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Myrj 51 as a suppository excipient: Influence on pharmaceutical availability and bioavailability of sodium valproate

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Summary

The nonionic, water-soluble surfactant myrj 51, which is known to be well tolerated physiologically, was tested in a preformulation study to analyze the physicochemical properties of suppositories containing this excipient. We also investigated the release-diffusion characteristics in vitro and in vivo, using the rabbit as an experimental model, of those formulations that fulfilled the specifications set down in different pharmacopeias. Three formulations were studied: one containing myrj 51 (formula I), one with Aerosil R 972 as an adjuvant (formula II), and one with Span 80 as an adjuvant (formula III). The release-diffusion concentration of sodium valproate (150 mg) from these formulations was nearly complete, peak concentrations ranging from 93.31 to 100.95% and reaching 50% of the release-diffusion concentration after approx. 30 min with formulae I and III, and after 63 min with formula II. Absorption was rapid, with peak concentrations of 123.33 (formula I), 113.21 (formula II) and 96.17 μg/ml (formula III) between 30 and 60 min after administration. Bioavailability approached that achieved via oral administration, amounting to 112.3, 111.9 and 94.1% with formulae I–III, respectively. We conclude that myrj 51 is an appropriate excipient in formulations designed for rectal administration.

Introduction

Most studies of pharmaceutical technology note the suitability of using nonionic surfactants, chemically related with polyethylene glycols, as suppository excipients, as a result of their ability to act as efficient vehicles for drug absorption via the rectal mucosa. Surfactants can be used alone, in combination, or in addition to classical lipophilic suppository excipients.

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The mechanism of action of surfactants is complex and is not fully understood due to the large variety of effects they can produce (Gibaldi and Feldman, 1970; Rieger, 1988). Drug release from suppositories is favored by: (1) an increase in the exposed surface area of the suppository mass in the rectal ampulla; (2) a decrease in interfacial tension between the excipient and the rectal fluid; and (3) enhanced wetting of the drug (Möes, 1976). Drug absorption is enhanced by an increase in permeability resulting from the penetration of the surfactant into the biological membrane, or impeded by drug-micelle interactions with the surfactant (Florence and Gillian, 1975).

The present preformulation study describes the analysis of the physicochemical properties of suppositories containing myrj 51. Those formulations that fulfilled the specifications set down in different pharmacopeias were further investigated in order to determine, on the basis of representative kinetic and pharmacokinetic parameters, the pharmaceutical availability and bioavailability of the anti-epileptic sodium valproate in laboratory white rabbits. Our ultimate goal was to shed light on the behavior of this excipient and to provide evidence for its inclusion in the list of useful suppository bases.

Materials and Methods

The nonionic o/w surfactant myrj 51 (Atlas Chemicals), with a hydrophilic-lipophilic balance (HLB) of 16, was used as the suppository base. The waxy solid is soluble in water and organic solvents, but insoluble in mineral oils. In pharmacological terms, it is characterized by its good physiological tolerance and low toxicity (Am. Pharm. Assoc. and Pharm. Soc. G. Br., 1986). Three qualitatively and quantitatively different formulations were prepared (Table 1), one with myrj 51 alone, and one each with Aerosil R 972 (Degussa), or Span 80 (Atlas Chemical) as an adjuvant. The active substance was sodium valproate (L. Labaz), a drug with physicochemical properties amenable to formulation in suppository form (Chang, 1979; Reynolds, 1982; Moffat et al., 1986). The suppositories were prepared by fusion in plastic molds to a final weight of approx. 1 g, and contained a dose of 150 mg sodium valproate (equivalent to 50 mg/kg animal body weight).

Technical assays

The appropriate assays for suppositories, according to the specification of the Pharmacopoeia Helvetica (1977), British Pharmacopoeia (1988) and Pharmacopée Européenne (1980), were performed: dimensions (vernier calipers), hardness (Erweka STB device), weight (Mettler precision balance), disintegration time (Erweka ZT 3) and dose (volumetry in anhydrous medium with 0.1 N perchloric acid) (Margarit et al., 1988).

