J. Pharm. Pharmacol. 1991, 43: 721–725
Received February 25, 1991

Rectal Bioavailability of Water-Soluble Drugs: Sodium Valproate

MARÍA VICTORIA MARGARIT, INÉS CARMEN RODRÍGUEZ AND ANTONIO CEREZO

Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Granada, E-18071 Granada, Spain

Abstract—The influence of adjuvants in suppository formulations on the release and absorption of sodium valproate, a water soluble anti-epileptic, was analysed in order to determine the optimal formula for rectal administration. Three formulations were prepared with Suppocire AS_2(formula I), Aerosil R 972 (formula II) or Span 80 (formula III). In-vivo and in-vitro release-diffusion studies were performed using white laboratory rabbits as the experimental model. The adjuvants decreased the percentage release of valproic acid to 96·7% (formula I) and 84·1% (formula II), and delayed peak release-diffusion concentration (210 and 150 min, respectively, with formulas II and III in comparison with 120 min with formula I). Their effect on bioavailability was observed as an increase in plasma levels of the active substance, with areas under the plasma concentration/time curve of 396·26 and 306·64 $\mu g\ h\ mL^{-1}$ (formulas II and III, respectively) and 243·28 $\mu g\ h\ mL^{-1}$ (formula I). The time to peak plasma concentration was also delayed with peaks at 30, 55 and 50 min with formulas I, II and III, respectively.

The processes of release and absorption of drugs from suppositories are complex. Once the suppository has melted or dissolved, it spreads to form a viscous film which coats the rectal mucosa and creates an aqueous/vehicle interface which permits the release of the active substance. The drug then crosses the biological membrane and enters the circulation. The process of absorption therefore takes place in three stages (Jaminet 1973): (i) destruction of the suppository, (ii) transfer from the excipient to the rectal medium, and (iii) absorption of the drug via the rectal mucosa.

Release and subsequent absorption depend to a great degree on the viscosity of the suppository mass, and on the mechanism of release from fatty bases. For water soluble drugs such as sodium valproate (Schoonen et al 1979; Crommelin 1980) these factors are influenced by the transport of particles of the drug toward the interface by sedimentation. Aerosil R 972 forms a lipophilic gel with the suppository excipient, thus delaying sedimentation of valproic acid toward the interface. Thus, absorption is limited by the drug's physicochemical properties.

The present study centered on the influence of formulation adjuvants (viscosity enhancing agents and surfactants) on the rectal absorption of sodium valproate, a water-soluble drug. The absence of rectal formulas for this anticonvulsive in the Spanish market led us to search for an optimal formula in suppository form. Previous studies showed Tween 61 (Margarit et al 1988) and Witepsol H-15 (Margarit et al 1989) to be appropriate bases. In the present study Suppocire AS_2 was chosen as the excipient.

Materials and Methods

Sodium valproate (Laboratorios Labaz, Madrid) was used as the active principle. Suppocire AS_2 (Gattefosse, Barcelona), semisynthetic glyceride, was used as the suppository base. Three qualitatively and quantitatively different formulations were tested: one which included the viscosizing agent Aerosil R 972 (Degussa, Frankfurt, Germany), one with Span 80 (Atlas Chemicals, Barcelona, Spain) as a surfactant and one with Suppocire AS_2 only as the base. The compositions and characteristics of the different formulations are summarized in Table 1. The suppositories were prepared in plastic moulds to a final weight of approximately 1·9 g, with 150 mg sodium valproate (50 mg kg^{-1}).

Sodium valproate content in the suppositories was determined by volumetry in an anhydrous medium with 0·1 M perchloric acid (1 mL perchloric acid $\cong$ 16·62 mg sodium valproate). In accordance with the Pharmacopoeia Helvetica (1977) the dose did not deviate more than $\pm$ 10% from the stated value. Disintegration time was determined at 39°C (the rectal temperature of rabbits) using an Erweka ZT 3 device (Huesenstamm, Germany). Both the British (1988) and European (1980) Pharmacopoeias establish a minimum of 30 min for lipophilic suppositories and a maximum of 60 min for hydrophilic formulations. Other parameters determined included dimensions (micrometer), hardness (Erweka SBT), weight (Mettler H-20 precision scale (Zurich), and melting point (Krowczynski device) using the modified technique of Fauli & del Pozo (1964).

