drug delivery system comprised of a capsule filled with floating pellets was proposed.

Solubility of V depends on pH [11,12]. V is a drug easily absorbed [14]. Maximum absorption may be expected with increasing solubility in acid environment. Hence the floating form was developed.

It was assumed that better solubility of V in an acidic environment of the stomach may result in a greater amount of the drug absorbed and its greater concentration in plasma. It was noted that frequent administration of the drug to humans with healthy liver results in increase of V bioavailability due to the so called saturable first-pass effect. That is a consequence of nonlinear pharmacokinetics of the drug [15,16]. In this paper the effect of F dosage releasing drug only in the stomach, solubility were of V is better, on pharmacokinetics of V is studied.

It is known that pellets constitute multiple-unit dosage forms which have many advantages as compared to tablets [17,18]. They spread more evenly in the stomach which

Table 1
Mean pharmacokinetics parameters of verapamil in volunteers after administration of flotation drug formulation and Staveran tablet

Parameter	Flotation drug	Staveran	Analysis of variance[a]
C_{max} (ng ml^{-1})	28.27 ± 5.73	33.07 ± 8.06	NS
t_{max} (h)	3.75 ± 0.97	1.21 ± 0.33	IS
AUC_{0-24} (ng ml^{-1} h)	280.83 ± 48.42	203.28 ±76.51	IS
$AUC_{0-\infty}$ (ng ml^{-1} h)	364.65 ± 86.10	224.22 ± 87.29	IS
EBA (%)	159.6	100.0	
K_a (h^{-1})	1.93 ± 1.17	2.20 ± 0.95	NS
$t_{0.5a}$ (h)	0.50 ± 0.29	0.36 ± 0.12	NS
K_{el} (h^{-1})	0.07 ± 0.02	0.12 ± 0.02	NS
$t_{0.5el}$ (h)	10.68 ± 4.38	6.17 ± 1.23	IS
Cl (ml min^{-1})	1924.16 ± 455.31	3311.39 ± 966.79	IS
V_d (l)	1679.94 ± 418.60	1698.46 ± 375.77	IS

[a] IS, statistically significant; NS, statistically insignificant; $P < 0.05$.

Table 2
Mean pharmacokinetics parameters of norverapamil in volunteers after administration of flotation drug formulation and Staveran tablet

Parameter	Flotation drug	Staveran	Analysis of variance
C_{max} (ng ml^{-1})	21.64 ± 4.41	28.99 ± 6.89	IS
t_{max} (h)	5.25 ± 1.42	1.29 ± 0.40	IS
AUC_{0-24} (ng ml^{-1} h)	241.53 ± 33.84	169.28 ±56.48	IS
$AUC_{0-\infty}$ (ng ml^{-1} h)	311.18 ± 82.97	185.68 ± 67.95	IS
EBA (%)	156.68	100.0	
K_a (h^{-1})	1.75 ± 0.99	2.27 ± 1.10	NS
$t_{0.5a}$ (h)	0.53 ± 0.36	0.39 ± 0.22	NS
K_{el} (h^{-1})	0.08 ± 0.02	0.13 ± 0.03	IS
$t_{0.5el}$ (h)	10.36 ± 4.43	5.73 ± 1.14	IS
Cl (ml min^{-1})	2265.89 ± 526.42	3981.62 ± 1231.45	IS
V_d (l)	1898.71 ± 334.52	1890.33 ± 425.39	NS

leads to a decreased risk of high local concentration and of adverse effects. Any disturbances at the administration stage, for example crushing with teeth, or otherwise changed release rate may not concern all pellets. Moreover, these forms are characterized by a high reproducibility of release due to a relatively large surface and a short diffusion way of the drug.

The idea of floating pellets was realized taking advantage of a change in physical properties of the drug form after its passing to the acidic environment of hydrochloric acid in vitro or to the acidic stomach environment in vivo. Thus, sodium hydrocarbonate was added as a component of the core of the pellets. This substance after reacting with hydrochloric acid, creates carbon dioxide whose bubbles adsorb on the surface of the spherical core of the pellets and cause their floating in the fluid in vitro or in vivo [19]. Aqueous acrylic dispersion of Eudragit NE-30 D was used as the main component of the coating mixture. This polymer creates an insoluble film which is diffusive in the range of pH 2–8 [20]. Eudragit L, which is insoluble in an acid environment, was introduced to film in order to slow down and control its diffusion process. A plasticizing agent, triethyl citrate, was also added, which is recommended in recent literature even in the concentration of up to 30% of the film mass [21].