In vitro release-diffusion test (availability)

An Erweka ZT 3 device (used to determine disintegration time) was adapted by incorporating a regenerated cellulose dialysis membrane (Visking 30/20). Assays were performed with deionized water at 39°C (rectal temperature of the

TABLE 1

Sodium valproate suppositories

Components	Formula (g/100 suppositories)		
	I	II	III
Sodium valproate	15.0	15.0	15.0
Myrj 51	77.95	72.99	58.13
Aerosil R 972 (5%)	–	4.95	–
Span 80 (20%)	–	–	19.81
Physicochemical properties			
System	suspension	suspension	suspension
Color	white	white	beige
Diameter (mm)	8.15	8.27	8.12
Length (mm)	20.50	20.67	19.82
Dose (mg) ($n = 10$)	158.06 ± 3.25	155.65 ± 1.66	145.26 ± 1.23 [a]
Weight (g) ($n = 20$)	0.99 ± 0.02	1.03 ± 0.01	0.93 ± 0.03
Hardness (kg) ($n = 10$)	3.90	3.24	1.08
Disaggregation (min) ($n = 6$)	39.98	48.40	40.52

[a] Mean ± S.D.

rabbit). The amount of sodium valproate released was measured as a function of time by volumetry in an anhydrous medium with 0.01 N perchloric acid) (Margarit et al., 1988).

In vivo assays

Groups of six albino laboratory rabbits (body weight approx. 3–4 kg each) were fasted for 37 h prior to testing, but allowed unlimited access to tap water. The different formulations (Table 1) were administered as a single dose of 50 mg/kg body weight and as a 150 mg/2 ml aqueous solution, considered as the standard solution, at intervals of 1 week. Blood samples (2 ml) were drawn from a marginal ear vein, and plasma was separated and frozen at −20°C until analysis. The plasma concentration of valproic acid was determined according to the homogeneous immunoenzymatic method (EMIT) (Elyas et al., 1980; Braun et al., 1981) with an Emit-Autolab 5000 system (Syva).

Results and Discussion

The formulae designed in this preformulation study (Table 1) fulfilled the specifications of the pharmacopeias cited above. The actual doses we used were within ±10% of the declared dose, in accordance with the Pharmacopoeia Helvetica (1977), and disintegration time was less than 60 min, the upper limit stipulated by the British Pharmacopoeia (1988) and the Pharmacopée Européenne (1980).

Addition of the adjuvants Aerosil R 972 or Span 80 decreased the variations in dose, reduced hardness in formulae II and III in comparison to formula I, and increased disintegration time in formulae II and III to 48.40 and 40.52 min, respectively, as compared to formula I (Table 1).

Although myrj 51 is considered a hydrophilic, solubilizing agent, our assays failed to detect such effects, thus valproic acid remained in suspension. This may be because the drug/excipient

