International Journal of Pharmaceutics, 14 (1983) 251–262
Elsevier Biomedical Press

Influence of physicochemical interactions on the properties of suppositories V. The in vitro release of ketoprofen and metronidazole from various fatty suppository bases and correlations with in vivo plasma levels

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(Received June 22nd, 1982)
(Accepted September 15th, 1982)

Summary

Various membrane and non-membrane methods of in vitro measurement of drug release from suppositories were examined from a literature survey and using 200 mg fatty suppository formulations containing 7.4 mg of ketoprofen or 46 mg of metronidazole. The fatty suppository formulations differed in the bases, which were either commercial bases or binary mixtures of pure triglycerides. Rotation about various axes of a cylindrical cell fitted with a membrane at each end gave essentially the same in vitro release profile provided that the molten base did not coat the membrane surface. Linear correlations between the drug concentration released in vitro and the in vivo levels in plasma at given time intervals after administration of various suppository formulations to rats were generally not statistically significant. On the other hand, comparison of these in vivo data with the non-membrane in vitro results using rank order correlation methods on paired data at each time interval for a number of suppository formulations showed statistically significant correlations. Although plastic viscosities did not correlate with in vitro release, the base with the lowest viscosity always gave the fastest release of either drug. On balance, non-membrane methods of measuring in vitro drug release are generally favoured.

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0378-5173/83/0000–0000/$03.00

Introduction

In previous papers in this series (Liversidge et al., 1981; Liversidge and Grant, 1982a and b; Grant and Liversidge, 1982) we have described thermal analytical, solubility, rheological and in vivo studies which relate to the physicochemical interactions in a number of proposed suppository formulations based on binary mixtures of triglycerides. The present report relates the in vitro release of the drugs from the proposed formulations to the physicochemical interactions and in vivo plasma levels of ketoprofen or metronidazole.

There is at present no satisfactory general in vitro method for predicting the in vivo bioavailability of drugs from suppositories. However, various in vitro techniques have proved successful for predicting in vivo release in specific cases. The most desirable in vitro apparatus would appear to be one that reproduces the conditions encountered in the rectum, including the properties of the rectal fluid, such as surface tension, viscosity, volume, temperature (37°C), pH, buffering capacity and area of contact between the base and the rectal fluid.

Two types of in vitro release apparatus can be identified, depending on whether or not they employ membranes. Membrane methods have been studied by Bhavnagri and Speiser (1971), Bornschein et al. (1978), Bornschein et al. (1980), Chongsathien and Plakogiannis (1980), Cid (1974), Ibrahim et al. (1980a and b), Kassem et al. (1975), Kerckhoffs and Huizinga (1967), Krowezynski (1982), Muranishi et al. (1979), Neuwald and Kunze (1964), Oroszne et al. (1979), Pasich et al. (1979, 1980), Setnikar and Fantelli (1962), Taylor (1979), and by Thomas and McCormack (1971). Non-membrane methods have been used by Baichwal and Lohit (1970), Gross and Becker (1953), Grzesiczak et al. (1980), Nerlo et al. (1979), Puech et al. (1977), Roseman et al. (1981), Schoonen et al. (1976, 1979) and by Stavchansky et al. (1979). Wolf and Voigt (1968) have reviewed the earlier methods.

Membrane systems have the following advantages: (a) they prevent mixing or emulsification of the base with the dissolution media; (b) the pressure or shear exerted on the suppository can be arranged to be similar to that in the rectum (Thomas and McCormack, 1971); (c) small amounts (2–3 ml) of liquid similar to that in the rectum can be placed with the suppository in a dialysis bag. The disadvantages of membrane systems are as follows (i–v). (i) The in vivo contact area, which is approximately 500 cm^2, cannot be simulated directly in vitro and may vary from vehicle to vehicle (Grant and Liversidge, 1982). Thus, the area available for diffusion is usually much less than the area of the rectum. (ii) The fatty base could coat the membrane in vitro and reduce the diffusion through it. (iii) Membranes can introduce a rate-limiting step into the system, the influence of which will depend on the relative magnitude of the release rate and the permeation rate. (iv) Osmotic attraction through the membrane towards the suppository may occur. This can be diminished by the proper choice of medium, but the amount of unstirred water around the suppository may remain uncertain. By analogy with release processes governed by diffusion, such a barrier might distort measurement of the actual release rate. (v) In most membrane methods, the interface between the suppository and the dissolution medium is not well-defined and, since spreading is often limited, the

thickness of the mass differs greatly from that occurring in vivo. Consideration of the above points suggests that the disadvantages of membrane systems appear to outweigh their advantages.

