ELSEVIER

International Journal of Pharmaceutics 133 (1996) 65–70

international journal of pharmaceutics

Effect of drug release rate on bioavailability of different aspirin tablets

S. Torrado*, R. Cadorniga, J.J. Torrado

Departamento de Farm. y Tec. Farm., Facultad de Farmacia; Univ. Complutense de Madrid, Madrid, Spain

Received 1 November 1995; accepted 5 December 1995

Abstract

The relationship between in vitro dissolution and in vivo characteristics of acetylsalicylic acid (ASA) from six different types of sustained-release tablet was evaluated. ASA pellets coated by Eudragit RS or L were tableted with different proportions of microcrystalline cellulose 0 or 25% (w/w). The ASA release rate from these tablets was adjusted to the Higuchi and Peppas equations. When microcrystalline cellulose was used at 25%, a faster disintegration time was obtained than when it was not used. The slope of the Higuchi plots of the microcrystalline cellulose formulation were always higher than the formulations without microcrystalline cellulose (matrix tablets). In the Peppas equation, the n values were higher for tablets containing Eudragit RS than for the tablets containing Eudragit L. The bioavailability of six different formulations were assayed in volunteers by urinary excretion data. Bioavailability was related to the dissolution release rate. Formulations with faster drug release rate showed higher bioavailability. Only the slowest formulations had a reduced bioavailability.

Keywords: Acetylsalicylic acid; Eudragit; Sustained-release; Bioavailability; Dissolution rate

1. Introduction

Different polymers are used in order to obtain sustained release formulations. Eudragit is one of the most commonly used (Kislalioglu et al., 1991; Fernandez-Arevalo et al., 1993; Jenquin and McGinity, 1994). Different Eudragit polymers are available to obtain drug formulations with different drug release profiles. Although it is known that drug release can affect drug bioavailability, this effect is difficult to predict. In the present work, five ASA oral formulations were obtained and their drug release characteristics were studied and compared with an acetylsalicyclic (ASA) comercial formulation. The 'in vitro' drug release profile was evaluated and the Higuchi and Peppas equations were used to study the release rate of each formulation. The meam dissolution time (MDT) was also calculated for each formulation.

The oral bioavailability of the six formulations was determined by urinary excretion data. The main purpose of this work is to correlete the in vitro drug release with the oral bioavailability of ASA formulations.

* Corresponding author.

SSDI 0378-5173(95)04411-3

Table 1
Characteristics of different formulation.

Formulations	Composition	Coating material	Dosage forms
C-T	Pellets	Etylcellulose	Disintegration tablet
T-1	ASA 75% microcrystalline cellulose 25%	Uncoated	Disintegration tablet
T-2	Pellets 75% microcrystalline cellulose 25%	Eudragit RS (20%)	Disintegration tablet
T-3	Pellets 75% microcrystalline cellulose 25%	Eudragit L (20%)	Disintegration tablet
T-4	Pellets 75%	Eudragit RS (20%)	Matrix tablet
T-5	Pellets 75%	Eudragit L (20%)	Matrix tablet

2. Materials and methods

2.1. ASA formulations

Six ASA tablet formulations were tested. The characteristics and type of coat used for each tablet are summarized in Table 1.

A commercial tablet C-T (Adiro) containg 500 mg of ASA, coated with a hydrophobic polymer (ethyl cellulose), was used as reference.

The Tablet T-1 corresponded to a non-coated formulation, containing 500 mg of ASA. These crystals were compressed with microcrystalline cellulose (25%).

Tablet T-2 is a disintegration tablet obtained by using 500 mg of ASA crystal coated with 20% different hydrophobic polymers (Eudragit RS). These pellets were then compressed with microcrystalline cellulose (25%).

Tablet T-3 is a disintegration tablet obtained by using 500 mg of ASA crystal coated with 20% different hydrophobic polymers (Eudragit L). These pellets were then compressed with microcrystalline cellulose (25%).