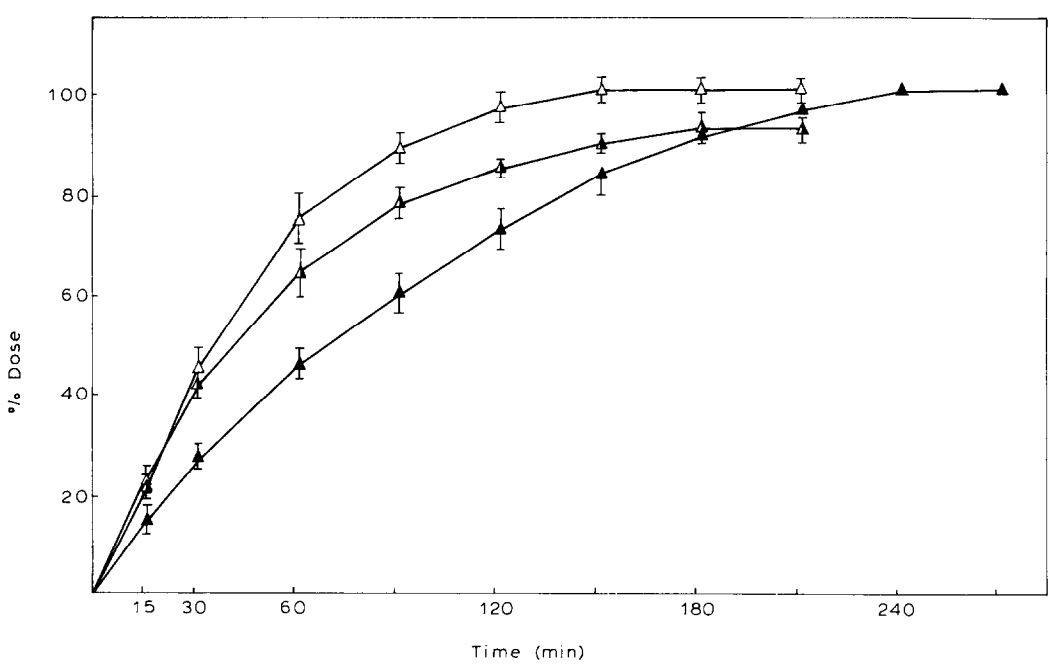

Fig. 1. Percentage of the dose in the suppository diffusion medium. Formula I (△), formula II (▲), formula III (▲).

ratio used surpassed the solubility coefficient of the drug in this excipient. If this were true, drug release from myrj 51 would occur through the combination of sedimentation of particles in the excipient/rectal fluid interphase (suspended drug), and diffusion to the aqueous medium (drug dissolved in the excipient).

The results of the release-diffusion assays were used to calculate the values of kinetic parameters and plot the findings for each formula investigated (Fig. 1). In formula I, 50% of the dose had reached the diffusion medium by 33.77 min, before disintegration was complete (39.98 min). In other words, by the time the suppository had completely disintegrated, half the dose was dissolved. This behavior may be due to limited retention of the drug in surfactant micelles, and to high solubility of sodium valproate in water, which would lead to a rapid rate of release ($K = 0.0325$ min^{-1}), with peak (total) values occurring at 150 min. The addition of Aerosil R 972 (formula II) delayed release-diffusion of sodium valproate, with a $t_{50\%}$ for diffusion of 63 min. At the end of the assay (270 min), all the dose had reached the receptor medium. The addition of Span 80 (formula III) produced an excipient composed of two surfactants that differed in nature and chemical structure, with HLB values of 16 and 4.3, respectively. The HLB of this mixture was 13; this surfactant would be expected to form a light or translucent dispersion, rather than a solution, and to give rise to an o/w emulsion. Consequently, the rate of release of drug from formula III was slowed than that from formula I ($K = 0.0148$ min^{-1}), with a $t_{50\%}$ of 39 min, and a peak concentration of 93% (stabilization) after 3 h.

As demonstrated by these data for the amount of unreleased drug at different times, release-diffusion occurred according to first-order kinetics, with a correlation coefficient approaching unity ($r = 0.99$) ($p < 0.001$). Since the kinetic data for formula II reflected neither first- nor zero-order kinetics, and since the correlation coefficients were low, we divided the curve into two parts. In the first period, from 0 to 120 min, the points fit a theoretical straight line with a correlation coefficient of 0.9976, and the release-diffusion rate constant was 0.0107 min^{-1}. In the second period, from 120 to 240 min, the correlation coefficient was 0.9861, and release was more rapid ($K = 0.0271$ min^{-1}). In each phase, $t_{50\%}$ was calculated separately as 4.57 and 6.63 min, however,

TABLE 2

Plasma concentration and pharmacokinetic data for the standard solution and formulae I–III