Non-membrane methods may avoid some of the disadvantages of membrane methods. Non-membrane models have the following advantages (i–ii). (i) They permit spreading of the molten suppository mass over a greater area, which by suitable experimental design, may approximate closely to the area corresponding to the rectum. (ii) There is no membrane to interfere with drug transport, so that the rate-limiting step tends to be controlled by the formulation under test instead of by the properties of the artificial membrane.

Non-membrane models can be subdivided into two types. (a) The first type comprises methods which use a standardized surface area for release, and which therefore give the release per unit area of molten base known as the intrinsic release. Cox and Breimer (1973) used an open cylindrical tube in which the suppository is retained during and after melting. (b) The second type includes methods that allow the suppository to spread freely over the surface of the dissolution medium. Schoonen et al. (1976) employed a variation of this procedure which involves a plate immersed in water, below which the suppository melts and spreads. Roseman et al. (1981) have proposed a method which, they claim, allows spreading of the suppository over the surface of beads immersed in the dissolution medium, thereby keeping the base confined. The advantages of the latter type (b) of non-membrane method is that it takes into account the spreading of the base in vivo whereas the former type of method (a) does not. Therefore, a suppository which spreads in the rectum and gives a high release rate on account of an increased surface area available for diffusion in methods (a) would show only an intrinsic release rate, which does not take into account the spreading in the rectum, whereas methods (b), which allow the suppository to spread, give a release rate that is more representative of the in vivo situation.

The disadvantages of the non-membrane models are as follows: (i) the base can be dispersed as small globules in the bulk of the dissolution medium; (ii) pressures similar to those occurring in the rectum cannot be applied; and (iii) if a melted suppository floats, a temperature gradient can arise between the bulk of aqueous solution and the air–liquid interface. However, this can be prevented by employing the method of Schoonen et al. (1976) or by maintaining the temperature of the air above the liquid surface at the same value as in the dissolution medium.

For all methods it is generally agreed that the temperature of the dissolution medium should be the same as that of the rectum, namely 37°C. The dissolution medium is usually buffered at pH 7.4 (often using Sörensen's phosphate buffer), although some workers use unbuffered distilled water (Puech et al., 1977).

In the present work the rates of drug release from suppositories in vitro were determined using a method without a membrane as well as a modified membrane method. The data from both in vitro methods were examined for correlations with the drug levels in vivo in the plasma of rats.

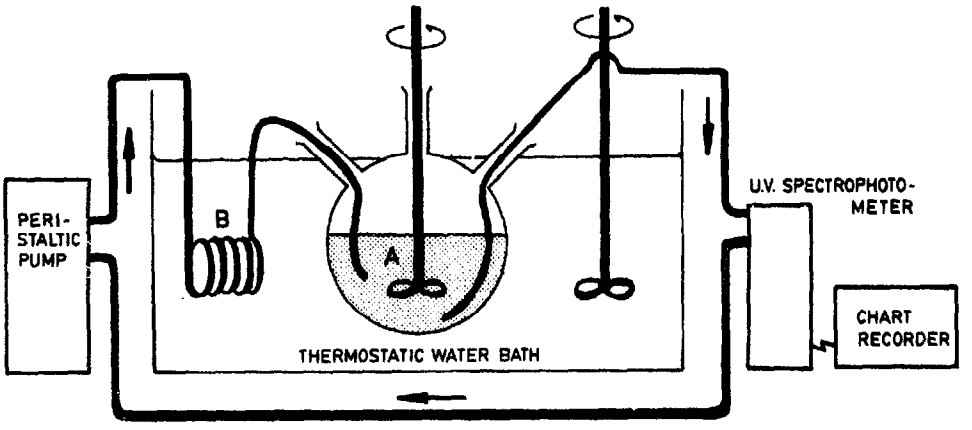

Fig. 1. Non-membrane method for determining the in vitro release of drugs from suppositories. Legend: A = dissolution medium to which the suppository is added; B = heat exchanger.

Materials and methods

The materials used and the formulation and preparation of the suppositories have been described previously (Liversidge et al., 1981; Grant and Liversidge, 1982; Liversidge and Grant, 1982a).