Tablet T-4 is a matrix tablet obtained by using 500 mg of ASA crystal coated with 20% different hydrophobic polymers (Eudragit RS). These pellets were then compressed.

Tablet T-5 is a matrix tablet obtained by using 500 mg of ASA crystal coated with 20% different hydrophobic polymers (Eudragit L). These pellets were then compressed.

2.2. In vitro drug release (USP 23, 1995).

The USP apparatus I (Turu-Grau) with a rotation speed of 100 rpm was used for drug release testing. The dissolution medium was 750 ml of 0.1N hydrochloric acid during the first 2 h of the study (acid phase), then 250 ml of 0.20 M tribasic sodium phosphate were added for the rest of the test, adjusting when necessary to a pH of 6.8 $\pm$ 0.5 (buffer phase). Samples were analyzed in a Beckman DU 6 spectrophotometer at 280 nm for the acid phase and 265 nm for the buffer phase. The studies were repited three times to obtain a medium value. Drug release data were adjusted to the Higuchi and Peppas equations.

2.3. Bioavailability study

Six healthy volunteers (age 28–30 years, weight 50–75 Kg) entered for the study which was conducted in a randomized and crossover manner under medical supervision.

Six different ASA formulations were administered. Tablets were administered orally with 150 ml of water.

Urine samples were taken at 0, 1, 2, 3, 4, 6, 8, 10, 24, 36 and 48 h after dosing. Isolated urine was stored at -20°C until assay.

2.4. Measurement of salicylic acid

Concentrations of salicylic acid in urine were measured using a colorimetric method previously described (Torrado et al., 1994).

The linear calibration curve was drawn by analysis of salicylic acid over a concentration range of 20–100 μg/ml.

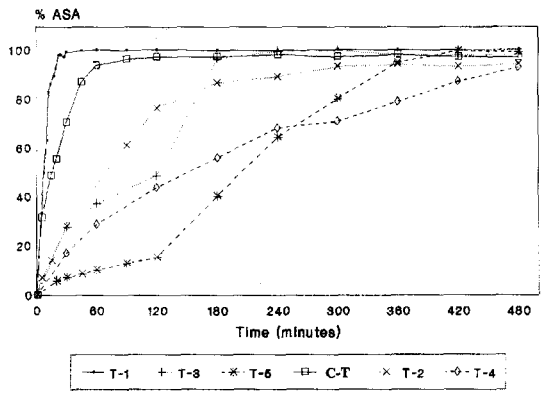

Fig. 1. ASA release profile of Eudragit RS and L sustained-release tablets and two fast formulations.

2.5. Data analysis

The mean dissolution time in vitro, MDT_{vitro}, was estimated from the time when 50% of drug has been dissolved (Wingstrand et al., 1990).

The area under the curve was determined by the linear trapezoidal rule (MK-Model program).

3. Results and discussion

Drug release profiles of the different tablet formulations are shown in Fig. 1. Depending on the drug release profile, the different tablets formulations can be classified in three groups: Fast-release tablets (T-1 and C-T), medium-release tablets (T-2 and T-3) and slow-release tablets (T-4 and T-5). The pH effect on drug release can be observed in Fig. 1. At 120 min, pH changes from 1.2 to 6.8. Mean drug release profiles from fast (T-1 and C-T), medium (T-2) and slow (T-4) release formulations are unaffected by changes in pH of the medium. This behaviour may be due to the characteristics of the polymers Eudragit RS (formulations T-2 and T-4) and ethyl cellulose (C-T formulation) which apparently remained intact in both dissolution media. The Eudragit L formulations (T-3 and T-5) dissolved much more rapidly in USP-simulated intestinal fluid than in USP-simulated gastric fluid. Drug release is constant by most of the formulations and only T-3 and T-5 formulations showed an important change in dissolution when simulated gastric acid media was changed to neutral pH media. T-3 and T-5 formulations contained Eudragit L which has a drug release pH-dependent behaviour.