The results of V release rate from the tested drugs are presented in Fig. 1. The S form quickly releases the whole dose of drug (30–40 min), whereas floating pellets release about 80% of the drug at a constant rate for 420 min. After dissolving the gelatin capsule, pellets floated all the time on the surface of the dissolution liquid. It was observed that pellets floated on the dissolution liquid even not being mixed.

A longer flotation effect in vitro was acquired by Chen and Hao [22] who proposed a capsule filled with a mixture of V, hydroxypropoxyl cellulose and effervescent ingredient. The capsule released the drug over 10 h at constant rate. It was discovered than entrapped air creates the diffusion barrier for V solution.

In the described flotation pellets, carbon dioxide bubbles on the core surface probably slow down the release rate, too.

The volunteers participating in bioavailability tests started the study after an overnight fast. They got their first standardized breakfast after 2 h of the experiment. According to Hla et al., food can influence bioavailability of V [23]. However, according to other authors, the presence of food in the stomach has rather an influence on the prolongation of the floating properties of the drug form than on its buoyancy [24,25].

Average of V and N pharmacokinetic parameters of the studied formulations are presented in Tables 1–4. The statistical evaluation of differences between the respective data for F and S calculated using ANOVA is also presented in Tables 1–4. Figs. 2 and 3 present time-dependent concen-

Table 3
Mean pharmacokinetics parameters of verapamil in women volunteers after administration of flotation drug formulation and Staveran tablet

Parameter	Flotation drug	Staveran	Analysis of variance
C_{max} (ng ml^{-1})	28.50 ± 4.8	31.33 ± 4.11	NS
t_{max} (h)	3.33 ± 0.82	1.16 ± 0.26	IS
AUC_{0-24} (ng ml^{-1} h)	266.77 ± 42.13	181.53 ± 46.26	IS
$AUC_{0-\infty}$ (ng ml^{-1} h)	328.62 ± 61.38	203.23 ± 61.74	IS
K_a (h^{-1})	1.87 ± 0.63	2.24 ± 0.87	NS
$t_{0.5a}$ (h)	0.42 ± 0.17	0.35 ± 0.14	NS
K_{el} (h^{-1})	0.08 ± 0.02	0.10 ± 0.03	NS
$t_{0.5el}$ (h)	9.28 ± 2.45	6.41 ± 1.49	IS
Cl (ml min^{-1})	2094.21 ± 424.86	3497.68 ± 894.62	IS
V_d (l)	1637.37 ± 299.46	1860.36 ± 286.93	NS

Table 4
Mean pharmacokinetics parameters of verapamil in men volunteers after administration of flotation drug formulation and Staveran tablet

Parameter	Flotation drug	Staveran	Analysis of variance
C_{max} (ng ml^{-1})	28.30 ± 6.94	34.80 ± 10.87	NS
t_{max} (h)	4.16 ± 0.98	1.33 ± 0.40	IS
AUC_{0-24} (ng ml^{-1} h)	294.88 ± 53.93	225.03 ± 97.99	IS
$AUC_{0-\infty}$ (ng ml^{-1} h)	400.68 ± 97.08	245.20 ± 206.78	IS
K_a (h^{-1})	1.99 ± 1.60	2.16 ± 1.10	NS
$t_{0.5a}$ (h)	0.52 ± 0.32	0.37 ± 0.13	NS
K_{el} (h^{-1})	0.06 ± 0.02	0.12 ± 0.02	IS
$t_{0.5el}$ (h)	12.08 ± 5.61	15.92 ± 0.98	IS
Cl (ml min^{-1})	1754.14 ± 454.03	3125.10 ± 990.50	IS
V_d (l)	1722.50 ± 539.88	1536.60 ± 406.71	NS