The apparatus for the non-membrane method of determining drug release in vitro is illustrated in Fig. 1. The conditions were as follows: stirrer speed, 70 rpm; buffer, Sörensen's pH 7.4; temperature, 37.4°C, within and above the buffer; drug assay by UV absorbance, for ketoprofen $\lambda_{max} = 265$ nm, and for metronidazole, $\lambda_{max} = 312$ nm. In the membrane method a beaker was substituted for the 3-necked flask, the stirrer was removed and the cell in the dissolution medium was rotated at 70 rpm in one of the modes illustrated in Fig. 2. Unless otherwise stated the cell dimensions

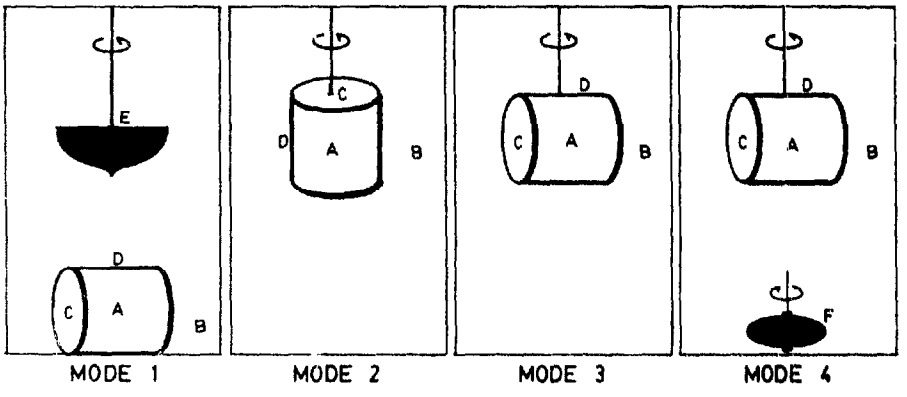

Fig. 2. The 4 modes of agitation of the membrane cell used for monitoring the in vitro release of drugs from suppositories. Legend: A = dissolution medium containing the suppository; B = external solution to be analyzed for the drug; C = cellulosic membrane (one at each end of the cylinder); D = cylindrical cell constructed from poly(methylmethacrylate) and described under Materials and methods; E = stirrer blade; F = magnetic follower.

were: length 2.0 cm, diameter 0.7 cm, volume 0.770 cm^3. Each circular end was fitted with a membrane to give a total surface area of 0.770 cm^2 for drug release. The membrane used was of pore diameter 3.0 μm and disc diameter 142 mm, Cellulosic 25EA 122112 (Nucleopore Cellulosic). The dissolution medium in the membrane cell was Sörensen's phosphate buffer, pH 7.4, potassium dihydrogen phosphate, 1.78 g/l, and disodium hydrogen phosphate dodecahydrate, 19.20 g/l.

Results and discussion

The membrane method is considered first. To investigate the influence of the degree of agitation, initially saturated solutions of metronidazole (1.25% w/v) in Sörensen's buffer were placed in the cell. Table 1 shows that the various modes of agitation, illustrated in Fig. 2, give essentially the same in vitro release profile and that the initial rate of mass transfer of metronidazole through the membrane of constant area is 0.147 $mg \cdot min^{-1}$ corresponding to an intrinsic release rate of 0.191 $mg \cdot min^{-1} \cdot cm^{-2}$.

The above experiment was repeated after having placed in the cell a 200 mg suppository containing 46 mg of metronidazole (a commercial May and Baker formulation) together with Sörensen's buffer at pH 7.4. As expected, the rate of metronidazole release is much lower from this suppository formulation (Table 2) than from the saturated solution (Table 1). Modes 1, 3 and 4 in Fig. 2 gave essentially the same in vitro release profile, the initial rate of mass transfer being 0.016 $mg \cdot min^{-1}$ corresponding to an intrinsic release rate of 0.0208 $mg \cdot min^{-1} \cdot cm^{-2}$. However, mode 2 gave an initial rate of mass transfer equal to 0.012 $mg \cdot min^{-1}$ which is much lower than that of the other 3 modes. The abnormally low

TABLE 1

THE EFFECT OF THE VARIOUS MODES OF AGITATION (FIG. 2) ON THE RELEASE OF METRONIDAZOLE THROUGH A 0.770 cm^2 MEMBRANE AREA FROM A 0.770 cm^3 CELL CONTAINING A SATURATED SOLUTION OF METRONIDAZOLE INTO A BEAKER CONTAINING 1 dm^3 OF SÖRENSEN'S BUFFER, pH 7.4

Time (min)	Metronidazole [a] (mg) released into 1 dm^3				Mean (mg) of modes 1–4	Standard deviation (mg) of modes 1–4
	Mode 1	Mode 2	Mode 3	Mode 4		
0	0	0	0	0	0	0
10	1.48	1.47	1.61	1.33	1.47	0.11
30	3.83	4.66	4.66	4.10	4.31	0.42
60	6.46	6.94	6.94	6.60	6.74	0.24
90	8.26	8.88	8.47	8.40	8.50	0.27
120	9.43	9.78	9.30	9.43	9.49	0.21

[a] Mean value for 3 determinations. Coefficient of variation < 3%.