The release profiles are significantly faster from disintegration formulations (T-2 and T-3) than matrix-tablets (T-4 and T-5). After 2 h of the dissolution test, the percentage dissolved for disintegration formulations is 75% for T-2 and 50% for T-3. Drug release from matrix-tablets after 2 h is 43% for T-4 and 15% for T-5.

3.1. Mechanism of release

To study the mechanism of ASA release, Higuchi equation (% dissolved vs $t^{1/2}$), and Peppas

Table 2
Comparison of computed parameters for drug release. Data fitted to the Higuchi and Peppas equations.

Formulations	Higuchi equation				Peppas equation		
	t_{lag} (min)*	Slope (%D $min^{1/2}$)	R^2	% Decrease in slope	K (min^{-n})	n	R^2
Fast							
T-1	0.492	25.168	0.9961	0.117	0.73	0.9981	
Adiro	0.003	12.671	0.9940	49.65	0.138	0.47	0.9935
Medium							
T-2	2.254	7.812	0.9948	68.96	0.026	0.72	0.9917
T-3	4.055	3.736	0.9982	85.16	0.071	0.40	0.9995
Slow							
T-4	2.316	4.585	0.9964	81.78	0.019	0.64	0.9974
T-5	0.516	1.463	0.9975	94.19	0.011	0.55	0.9986

*The lag time was computed as the square of the abcissa intercept of plots of percentage dissolved vs $t^{1/2}$.

equation (diffusional exponent, n) were used. The results are summarized in Table 2. These mathematical approach models fitted 60–80% of drug dissolved from the formulations T-1, C-T, T-2 and T-4. Similar results, reported by Baveja et al. (1987), derived simplified relationships based on Fick's laws of diffusion to describe the release of soluble drugs from various matrices. Eudragit L-coated formulations (T-3 and T-5) were fitted to the Higuchi and Peppas equations only during the first 2 h of the dissolution test.

The data in Table 2 show a general trend of a shorter lag time for fast-release formulations (T-1 and C-T) as compared to medium-release tablets (T-2 and T-3) and slow-release matrix-tablets (T-4). The slopes of the disintegration formulations (T-2 and T-3) (Higuchi equation) are significantly greater ($P < 0.05$) than for those of the matrix-tablet (T-4 and T-5). In Table 2, it is possible to observe that for the same polymer Eudragit RS there is a more important decrease in slope (%) for the matrix-formulation T-4 (81.78%) than the disintegration tablet T-2 (68.96%). Similar results were observed for the polymer Eudragit L. The linearity of these data ($R^2 > 0.9940$) seems to indicate that diffusion is the predominant release mechanism (Kislalioglu et al., 1991; Fernandez-Arevalo et al., 1993).

In order to characterize this release mechanism, Table 2 presents the fitted results for differents formulations of disintegration tablets and matrix-tablets. The values of the diffusional exponent, n, were 0.40 and 0.47 for the disintegration formulations T-3 and C-T, respectively. These values are characteristics of a Fickian diffusion mechanism for drug release. The values obtained for the diffusional exponen, n, range from 0.55 to 0.73 are characteristics of a mixture of diffusional and relaxation release mechanisms [so-called anomalous diffusion (Reza and Ritschel, 1993)]. These results are similar to those obtained by Ford et al. (1987) who reported values of n that ranged from 0.64 to 0.71 for the release of the matrix-tablets containing HPMC. In addition, these results fitted the Higuchi equation with a good correlation as noted above (Table 2); this is somewhat deceiving because examination of these results alone may lead one to conclude that the in vitro release is controlled by simple Fickian diffusion. But this hypothesis may not be so when the matrix size (matrix or pellets) decreases with time. This erosion rate of the matrix combined with a decrease in the solvent penetration rate into the matrix (Padmalatha et al., 1989) may cause the net effect of a good linearity in the Higuchi equation.