Time (min)	Concentration (μg/ml)			
	Standard	Formula I	Formula II	Formula III
30	74.58 ± 15.7 [a]	121.17 ± 36.05	109.17 ± 21.17	94.00 ± 21.12
60	59.58 ± 8.4	111.17 ± 44.75	111.00 ± 22.80	86.83 ± 15.18
120	46.17 ± 11.2	70.83 ± 31.22	75.17 ± 18.22	54.17 ± 15.14
180	33.50 ± 9.3	38.50 ± 15.08	41.00 ± 14.17	30.17 ± 9.11
240	24.08 ± 7.1	21.67 ± 7.86	22.67 ± 6.71	17.67 ± 4.50
300	20.92 ± 5.9	15.67 ± 3.39	14.17 ± 4.07	10.67 ± 3.20
$(AUC)_5$ (μg h ml^{-1})	203.86 ± 32.18	290.58 ± 106.86	290.78 ± 64.85	225.53 ± 47.92
$(AUC)_\infty$ (μg h ml^{-1})	271.35	321.03	315.12	247.25
C_{max} (μg ml^{-1})	74.58 ± 15.7	123.33 ± 38.31	113 ± 21.33	96.17 ± 20.38
T_{max} (min)	30	35.00 ± 12.25	50 ± 15.49	50.00 ± 15.49
K (h^{-1})	0.2876	0.4872	0.5598	0.5032
$T_{1/2}$ (h)	2.4096	1.4224	1.2379	1.3772
(FD)5 (%)	101.93	100.53	100.31	99.79
V_d (l kg^{-1})	0.56	0.29	0.25	0.33
Cl (l kg^{-1} h^{-1})	0.16	0.14	0.14	0.17
F rel. (%)		112.27	111.91	94.09

[a] Mean ± S.D.

since these values were not significant, the $t_{50\%}$ for the entire assay was estimated as approx. 63 min by interpolation of the linear portion of the plot for the first 120 min. According to this formula, drug release occurred in two successive stages, both reflecting first-order kinetics, although the first stage was slower than the second.

This behavior, differing from that of the other two excipients tested, may have appeared because the surfactant acted on two fronts, favoring the formation of micelles that trapped the drug, or creating a homogeneous, structured, fluid dispersion that coated the inner surface of the dialysis membrane and impeded the diffusion of sodium valproate.

To investigate bioavailability, we recorded the evolution of plasma concentrations of valproic acid with time after the oral administration of 150 mg of sodium valproate (standard solution) and after rectal administration. The results are listed in Table 2, and the plasma level/time curves are reproduced in Fig. 2.

Absorption was rapid and complete, with peak concentrations appearing within 1 h of administration in all formulations. The C_{max} values differed significantly between the suppository formulae and the oral solution, whereas t_{max} for formula I was closer to that for the oral solution than for either of the other two formulae (Table 2). This finding was probably due to the presence

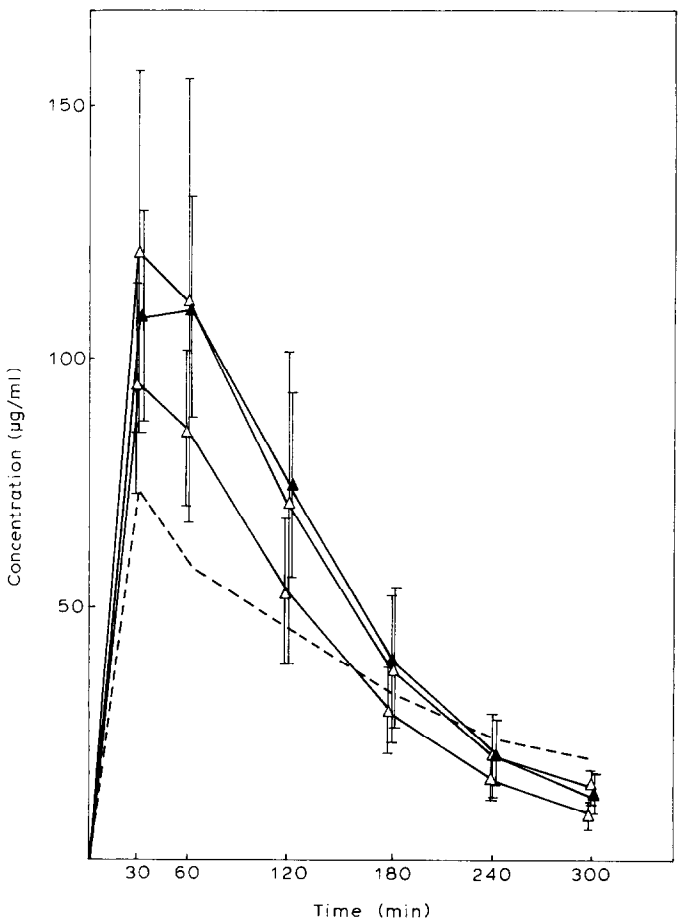

Fig. 2. Plasma concentration curves. Formula I (△), formula II (▲), formula III (▲), standard solution (- - -).