In-vitro release-diffusion tests were performed by adapting an Erweka ZT 3 device with a regenerated cellulose dialysis membrane (Visking 30/20 tubular membrane, Medicell International, London). One thousand mL of deionized water was used as the receptor medium, and 10 mL aliquots were withdrawn at fixed intervals. After drying and subsequent dissolution in 20 mL glacial acetic acid, determinations were performed with 0·01 M perchloric acid. The results were the means of six determinations, and were expressed as the percentage of the initial dose of drug dissolved at different times. In-vivo release-diffusion tests were carried out in groups of 6 white laboratory rabbits weighing 3–4 kg each. The animals were fasted for 37 h before the assays, but had free access to water. The different formulations (Table 1) were administered as a single dose of 50 mg kg^{-1} (rectal) and as a 150 mg/2 mL aqueous solution (oral), considered as the

Correspondence: M. V. Margarit, Departamente de Farmacia y Tecnologia Farmaceútica, Facultad de Farmacia, Universidad de Granada, E-18071 Granada, Spain.

Table 1. Pharmaceutical characteristics of suppositories containing sodium valproate.

	Formula (g/100 suppositories)		
Composition	I	II	III
Sodium valproate	15·0	15·0	15·0
Suppocire AS_2	74·22	69·95	57·14
Aerosil R 972 (5%)	—	4·27	—
Span 80 (20%)	—	—	17·08
Form	Suspension	Suspension	Suspension
Colour	White	White	Tan
Diameter (mm)	8·16	8·30	8·22
Length (mm)	20·30	20·55	20·62
Dose (mg) (n = 10)	148·33 ± 4·38 (2·95)*	154·07 ± 2·48 (1·61)	146·50 ± 3·74 (2·55)
Weight (g) (n = 20)	0·86 ± 0·02 (2·39)	0·98 ± 0·02 (1·87)	0·92 ± 0·02 (1·61)
Hardness (kg) (n = 10)	1·820	2·210	1·050
Melting point (°C) (n = 5)	35	36	34·6
Disintegration time (n = 6) (min)	4·60	6·98	4·80

* Mean ± s.d. The values in parentheses are coefficients of variation.

standard solution, at one week intervals. Blood samples (2 mL) were drawn from the marginal vein of the ear, and plasma was separated and frozen at −20°C until analysis. Valproic acid in plasma was quantified by the homogeneous immunoenzymatic method (EMIT) (Elyas et al 1980; Braun et al 1981) with an Emit-Autolab 5000 system (Syva, Barcelona, Spain).

Results and Discussion

The suppositories used in this study conformed to the specifications of the pharmacopoeias consulted. Aerosil R 972 (a lipid gelling agent) increased the dose, weight, hardness, melting temperature and melting time, whereas Span 80 (a non-ionic water/oil surfactant), led to a non-significant decrease in dose and melting temperature and a significant decrease in hardness, while causing slight increase in weight and disintegration time.

The mean release-diffusion values of the different formulations are presented in Table 2, and the evolution of these values over time is plotted in Fig. 1. The adjuvants clearly decreased the rate of release and the dose released in formulas II and III in comparison with formula I. The release-diffusion of sodium valproate from formula I was rapid and nearly complete, with the maximum concentration of the dose (approximately 97% of the actual dose) appearing in the receptor medium at 2 h with a t50 of 15·22 min. The rapid appearance of sodium valproate in the receptor medium was unsurprising, given the temperature at which the tests were performed (39°C) and the drug's affinity to water.