TABLE 2

THE EFFECT OF THE VARIOUS MODES OF AGITATION (FIG. 2) ON THE RELEASE OF METRONIDAZOLE FROM A COMMERCIAL 200 mg SUPPOSITORY THROUGH A 0.770 cm^2 MEMBRANE AREA FROM A 0.770 cm^3 CELL INTO A BEAKER CONTAINING 1 dm^3 OF SÖRENSEN'S BUFFER, pH 7.4

Time (min)	Metronidazole (mg) released into 1 dm^3				Mean (mg) of modes 1, 3, 4	Standard deviation (mg) of modes 1, 3, 4
	Mode 1 [a]	Mode 2 [b]	Mode 3 [a]	Mode 4 [a]		
0	0	0	0	0	0	0
10	0.16	0.12	0.15	0.17	0.16	0.01
30	0.45	0.25	0.47	0.49	0.47	0.02
60	1.05	0.67	0.96	1.00	1.00	0.05
90	1.53	0.84	1.55	1.48	1.52	0.04
120	2.00	1.07	1.97	1.95	1.97	0.03

[a] Mean value for 3 determinations. Coefficient of variation < 5%.
[b] Mean value for 3 determinations. Coefficient of variation < 10%.

flux in mode 2 probably arises from a reduction in porosity of the upper membrane by coating with the molten fatty triglyceride base as it floats to the upper-most surface.

The mean values (Table 2) for the in vitro release of metronidazole from the commercial suppository in modes 1, 3 and 4 were plotted against the corresponding plasma levels in vivo (Table 3) at corresponding time intervals and were subjected to linear regression analysis. The regression coefficient (slope) is found to be 0.0369 while the y-intercept is 0.0437 $mg \cdot dm^{-3}$. Although the correlation coefficient is 0.8199 the probability that it deviates from zero is approximately equal to 0.5. Since

TABLE 3

RAT PLASMA LEVELS OF METRONIDAZOLE OR KETOPROFEN AFTER ADMINISTRATION OF COMMERCIAL 200 mg SUPPOSITORIES CONTAINING 46 mg OF METRONIDAZOLE OR 7.4 mg OF KETOPROFEN

Time [a] (min)	Metronidazole			Ketoprofen		
	Mean (μg/ml)	Standard deviation (μg/ml)	$\pm t_{0.05}$ (S.E.M.) (μg/ml)	Mean (μg/ml)	Standard deviation (μg/ml)	$\pm t_{0.05}$ (S.E.M.) (μg/ml)
10	14.8	4.0	5.0	40.3	10.2	17.0
30	30.5	7.6	9.5	57.8	5.5	9.2
60	31.7	9.4	11.7	47.0	6.1	10.2
90	28.7	-	-	36.5	-	-
120	28.1	-	-	29.4	-	-

[a] Time after administration of the suppository.

TABLE 4

IN VITRO RELEASE OF METRONIDAZOLE FROM VARIOUS SUPPOSITORY FORMULATIONS (LISTED IN TABLE 6) INTO 1 dm^3 SÖRENSEN'S BUFFER, pH 7.4 AT 37.4°C

Time (min)	Concentration [a] of metronidazole ($mg \cdot dm^{-3}$) released into solution					
	tc_{1m}	tc_{2m}	tc_{3m}	tc_{4m}	tc_{5m}	tc_{6m}
0	0	0	0	0	0	0
10	41.06	0.88	0.53	2.14	2.41	8.11
30	46.73	1.17	0.80	2.58	2.62	11.28
60	46.73	1.45	1.08	3.06	3.17	13.75

[a] Coefficient of variation < 5%.

this may be considered as a measure of the standard error, the correlation coefficient may be regarded as not being significant. Cells of various sizes were tested but all gave similar statistical results. Hence the release patterns obtained using cells with membranes did not correlate satisfactorily with the plasma levels in animals and in some cases an unquantifiable variable, coating of the membrane, was observed. Consequently, the non-membrane model was investigated in subsequent work.