trations of V and N in volunteers' plasma. The average maximum concentration (C_{max}) of V for F form was slightly lower than that for S form, and amounted to 28.27 ng/ml and 33.07 ng/ml, respectively (Table 1). The determined values of C_{max} of the tested drugs are comparable with the literature data for oral V dose of 40 mg [26]. Pharmacokinetic study of V from conventional tablet, in doses of 80 mg and 120 mg, in comparison with slow release tablets, in a dose of 120 mg, provided interesting results [27]. It was discovered that pharmacokinetic parameters from conventional forms increased disproportionately for doses 80 and 120 mg. C_{max} for conventional tablets in doses 80 mg and 120 mg amounted to 140.1 ng ml^{-1} and 293.1 ng ml^{-1}, respectively and for slow release tablets in dose of 120 mg 189.5 ng ml^{-1}. $AUC_{0-\infty}$ values for those drugs amounted to 946.5 ng ml^{-1} h, 1943.0 ng ml^{-1} h, 1641.0 ng ml^{-1} h, respectively. However, slowing down in vitro release from modified release tablets causes an increase of t_{max} up to 3.5 h.

Flotation pellets allow for longer stay in the maximum solubility conditions unlike conventional tablets. Prolongation of the release time from F form in stomach to 6 h increases the time of reaching the maximum drug concentration (t_{max}) to 3.75 h as compared to 1.21 h for S. The value of the area under the time–concentration curve (AUC) is greater is for F form as compared to S. The amounts in time interval 0–24 h reach 280.83 ng ml^{-1} h and 203.28 ng ml^{-1} h, respectively. The AUC values in time interval 0–∞ for F and S forms reach 364.65 ng ml^{-1} h and 224.22 ng ml^{-1} h, respectively (Table 1). The greater values of AUC observed for the F form in comparison to S form of V are a consequence of a greater value of t_{max} for F than for S. Thus, the degree of bioavailability (EBA) of V from F is 59.6% higher.

Controlled release rate of V from the floating form contributes to the slowing down of the elimination phase of the drug. Elimination constant (K_{el}) reaches 0.07 h^{-1} for F and 0.12 h^{-1} for S (Table 1). The significant differences in V clearance (Cl) between F and S, 1924.16 ml min^{-1} and 3311.39 ml min^{-1}, respectively, demonstrate differences in V bioavailability (Table 1).

The mean concentration profile of V in volunteers is presented in Figs. 4 and 5, for men and women separately. Much bigger individual differences were discovered in volunteers after administering tablet S than after administering the F form. This is related to the kinetics of the passage through the gastrointestinal tract. The tablet passes from the stomach to the intestine probably only in the third phase of digestion, which occurs every 2 h. Indeed, the volunteers took the drugs on an empty stomach; however, they had a standard breakfast after 2 h. A scintigraphic study showed considerable differences in food transport time in humans [28]. In the case of the stomach it ranges from 0.4 to 9 h, and in the case of the intestine from 1.2 to 6.2 h. Motility of particular sections of the gastrointestinal tract may also vary, which causes that the retention time of the

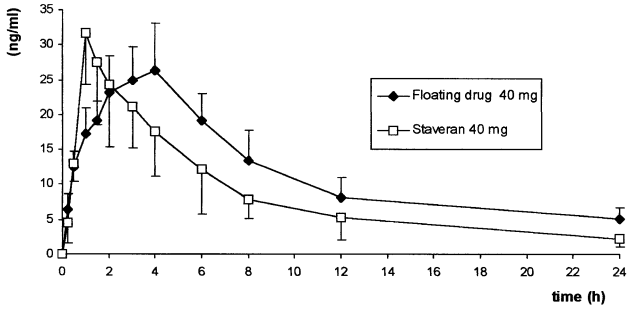

Fig. 2. Mean plasma concentrations of verapamil in 12 volunteers after administration of flotation drug formulation 40 mg and Staveran tablet 40 mg.