Aerosil R 972 (formula II) led to a slow release during the first 60 min (t50 = 81·72 min), followed by a faster rate of diffusion until t = 150 min, with maximum release at 3·5 h. This could have been due to the increased viscosity of the mass and the subsequent appearance of a small lipid/water interface; entrapment of the drug particles in the matrix may have delayed sedimentation. This is borne out by the data in columns 1 and 2 in Table 2, which compare the formula containing excipient alone (Suppocire AS_2)with that prepared with the adjuvant Aerosil R 972. These findings probably account for the low release seen toward the end of the assay (84% of the total dose).

The surfactant significantly influenced the release of

Table 2. Pharmaceutical availability (in-vitro diffusion) of the different formulas of suppositories.

Time (min)	% Dose in the liquid receptor medium		
	Formula I	Formula II	Formula III
15	38·040 ± 7·356 (7·720)*	5·263 ± 0·832 (0·873)	27·906 ± 5·898 (6·190)
30	69·400 ± 3·375 (3·542)	12·553 ± 2·319 (2·434)	50·556 ± 6·759 (7·095)
60	88·085 ± 1·905 (1·999)	28·907 ± 9·080 (9·530)	72·277 ± 5·017 (5·265)
90	93·511 ± 1·963 (2·060)	53·538 ± 10·720 (11·252)	81·987 ± 3·677 (3·859)
120	96·705 ± 1·924 (2·019)	70·078 ± 6·128 (6·432)	86·712 ± 2·933 (3·078)
150	96·705 ± 1·924 (2·019)	78·226 ± 5·060 (5·311)	91·938 ± 2·519 (2·644)
180	96·705 ± 1·924 (2·019)	82·061 ± 5·346 (5·611)	91·938 ± 2·519 (2·644)
210		84·119 ± 5·707 (5·989)	91·938 ± 2·519 (2·644)
240		84·119 ± 5·707 (5·989)	
270		84·119 ± 5·707 (5·989)	
Kinetic order	First	First	First
Intercept	4·324	4·739	4·386
K (min^{-1})	−0·0271	−0·0101	−0·0156
$r_{exptl.}$	−0·9895	−0·9890	−0·9929
t50 (min)	15·22	81·72	30·40

* Mean ± s.d. The values in parentheses are the confidence intervals.

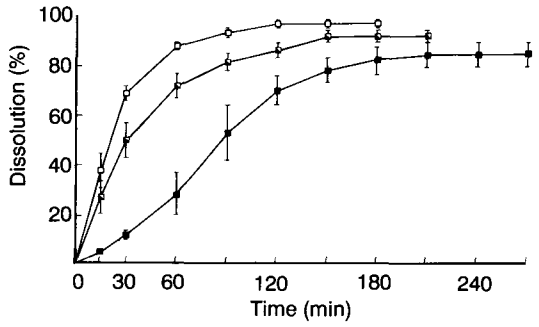

FIG. 1. Percentage of the dose in the suppository diffusion medium. Formula I (□), formula II (■), formula III (□).

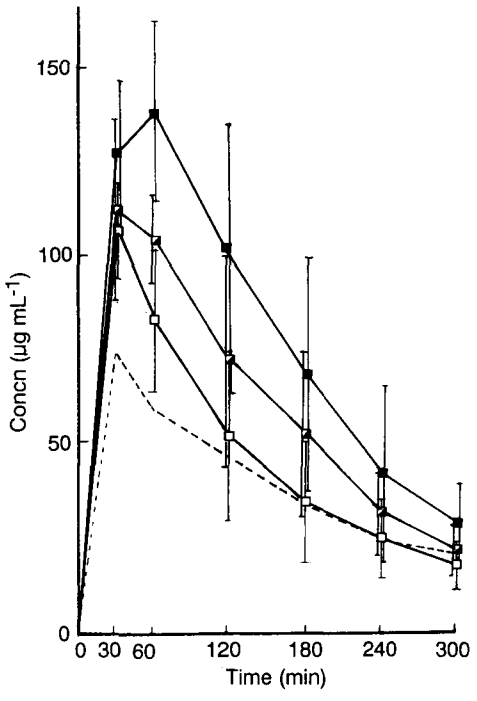

FIG. 2. Plasma concentration curves. Formula I (□), formula II (■), formula III (□), standard solution (- - -).