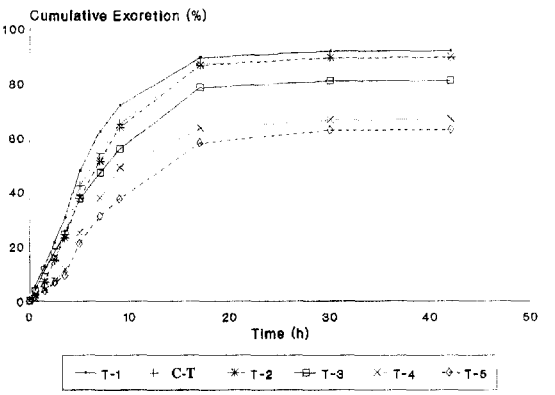

Fig. 2. Cumulative excretion of total salicylates profiles following the administration of one ASA tablet (dose of 500 mg) of T-1, C-T, T-2, T-3, T-4 and T-5.

3.2. Relative bioavailability

Fig. 2 showed the cumulative excretion of total salicylates following the administration of different formulations. It is well known that the urinary excretion rate of total salicylate reflects the relative absortion rate of the drug and that the cumulative amount of total salicylate ultimately excreted in the urine serves as a quantitative index of the extent of absorption (Gadalla et al., 1989).

Table 3 summarizes the statistical study including the bioavailability and pharmacokinetic parameters values obtained with the different formulations. The values of maximun urinary excretion rate (V_{max}) of our formulations are in a range from 23.71 to 46.58 μg/ml h. Our fast release rate formulations (T-1 and C-T) have similar values of maximun urinary excretion rate than those reported by Gadalla et al. (1989). The accumulated amount of total salicylates excreted after 48 h for all formulations is between 313.90 and 457.55 mg. There are no signifficant differences for the $X_{u\,ex}$ values of the T-1, C-T, T-2 and T-3 formulations. However the $X_{u\,ex}$ are significantly smaller ($P < 0.05$) for the matrix-tablets (T-4 and T-5).

Table 3
Urinary excretion parameters for the six different formulations of 500 mg of ASA after oral administration (n = 6).

Parameter	Formulation	Mean	Range
V_{max} μg/ml	T-1	45.53 ± 3.12	42.37–54.69
T-1 = C-T > T-2 > T-3 >> T-4 = T-5	C-T	46.58 ± 2.66	42.56–50.03
	T-2	40.65 ± 3.53	37.42–44.42
	T-3	33.13 ± 1.94	30.17–35.68
	T-4	27.83 ± 1.22	24.64–29.51
	T-5	23.71 ± 4.18	19.51–27.07
T_{max} (h)	T-1	3.66 ± 1.12	2.5–5.0
T-3 > T-1 = C-T = T-3 >> T-4 > T	C-T	3.75 ± 0.61	3.5–5.0
	T-2	2.17 ± 0.82	1.5–5.0
	T-3	3.90 ± 1.08	3.5–5.0
	T-4	7.26 ± 2.54	7.0–9.0
	T-5	8.60 ± 0.89	7.0–9.0
$X_{U\ ac,}^{\infty}$ (mg)	T-1	457.55	438.27–469.50
T-1 = C-T = T-2 > T-3 >> T-4 = T-5	C-T	446.39	410.40–460.81
	T-2	446.24	425.95–479.89
	T-3	403.51	388.14–447.18
	T-4	332.94	304.62–363.48
	T-5	313.90	278.26–341.38
$AUC_{0-\infty}$	T-1	476.2	459.8–487.8
T-1 = C-T = T-2 > T-3 >> T-4 = T-5	C-T	475.4	450.5–486.2
	T-2	468.8	455.9–487.6
	T-3	445.9	424.1–464.1
	T-4	338.5	305.8–365.8
	T-5	324.7	311.2–338.5
Relative bioavailability (Product T-1 used as reference)	T-1	1.00	0.96–1.02
T-1 = C-T = T-2 = T-3 >> T-4 = T-5	C-T	1.00	0.95–1.02
	T-2	0.98	0.96–1.02
	T-3	0.94	0.89–0.97
	T-4	0.71	0.64–0.77
	T-5	0.68	0.65–0.71