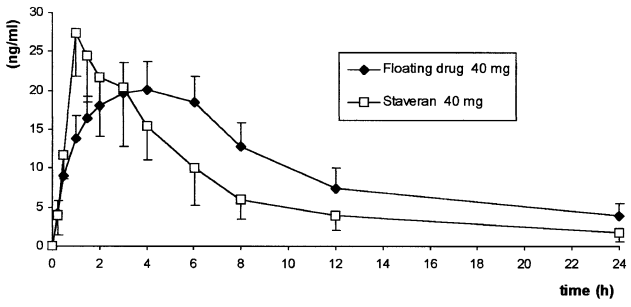

Fig. 3. Mean plasma concentrations of norverapamil in 12 volunteers after administration of flotation drug formulation 40 mg and Staveran tablet 40 mg.

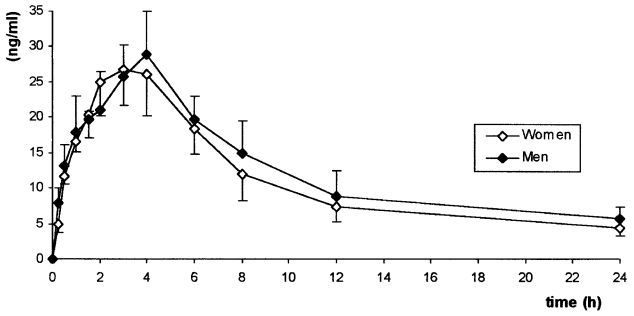

Fig. 4. Mean plasma concentrations of verapamil in six women and six men after administration of flotation drug formulation 40 mg.

gastric content is 0.5–1.6 h in the fasting condition and after eating, 50 min–9 h. The amount of drug released from the tablet in the stomach was evaluated to be 20–90% [28]. For floating pellets, smaller individual differences result from smaller differences in time and rate of V absorption, due to longer release time of the drug in stomach.

Pharmacological activity of metabolite N is 20% of that of V as concerns the vasodilatory effect but N does not exert antiarrhythmic activity [29]. The calculated average value of t_{max} for N for reaches 5.25 h for F and 1.29 for S (Table 2). The values of other pharmacokinetic parameters like elimination half-life time ($t_{0.5}$) in the absorption and elimination phase and volumes of distribution (V_d) can be considered as similar for V and N (Tables 1 and 2). These results confirm literature data showing similar or even higher concentration levels in plasma are found for N than V [30].

Krecic-Shepard et al. [31] suggested differences in pharmacokinetics of V depending on sex. They studied pharmacokinetics of 120 mg of V administered orally as sustained release formulation and conventional tablet in healthy middle-aged or older men and women. For both men and women, bioavailability was lower after sustained release fast formulation compared with release formulation without changes in the ratios of the N to V AUCs, suggesting an intestinal mechanism. They found that V clearance was faster in men compared with women when administered as either a sustained-release or fast-release formulation.

In this work no crucial influence of sex on V pharmacokinetics was found, similar to a study by Sasaki et al. [5].

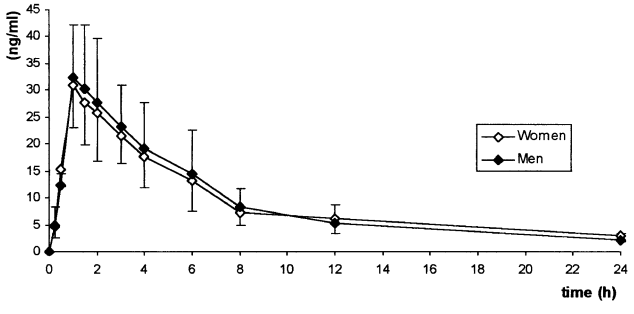

Fig. 5. Mean plasma concentrations of verapamil in six women and six men after administration of Staveran tablet 40 mg.

Mean values of pharmacokinetic parameters, for men and women separately are presented in Tables 3 and 4. F and S values are comparable with the data in Tables 1 and 2. It was discovered that mean value of t_{max} and $AUC_{0-\infty}$ for F is higher for men than for women. t_{max} amounted to 4.16 h for men and 3.33 h for women and $AUC_{0-\infty}$ was 400.68 ng ml^{-1} h and 328.62 ng ml^{-1} h, respectively. The value of other parameters is comparable. It should be stressed that Cl values for F and S are longer for women than for the men (Tables 3 and 4).