sodium valproate, as seen in Table 2 and Fig. 1. Maximum diffusion was recorded at 2·5 h, with release of 92% of the dose. Half of the dose (t50) was released at 30·4 min. This decrease in release-diffusion may be due to the nature of the excipient itself: a water/oil emulsion may have formed, trapping the drug in the internal phase and thus impeding release and delaying diffusion. The formation of such an emulsion was suggested by the appearance of a milky, homogeneous liquid on the inner surface of the dialysis membrane.

A study of the release-diffusion kinetics—the dose not diffused at a given time—shows that the formulas release the drug according to first-order kinetics. However, the adjuvants retarded this process, as indicated by the decreases in the specific rate constants (Table 2).

The data for plasma concentration and pharmacokinetic parameters of the standard solution (orally administered 150 mg/2 mL aqueous solution) and the suppository formulations are summarized in Table 3. Fig. 2 shows the corresponding plasma concentration/time curves.

After administering the suppositories to rabbits, we studied the evolution of plasma concentration of valproic acid over time. The kinetics followed an open, one-compartment model. Maximum plasma concentration increased significantly, to above the maximum therapeutic concentration (100 $\mu g\ mL^{-1}$), and was reached after 30, 55 and 50 min respectively in formulas I, II and III. The differences in the area under the plasma concentration/time curve and in plasma clearance were also significant (Table 3). The differences in the other pharmacokinetic parameters were less marked, with rapid elimination and half-life (approx. 1·5 h), as shown by the pronounced drop in the plasma concentra-

Table 3. Plasma concentration and pharmacokinetics data of the standard solution and of the different suppository formulas.

Time (min)	Concentration ($\mu g\ mL^{-1}$)			
	Standard sol.	Formula I	Formula II	Formula III
30	74·58 ± 15·7*	106·00 ± 12·63	127·00 ± 20·81	111·67 ± 24·38
60	59·58 ± 8·4	82·67 ± 19·44	138·50 ± 23·79	104·17 ± 12·67
120	46·17 ± 11·2	51·83 ± 23·21	99·00 ± 36·20	71·83 ± 29·43
180	33·50 ± 9·3	34·67 ± 16·17	67·67 ± 31·78	52·00 ± 21·91
240	24·08 ± 7·1	24·83 ± 10·63	41·83 ± 23·97	31·67 ± 11·13
300	20·92 ± 5·9	17·83 ± 6·61	28·33 ± 11·02	22·33 ± 6·74
AUC_5 ($\mu g\ h\ mL^{-1}$)	203·86 ± 32·18	243·28 ± 68·78	396·25 ± 104·91	306·64 ± 81·37
AUC_∞ ($\mu g\ h\ mL^{-1}$)	271·35	285·73	467·37	368·53
C_{max} ($\mu g\ mL^{-1}$)	74·58 ± 15·7	106·00 ± 12·63	149·67 ± 17·18	114·67 ± 20·57
t_{max} (min)	30	30	55 ± 35·07	50 ± 15·49
K_1 (h^{-1})	0·2876	0·3957	0·4035	0·3699
$t_{\frac{1}{2}}$ (h)	2·4096	1·7517	1·7175	1·8735
FD_5 (%)	101·93	100·91	99·80	99·58
Vd ($L\ kg^{-1}$)	0·56	0·37	0·23	0·30
CL ($L\ kg^{-1}\ h^{-1}$)	0·16	0·15	0·09	0·11
F_{rel} (%)		106·48	167·68	139·06

*Mean ± s.d.

tion/time curve, and a small apparent distribution volume.