For the non-membrane model the mean results of two readings are summarized in Table 4 for metronidazole and in Table 5 for ketoprofen, while the constituents of the suppository are summarized in Table 6. The release data for each formulation were compared with those obtained in vivo (Liversidge and Grant, 1982b). The in vitro release data in Table 4 were plotted against the in vivo plasma levels (Table 3; Liversidge and Grant, 1982b) obtained with a given formulation at corresponding time intervals and were subjected to linear regression analysis. The linear regressions for metronidazole (Table 7) and for ketoprofen (Table 8) show that only formulation tc_{4m} and tc_{2k} gave linear in vitro–in vivo correlations of statistically significant probability.

When the in vivo and in vitro data are compared using the Wilcoxon (1945) rank

TABLE 5

IN VITRO RELEASE OF KETOPROFEN FROM VARIOUS SUPPOSITORY FORMULATIONS (LISTED IN TABLE 6) INTO 1 dm^3 SÖRENSEN'S BUFFER, pH 7.4 AT 37.4°C

Time (min)	Concentration [a] of ketoprofen ($mg \cdot dm^{-3}$) released into solution					
	tc_{1k}	tc_{2k}	tc_{3k}	tc_{4k}	tc_{5k}	tc_{6k}
0	0	0	0	0	0	0
10	7.45	0.51	0.86	1.65	1.29	3.78
30	7.45	1.26	1.61	2.56	2.25	6.03
60	7.45	1.58	2.10	3.31	3.03	6.64

[a] Coefficient of variation < 5%.

TABLE 6

COMPOSITION OF THE SUPPOSITORIES USED IN THE IN VIVO EXPERIMENTS

Formulation code [a]	Composition of 200 mg suppository		
	Drug (mg)	Excipient expressed as % w/w ratio (and in mg)	
		Tricaprin (mg)	Other triglyceride (mg)
tc_{1m}	Metronidazole (46.0)	60 (92.4)	40 trilaurin (61.6)
tc_{2m}	Metronidazole (46.0)	40 (61.6)	60 trilaurin (92.4)
tc_{3m}	Metronidazole (46.0)	75 (127.8)	25 trimyrstin (26.2)
tc_{4m}	Metronidazole (46.0)	90 (144.8)	10 tripalmitin (9.2)
tc_{5m}	Metronidazole (46.0)	92 (146.3)	8 tristearin (7.7)
tc_{1k}	Ketoprofen (7.4)	60 (115.6)	40 trilaurin (77.0)
tc_{2k}	Ketoprofen (7.4)	40 (77.0)	60 trilaurin (115.6)
tc_{3k}	Ketoprofen (7.4)	75 (159.9)	25 trimyrstin (32.7)
tc_{4k}	Ketoprofen (7.4)	90 (181.1)	10 tripalmitin (11.6)
tc_{5k}	Ketoprofen (7.4)	92 (183.0)	8 tristearin (9.6)
tc_{6m}	Metronidazole (46.0)	Commercial (May and Baker) formulation	
tc_{6k}	Ketoprofen (7.4)	Commercial (May and Baker) formulation	

[a] These codes are referred to in Tables 4 and 5.

sum test on paired (in vitro and in vivo) data at each time interval, there is a significant difference between the in vivo and in vitro data with a probability of < 0.1 as shown in Tables 9 and 10. This suggests that a further non-parametric statistical treatment of the in vitro and in vivo data may be of value, and so the rank correlation (τ) method of Kendall (1970) was applied. Since there are tied ranks in the data, Kendall's modified formula for tied ranks was applied with a modified

TABLE 7

LINEAR CORRELATIONS BETWEEN THE IN VIVO PLASMA LEVELS AND THE IN VITRO RELEASE DATA FOR METRONIDAZOLE FROM GIVEN FORMULATIONS AT THE SAME TIME INTERVALS

Linear regression parameter	Formulation code (see Table 6)					
	tc_{1m}	tc_{2m}	tc_{3m}	tc_{4m}	tc_{5m}	tc_{6m}
regression [a] coefficient ($mg \cdot dm^{-3} \cdot min^{-1}$)	1.00	46.0	16.2	44.6	26.5	3.09
y-intercept [a] ($mg \cdot dm^{-3}$)	7.29	−36.1	15.3	−68.4	−28.9	−8.47
correlation coefficient	0.697	0.925	0.688	0.995	0.983	0.926
t score	0.971	2.44	0.948	10.1	5.35	2.45
probability	> 0.5	≈ 0.25	> 0.5	≈ 0.06	≈ 0.12	≈ 0.25

[a] y-axis corresponds to the in vivo plasma levels.