Controlled release of the drug in the stomach does not always contribute to its increased bioavailability. Rouge et al. [32] studied pharmacokinetics at atenolol administered as a conventional tablet and floating form (minitablets). Atenolol, a cardioselective β-blocker, was chosen because of its poor absorption in lower sections of the digestive tract. However, considerably lower bioavailability of atenolol from floating forms than from a tablet was obtained in those experiments. Probably, the residence time of minitablets in the stomach was too short and they managed to leave the stomach before releasing the whole dose.

Some sceptical opinions exist that the floating properties of the drug form should be referred only to water and should concern in vitro conditions [33]. In view of the results of the presented study it can be assumed that controlled release of V in the stomach for a long time is possible. Among the 'triad' bioavailability parameters, only C_{max} for S tablets is slightly greater than for F pellets. On the other hand, the mean values of t_{max} and AUC_{0-24}, $AUC_{0-\infty}$ for V and N are greater for pellets. This may have a considerable significance for dosing frequency, for example 1 or 2 capsules a day, while Staveran tablets in angina pectoris therapy are used 3–4 times a day.

The obtained values of pharmacokinetic parameters suggest that a multiple-unit floating pellet dosage form may be a more effective delivery system than the conventional tablet.

Acknowledgements

The author wishes to express his deep gratitude to Dr. M. Migdal, the coordinator of the Clinical Pharmacology Unit of the Child Health Center Monument Institute, Warsaw, Poland for organizing and supervising the clinical phase of the experiments.

References

[1] N. Follonier, E. Doelker, Biopharmaceutical comparison of oral multiple-unit and single-unit sustained-release dosage forms, STP Pharma Sci. 2 (1992) 141–158.
[2] C.G. Wilson, N. Washington, Assessment of disintegration and dissolution of dosage forms in vivo using gamma scintigraphy, Drug Dev. Ind. Pharm. 14 (1988) 211–281.
[3] G. Parker, C.G. Wilson, J.G. Hardy, The effect of capsule size and