The effect of the adjuvants on the absorption of sodium valproate was similar to that seen in the in-vitro release-diffusion studies, as they retarded the time to maximum plasma concentration in-vivo (formulas II and III vs formula I, Table 3). Through its gelling effect, Aerosil R 972 increases the viscosity of the suppository mass, reducing its spreading capacity in the rectum and hence the surface of exposure. Due to the limited spread of the suppository mass in the rectum, sodium valproate is absorbed via the lower and medial, but not by the upper haemorrhoidal veins, and thus directly enters the general circulation, bypassing the liver and first-pass metabolism. This would explain the high plasma concentration of formula II, in agreement with earlier studies (Quevauviller & Juhd 1951; Jay et al 1985). However, it is not clear whether sedimentation is the only limiting factor in sodium valproate absorption.

The effect of surfactant agents on drug absorption can vary (Gibaldi & Feldman 1970; Florence & Gillan 1975). In our study, the effects of Span 80 can be traced to the increased permeability of the biological membrane, caused by the penetration of the lipid layer of the membrane by the surfactant, thus enhancing absorption.

An overall analysis of the results shown in Table 3 underscores the significant differences in the pharmacokinetic parameters and the relative bioavailability (F_{rel}) (calculated by comparing the area under the plasma concentration time curve (AUC_x)), found after oral and rectal administration. Bioavailability approached that obtained after oral administration for formula I (106·48%) and above for both formula II (167·68%) and formula III (139·06%).

To study the correlation between in-vitro and in-vivo findings, we compared analogous parameters, e.g. percentage of the dose released (%D) against fraction of the dose absorbed (FD%) at each sampling time and after the same period (Fig. 3). Linear regression analyses detected no significant correlation at the 0·05 level of probability. An inverse relationship between these two parameters appeared in formula I, since the absence of adjuvant led to quicker absorption with a lower peak plasma concentration in comparison with formulas II and III. Since valproate was rapidly eliminated, the values of FD% used in the correlation corresponded to the portion of the plasma concentration curve when elimination was the predominant trend. Thus the data for FD% actually represent the amount of drug remaining in the circulation, whereas the values of %D correspond to the initial release-diffusion phase. This situation was not observed in previous experiments with formulations of sodium valproate with different suppository excipients, including Witepsol H-15 (Margarit et al 1989), Myrj 51 and polyethelene glycol 1500 (Margarit et al unpublished data), in which the correlation was always positive.

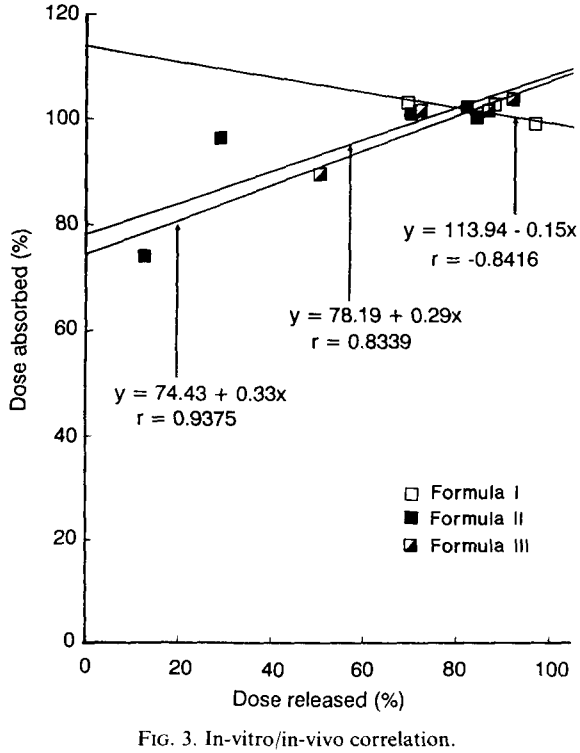

FIG. 3. In-vitro/in-vivo correlation.

It should nevertheless be recalled that the correlation between in-vivo and in-vitro findings is influenced by the in-vitro method used (dialysis membrane) as well as by biological factors in-vivo such as intrarectal pressure, membrane transport across the biological membrane, location of the suppository within the rectum and first pass metabolism.

Conclusions

The in-vitro release-diffusion of sodium valproate through cellulose membranes in our preparations was nearly complete (80–97%), and can be considered a process of first order kinetics.