TABLE 8

LINEAR CORRELATIONS BETWEEN THE IN VIVO PLASMA LEVELS AND THE IN VITRO RELEASE DATA FOR KETOPROFEN FROM GIVEN FORMULATIONS AT THE SAME TIME INTERVALS

Linear regression parameter	Formulation code (see Table 6)					
	tc_{1k}	tc_{2k}	tc_{3k}	tc_{4k}	tc_{5k}	tc_{6k}
regression coefficient [a] ($mg \cdot dm^{-3} \cdot min^{-1}$)	1.00	19.6	8.36	1.18	2.84	3.84
y-intercept [a] ($mg \cdot dm^{-3}$)	55.60	12.1	37.6	58.4	54.3	27.3
correlation coefficient	0.354	0.990	0.627	0.447	0.443	0.654
t score	0.409	7.10	0.626	0.499	0.443	0.865
probability	> 0.5	≈ 0.08	> 0.5	> 0.5	> 0.5	> 0.5

[a] y-axis corresponds to the in vivo plasma levels.

TABLE 9

WILCOXON (1945) TEST OF SIGNIFICANCE OF DIFFERENCE BETWEEN IN VIVO AND IN VITRO PAIRS OF METRONIDAZOLE DATA MATCHED BY FORMULATION (TABLE 6) AND TIME

Formulation (and time) [a] for in vitro–in vitro pairs	Metronidazole concentration ($mg \cdot dm^{-3}$)			Rank	Signed rank [b]
	in vivo (y)	in vitro (x)	difference (y − x)		
tc_{1m} (10)	33.93	41.06	−7.13	4	−4
tc_{1m} (30)	47.03	46.73	0.30	1	1
tc_{1m} (60)	61.84	46.73	15.11	6	6
tc_{2m} (10)	7.49	0.88	6.61	2	2
tc_{2m} (30)	11.59	1.17	10.42	5	5
tc_{2m} (60)	33.86	1.45	32.41	12	12
tc_{3m} (10)	21.16	0.53	20.63	9	9
tc_{3m} (30)	33.71	0.80	32.91	13	13
tc_{3m} (60)	30.16	1.08	29.08	11	11
tc_{4m} (10)	25.81	2.14	23.67	10	10
tc_{4m} (30)	49.01	2.58	46.43	16	16
tc_{4m} (60)	66.91	3.06	63.85	18	18
tc_{5m} (10)	36.56	2.41	34.15	14	14
tc_{5m} (30)	38.38	2.62	35.76	15	15
tc_{5m} (60)	55.73	3.17	52.56	17	17
tc_{6m} (10)	14.79	8.11	6.68	3	3
tc_{6m} (30)	30.50	11.28	19.22	8	8
tc_{6m} (60)	31.71	13.75	17.96	7	7

[a] Example: tc_{1m} (10) signifies formulation tc_{1m} in Table 6 at time 10 min.
[b] Total of plus ranks is 167; total of minus ranks is 4; probability < 0.01.

TABLE 10

WILCOXON (1945) TEST OF SIGNIFICANCE OF DIFFERENCE BETWEEN IN VIVO AND IN VITRO PAIRS OF KETOPROFEN DATA MATCHED BY FORMULATION (TABLE 6) AND TIME

Formulation (and time) [a] for in vivo–in vitro pairs	Ketoprofen concentration ($mg \cdot dm^{-3}$)			Rank	Signed rank [b]
	in vivo (y)	in vitro (x)	difference (y − x)		
tc_{1k} (10)	61.26	7.45	53.81	10	10
tc_{1k} (30)	60.83	7.45	53.38	9	9
tc_{1k} (60)	67.02	7.45	59.57	16	16
tc_{2k} (10)	21.60	6.51	21.09	1	1
tc_{2k} (30)	38.50	1.26	37.24	3	3
tc_{2k} (60)	41.87	1.58	40.29	4	4
tc_{3k} (10)	41.86	0.86	41.00	6	6
tc_{3k} (30)	58.52	1.61	56.91	13	13
tc_{3k} (60)	50.67	2.10	48.57	7	7
tc_{4k} (10)	59.30	1.65	57.65	14	14
tc_{4k} (30)	63.66	2.56	61.10	17	17
tc_{4k} (60)	61.04	3.31	57.73	15	15
tc_{5k} (10)	55.35	1.29	54.06	11	11
tc_{5k} (30)	66.43	2.25	64.18	18	18
tc_{5k} (60)	59.69	3.03	56.66	12	12
tc_{6k} (10)	40.26	3.78	36.48	2	2
tc_{6k} (30)	57.80	6.03	51.77	8	8
tc_{6k} (60)	47.04	6.64	40.40	5	5