density on transit through the proximal colon, J. Pharm. Pharmacol. 40 (1988) 376–377.
[4] R. Kirsten, K. Nelson, D. Kirsten, B. Heintz, Clinical pharmacokinetics of vasodilators, Clin. Pharmacokinet. 34 (1998) 457–482.
[5] M. Sasaki, T. Tateishi, A. Ebihara, The effects of age and gender on the stereoselective pharmacokinetics of verapamil, Clin. Pharmacol. Ther. 54 (3) (1993) 278–285.
[6] S.K. Gupta, S. Hwang, L. Atkinson, J. Longstreth, Simultaneous first-order and capacity-limited elimination kinetics after oral administration of verapamil, J. Clin. Pharmacol. 36 (1996) 25–34.
[7] J. Vlcek, K. Macek, P. Hulek, M. Bratova, Z. Fendrich, Pharmacokinetic parameters of verapamil and its active metabolite norverapamil in patients with hepatopathy, Arzneim-Forsch. Drug Res. 45 (1995) 146–149.
[8] W. Sawicki, S. Janicki, Model of a buccal drug form with verapamil. Part I. Preparation and in vitro release, Farm. Pol. 51 (1995) 599–603.
[9] W. Sawicki, S. Janicki, Influence of polyoxyethylene-10-oleylether on in vitro verapamil hydrochloride penetration through mucous membrane from a model buccal drug formulation, STP Pharma Sci. 8 (1998) 107–111.
[10] K. Goracinova, L. Klisarova, A. Simov, E. Fredro-Kumbaradzi, Physico-chemical stability of controlled-release solid dispersion granules containing verapamil HCL as active substance, Acta Pharm. 48 (1998) 93–100.
[11] W. Sawicki, S. Janicki, P. Pietkiewicz, A method of obtaining floating tablets with verapamil, Farm. Pol. 53 (1997) 698–701.
[12] W. Sawicki, A dry granulation method of obtaining floating granules with verapamil, Farm. Pol. 56 (2000) 116–120.
[13] W. Sawicki, A validated method for the determination of verapamil and norverapamil in human plasma, J. Pharm. Biomed. Anal. 25 (2001) 689–694.
[14] R. Löbenberg, G.L. Amidon, Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards, Eur. J. Pharm. Biopharm. 50 (2000) 3–12.
[15] S. Harder, M. Siewert, P. Thurmann, H. Blume, N. Rietbrock, B. Siewert, Plasma concentrations of S-verapamil after single doses of two different galenic formulation of racemic verapamil, Arzneim-Forsch. Drug Res. 5 (1993) 520–521.
[16] D. Lalka, R. Griffith, C.L. Cronenberger, The hepatic first-pass metabolism of problematic drugs, J. Clin. Pharmacol. 33 (1993) 657–669.
[17] R. Bodmeier, Tableting of coated pellets, Eur. J. Pharm. Biopharm. 43 (1997) 1–8.
[18] S. Janicki, Realization of the idea of multiparticulate dosage form, Farm. Pol. 55 (1999) 139–148.
[19] A.J. Moes, Gastroretentive dosage forms, CRC Crit. Rev. Ther. Drug Carrier Syst. 10 (1993) 143–195.
[20] K.H. Bauer, K. Lehmann, H.P. Osterwald, G. Rothgang, Film coatings, in: G. Lee (Ed.), Coated Pharmaceutical Dosage Forms, CRC Press, Stuttgart, 1998, pp. 65–119.
[21] C.C. Wang, G. Zhang, N.H. Shah, M.H. Infeld, A.W. Malick, J.W. McGinity, Influence of plasticizers on the mechanical properties of pellets containing Eudragit RS 30 D, Int. J. Pharm. 152 (1997) 153–163.
[22] G.L. Chen, W.H. Hao, In vitro performance of floating sustained-release capsule of verapamil, Drug Dev. Ind. Pharm. 24 (1998) 1067–1072.
[23] K.K. Hla, A.N. Latham, J.A. Henry, Influence of time of administration on verapamil pharmacokinetics, Clin. Pharmacol. Ther. 51 (1992) 366–370.
[24] V.B. Babu, K. Khar, In vitro and in vivo studies of sustained release floating dosage forms containing salbutamol sulfate, Pharmazie 45 (1990) 268–270.
[25] N. Mazer, E. Abisch, E. Gfeller, J.C. Laplanche, P. Bauerfeind, Intragastric behavior and absorption kinetics of a normal and 'floating' modified-release capsule of isradipine under fasted and fed conditions, J. Pharm. Sci. 77 (1988) 647–657.
[26] D.N. John, S. Fort, M.J. Lewis, D.K. Luscombe, Pharmacokinetics and pharmacodynamics of verapamil following sublingual and oral administration to healthy volunteers, Br. J. Clin. Pharmacol. 33 (1992) 623–627.
[27] A. Jankowski, A. Marzec, H. Lamparczyk, Comparative bioavailability of verapamil from rapidly absorbed and slow release preparations, J. Pharm. Biomed. Anal. 10 (1992) 1101–1103.
[28] L. Krówczynski, In vitro drug release testing, Farm. Pol. 4 (1996) 159–167.
[29] G. Neugebauer, Comparative cardiovascular actions of verapamil and its major metabolites in the anaesthetised dog, Cardiovasc. Res. 12 (1978) 247–254.
[30] S.K. Gupta, L. Atkinson, F. Theeuwes, P. Wonk, P.J. Gilbert, J. Longstreth, Pharmacokinetics of verapamil from an osmotic system with delayed onset, Eur. J. Pharm. Biopharm. 42 (1) (1996) 74–81.
[31] M.E. Krecic-Shepard, C.R. Barnas, J. Slimko, J.B. Schwartz, Faster clearance of sustained release verapamil in men versus woman: Continuing observations on sex-specific differences after oral administration of verapamil, Clin. Pharmacol. Ther. 68 (2000) 286–292.
[32] N. Rouge, E. Allemann, M. Gex-Fabry, L. Balant, E.T. Cole, P. Buri, E. Doelker, Comparative pharmacokinetic study of floating multiple-unit capsule, a high-density multiple-unit capsule and an immediate-release tablet containing 25 mg atenolol, Pharm. Acta Helv. 73 (1998) 81–87.
[33] J. Timmermans, A.J. Moes, Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy, J. Pharm. Sci. 83 (1994) 18–24.