The adjuvants Aerosil R 972 and Span 80 decreased the rate and magnitude of release-diffusion, but the effect of the former was more pronounced.

The pharmacokinetics of sodium valproate administered rectally to white laboratory rabbits reflected an open, one-compartment model with a first order elimination constant and rapid absorption. Plasma concentrations were higher than the therapeutic concentration and the concentrations recorded after oral administration.

The presence of the adjuvants significantly modified the pharmacokinetic data. Aerosil R 972 and Span 80 had similar effects, increasing plasma concentrations of the drug and delaying maximum concentration. The absorption profiles for both formulations were similar, with larger AUC values after rectal than after oral administration, suggesting that sodium valproate is absorbed more effectively when administered as a suppository. Sedimentation may not be the only inhibiting factor involved in the absorption of water soluble drugs.

We conclude that sodium valproate can be effectively formulated for rectal adminstration in fatty based suppositories.

Acknowledgements

This study was awarded the Enrique Gelabert Prize (Royal Academy of Medicine and Surgery of Murcia, Spain) in 1989. We thank Laboratorias Labaz in Madrid for supplying sodium valproate, and Jean Sanders and Karen Shashok for translating the original manuscript into English.

References

Braun, S.L., Tausch, A., Vogt, W., Jacob, K., Knedel, M. (1981) Evaluation of a new valproic acid enzyme immunoassay and comparison with a capillary gas-chromatographic method. Clin. Chem. 27: 169–172

British Pharmacopoeia (1988) Vol II, Her Majesty's Stationery Office, London, A 142

Crommelin, D. J. A. (1980) In vitro release studies on drugs suspended in non-polar media. The release of sodium chloride, paracetamol and chloramphenicol from suspensions in liquid paraffin. Pharm. Weekblad 115: 578–579

Elyas, A. A., Goldberg, V. D., Ratneraj, N., Lascelles, P. T. (1980) Valproic acid estimation by enzyme immunoassay. Ann. Clin. Biochem. 17: 307–310

Fauli, C., del Pozo, A. (1964) Temperatura de fusión de los supositorios. Galénica Acta 17: 283–318

Florence, A. T., Gillan, J. M. N. (1975) Non-ionic surfactants and membrane transport of thioridazine in goldfish. J. Pharm. Pharmacol. 27: 152–159

Gibaldi, M., Feldman, S. (1970) Mechanisms of surfactant effects on drug absorption. J. Pharm. Sci. 59: 579–589

Jaminet, F. (1973) Aspects biopharmaceutiques de la formulacion des suppositoires. In: Guillot, B. R., Lombard, A. P. (eds) Le Suppositoire. Maloine S. A., Paris, pp 117–134

Jay, M., Beihn, R. M., Digenis, G. A., Deland, F. H., Caldwell, L., Mlodozeniec, A. R. (1985) Disposition of radiolabelled suppositories in humans. J. Pharm. Pharmacol. 37: 266–268

Margarit, M. V., Rodríguez, I. C., Cerezo A. (1988) Biodisponibilidad rectal en conejos de valproato sódico en formulaciones con tween 61. XXXIII Congreso Nacional de la A.E.F.H. Córdoba, pp 485–491

Margarit, M. V., Rodríguez, I. C., Cerezo, A. (1989) Aspectos farmacocinéticos del valproato sódico administrado por via rectal a conejos. An. Real Acad. Pharm. 55: 485–496

Pharmacopée Européenne (1980) 2nd edn, Maisonneuve S.A, parte II, pp 54–55

Pharmacopoeia Helvetica VI (1977) Francaise edn, vol. III, Berne, pp 565–566

Quevauviller, A., Juhd, Y. (1951) La médication par voie rectale évite-t-elle la barrière hépatique? Ann. Pharm. Franç. 9: 593–598

Schoonen, A. J. M., Moolenaar, F., Huizinga, T. (1979) Release of drugs from fatty suppository bases I. The release mechanism. Int. J. Pharm. 4: 141–152