[a] Example: tc_{1k} (10) signifies formulation tc_{1k} in Table 6 at time 10 min.
[b] Total of plus ranks is 171; total of minus ranks is 0; probability < 0.01.

probability equation (Swinscow, 1980). For metronidazole, the rank order correlation (τ) between this in vivo and in vitro data is 0.4262 with a probability of approximately 0.01, whereas τ for ketoprofen is 0.4951 with a probability better than 0.01. Hence these correlations differ from zero and are therefore significantly valid.

Attempts to correlate the in vitro release data with the plastic viscosities, η_{pl}, of the suppositories (Grant and Liversidge, 1982) proved to be inappropriate, because the systems for studying drug release in vitro do not contain pressures or shear stresses comparable to the measured plastic yield values. However, the formulation possessing the lowest viscosity, namely tc_1, always gave the fastest in vitro release of ketoprofen or metronidazole.

Acknowledgements

We thank May and Baker Ltd., Dagenham, U.K. and the U.K. Science Research Council for a CASE award for G.G.L. and Dynamit-Nobel A.G., Troisdorf, F.R.G., for gifts of pure triglycerides.

References

Baichwal, M.R. and Lohit, T.V., Medicament release from fatty suppository bases. J. Pharm. Pharmacol., 22 (1970) 427–432.

Bhavnagri, V.P. and Speiser, P., In vitro kinetics of drug release from oral dosage forms, lyophilized and conventional rectal suppositories. Pharm. Acta Helv., 51 (1976) 10–18.

Bornschein, M., Grohmann, A. and Voigt, R., Zum Einfluss der Lagerung auf die Liberation von Trapidil aus Suppositorien. Pharmazie, 35 (1980) 40–42.

Bornschein, M., Voigt, R. and Petri, U., Zum Einfluss von Partialglyceriden auf die Liberation von Aminophenazon aus Suppositorien. Pharmazie, 33 (1978) 591–593.

Chongsathien, G. and Plakogiannis, F.M., Medicament release from suppository bases: II. Naproxen physicochemical characteristics and bioavailability in rabbits. Drug Dev. Ind. Pharm., 6 (1980) 255–278.

Cid, E., Absorption rectale de médicaments. Influence de la taille de cristaux d'acide acétylsalicylique. Ann. Pharm. France, 32 (1974) 273–281.

Cox, H.L.M. and Breimer, D.D., Biopharmaceutical aspects of hexobarbital in different pharmaceutical preparations. Abstracts F.I.P. Congress, Stockholm, 1973, p. 186.

Grant, D.J.W. and Liversidge, G.G., Influence of physicochemical interactions on the properties of suppositories. III. Rheological behaviour of fatty suppository bases and its effect on spreading in rats. Drug. Dev. Ind. Pharm., (1982) in press.

Gross, H.M. and Becker, C.H., A study of suppository bases. II. A colorimetric method for measuring medicinal release from suppository bases. J. Am. Pharm. Ass., Sci. Edn., 42 (1953) 96–100.

Grzesiczak, A., Ludwicki, H. and Oetrowska, E., Studies on liberation of active substances from suppository bases. I. In vitro liberation of phenobarbital. Acta Polon. Pharm., 37 (1980) 343–349.

Ibrahim, S.A., Abd Elbary, A., Elsorady, H. and Abd Elmonem, H., Release characteristics of oxyphenbutazone from different suppository bases. Pharmazie, 35 (1980a) 170–173.

Ibrahim, S.A., Abd Elbary, A., Elsorady, H. and Abd Elmonem, H., Availability of oxyphenbutazone from different suppository formulations. Pharmazie, 35 (1980b) 213–216.

Kassem, A.A., Nour El-Din, E., Abd Elbary, A. and Fadel, H.M., In vitro release of chloramphenicol from different suppository bases. Pharmazie, 30 (1975) 472–475.