of colloidal silica and Span 80 with formulae II and III, respectively. These two adjuvants have different mechanisms of action: in the presence of rectal water, Aerosil R 972 forms a hydrophilic gel (excipient gelling) that traps the drug, which is highly water-soluble. This, together with the extended disintegration time (48.40 min), may have delayed t_{max}. In formula III, the HLB was 13, which may have favored the formation of micelles that trapped the drug. This, in combination with the fact that the mixture of surfactants can form a viscous dispersion coating the rectal mucosa, may have prevented passage of the drug through the biological membrane, a phenomenon that may explain why plasma levels with formula III were the lowest of all formulae tested.

The elimination kinetics (K and $T_{1/2}$; Table 2) of valproic acid after a single rectal administration were similar in all three formulae. However, these results differed significantly from the values yielded by the standard solution.

Relative bioavailability was comparable in formulae I and II, but reduced in formula III (Table 2).

Statistical analysis of the in vitro/in vivo correlation between values for analogous parameters, e.g., percentage dose released (%D) and fraction of dose absorbed (FD%) at each sampling time and for the same period (Fig. 3), revealed a lack of correlation between the two sets of parameters at a level of significance of $p < 0.05$. This finding may be due to interference by the dialysis membrane used in the release-diffusion assays, which may have delayed passage of the drug to the diffusion medium. In addition, physiological factors inherent to the biological milieu of the in vivo studies, e.g., intrarectal pressure, transport across the biological membrane, and metabolic influences, may have affected the results.

The formulae designed and tested in this study complied with the specifications for suppositories set down in three authoritative European pharmacopeias: uniform dose, and appropriate weight, disintegration time and hardness.

Release-diffusion studies showed that the excipient myrj 51 was a good vehicle for the rectal administration of sodium valproate, releasing almost the entire dose (93.3–100%). The release

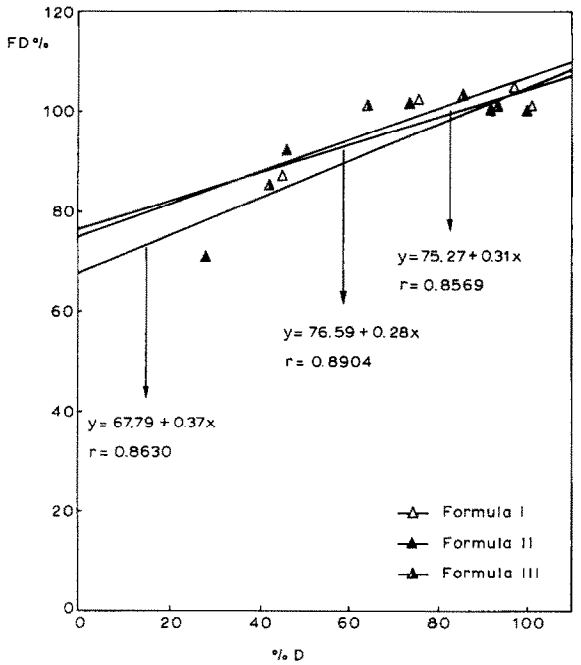

Fig. 3. In vitro/in vivo correlation. Formula I (△), formula II (▲), formula III (▲).

kinetics were of the first-order type, and were slowed by the adjuvants Aerosil R 972 and Span 80.

The absorption of sodium valproate from this vehicle was rapid and complete, and produced therapeutic plasma concentrations higher than those recorded for oral administration. No significant differences between the three formulae were observed for the pharmacokinetic characteristics and bioavailability.

Our observation may be applicable to other water-soluble drugs, therefore, myrj 51 is likely to prove a suitable vehicle for the rectal administration of water-soluble agents that act on a systemic level.

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