Kendall, M.G., Rank Correlation Methods, 4th Edn. Griffin, London, 1970.

Kerckhoffs, H.P.M. and Huizinga, T., Vergelijkend onderzoek over het opnemen van geneesmiddelen langs orale, rectale and parentale weg. Pharm. Weekbl., 102 (1967) 1183–1200.

Krowezynski, L., Time for complete deformation of suppository and the capability for liberation of drugs as indices of suitability of modern bases, Part II. Acta Polon. Pharm., 19 (1962) 127–142.

Liversidge, G.G., Grant, D.J.W. and Padfield, J.M., Influence of physicochemical interactions on the properties of suppositories. I. Interactions between the constituents of fatty suppository bases. Int. J. Pharm., 7 (1981) 211–223.

Liversidge, G.G. and Grant, D.J.W., Influence of physicochemical interactions on the properties of suppositories. II. Interactions between the constituents of fatty suppository bases and ketoprofen or metronidazole. Drug Dev. Ind. Pharm., (1982a) in press.

Liversidge, G.G. and Grant, D.J.W., Influence of physicochemical interactions on the properties of suppositories. IV. Factors influencing the in vivo release of ketoprofen or metronidazole from fatty suppository bases. Int. J. Pharm., (1982b) in press.

Muranishi, S., Okuler, Y. and Sezaki, H., Manufacture and examination of apparatus for drug release from suppositories. Yakuzaigaku, 39 (1979) 1–7.

Nerlo, H., Kosier, A. and Czamecki, W., Release of drugs from suppositories. Part I. Apparatus for estimation of drug release from rectal suppositories. Farmcja Polska, 35 (1979) 473–475.

Neuwald, V.F. and Kunze, F., Vergleichende Untersuchungen über die Abgabe von Salicylaten aus Suppositorienfettgrundmassen in vitro and in vivo. Arzneim.-Forsch., 14 (1964) 1162–1167.

Oroszne, S.M., Regon, G. and Regon, G., Physical parameters and in vitro drug release of rectal suppositories containing sulphadimidine sodium. Gyogyszereszet, 23 (1979) 454–458.

Pasich, J., Brobnicka, B. and Kasprzyk, A. Dynamik der Arzneimittelabgabe aus Suppositorien. 6.

Mitteilung: Einfluss lipophiler und hydrophiler Zäpfchengrundlagen auf die Liberation von Adiphenin. Pharmazie, 35 (1980) 416–417.

Pasich, J., Galoch, B. and Kustra, K., Dynamik der Arneimittelabgabe aus Suppositorien. 2. Mitteilung: Phenylpyrazolonderivate im Tierversuch. Pharmazie, 34 (1979) 413–414.

Puech, A., Lasserre, Y. and Jacob, M., Cinétique de libération, in vitro, de principes actifs. à partir de suppositoires. 1. Etude d'un nouvelle appareillage. Trav. Soc. Pharm. Montpellier, 37 (1977) 165–172.

Roseman, T.J., Derr, G.R., Nelson, K.G., Lieberman, B.L. and Butler, S.S., Continous flow bead-bed dissolution apparatus for suppositories. J. Pharm. Sci., 70 (1981) 646–651.

Schoonen, A.J.M., Moolenaar, F., Haverschmidt, C. and Huizinga, T., The interphase transport of drugs from fatty suppository bases. Pharm. Weekbl., 111 (1976) 585–589.

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

Setnikar, I. and Fantelli, S., Metode de controllo farmaceutico delle supposte. II Farmaco Ed. Prat., 17 (1962) 218–230.

Stavchansky, S., Garabedian, M., Wu, P. and Martin, A., Influence of dielectric constant of the base on the release of acetaminophen from suppositories. Drug Dev. Ind. Pharm., 5 (1979) 507–521.

Swinscow, T.D.V., Statistics at Square One, 7th Edn., British Medical Association, London, 1980, pp. 73–76.

Taylor, J., personal communication, 1979.

Thomas, W.H. and McCormack, R., The drug release characteristics of various rectal suppositories as determined by specific ion electrodes. J. Pharm. Pharmacol., 23 (1971) 490–494.

Wilcoxon, F., Individual comparisons by ranking methods. Biometrics Bull., 1 (1945) 80–83.

Wolf, C. and Voigt, R., Arzneimittelfreisetzung und Resorption aus Fettgrundmassen. Pharmazie, 23 (1968) 345–353.