The relative bioavailability of the disintegration formulations ranged from 79 to 92%. There are no significant differences in this relative bioavailability between gastric-resistent polymer (Eudragit L) and the sustained-release polymer (Eudragit RS) for the formulations T-2 and T-3. Also, there are no significant differences in the relative bioavailability between fast and medium-release rate formulations T-1, C–T, T-2 and T-3. However, the bioavailability are significantly lower ($P < 0.05$) for matrix-tablets in slow formulations (T-4 and T-5). The fact that the differences observed between the disintegration and matrix-tablets are relatively high could relate to the type of ASA formulations, the extent of absortion from these controlled release formulations is greatly influenced by these dissolution times. There is a good correlation between the MDT_{vitro} and AUC values for the fast and medium tablets (disintegration), however there was a tendency for lower bioavailabilty with the slow formulations (matrix tablets); this relationship is shown in Fig. 3.

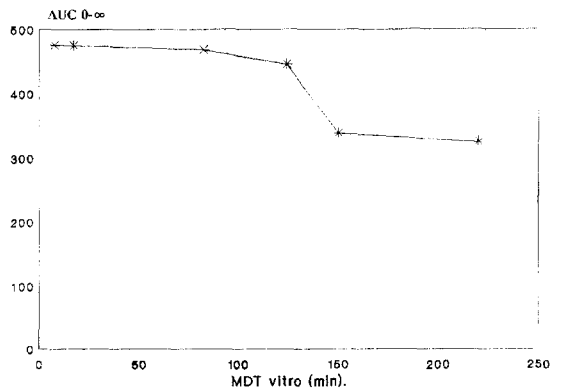

Fig. 3. $AUC_{0-\infty}$ in vivo for ASA tablets as a function of the mean dissolution time in vitro (MDT).

Slow release formulations (T-4 and T-5) have poorer bioavailability than the others. These effects can be due to the poorer absortion of the lower part of the gastrointestinal tract in comparison to the first intestine portion, as has been pointed out by Soons et al. (1989) and Wingstrand et al. (1990).

References

Baveja, S.K., Ranga Rao, K.V. and Padmalatha, D., Zero-order release hydrophilic matrix tablets of β-adenergic blockers. *Int. J. Pharm.*, 39 (1987) 39–45.

Fernandez-Arevalo, M., Holgado-Villafuerte, M.A., Gines-Dorado, J.M. and Rabasco-Alvarez, A.M., Effects of different fillers and wetting liquids on the dissolution behavior of carteolol hydrochloride controlled release inert matrix tablets. *Int. J. Pharm.*, 95 (1993) 117–125.

Ford, J.L., Rubinstein, M.H., Mc Caul, F., Hogan, J.E. and Edgar, P.J., Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethyl-cellulose matrix tablets. *Int. J. Pharm.*, 40 (1987) 223–234.

Gadalla, M.A.F., Ismail, A.A. and Abd El-Hameed, M.H., In vivo evaluation of different types of commercial aspirin tablets. *Drug Dev. Ind. Pharm.*, 15 (1989) 447–472.

Jenquin, M.R. and McGinity, J.W., Characterization of acrylic resin matrix films and mechanisms of drug-polymer interations. *Int. J. Pharm.*, 101 (1994) 23–34.

Kislalioglu, M.A., Khan, M.A., Blount, C., Goettsch, R.W. and Bolton, S., Physical characterization and dissolution properties of ibuprofen: Eudragit coprecipitates. *J. Pharm. Sci.*, 80 (1991) 799–804.

Padmalatha, K.D., Ranga Rao K.V., Baveja, S., Marc, F. and Marc, R., Zero-order release formulation of oxprenolol hydrocloride with swelling and erosion control. *Pharma Res.*, 6 313–317 (1989).

Reza, A.F. and Ritschel, W.A., Multiple-Layer, Direct-Compression, Controlled-Release System: In Vitro and In Vivo Evaluation. *J. Pharm. Sci.*, 87 (1993) 750–754.

Soons, P.A., De Boer, A.G., Van Brummelen, P. and Breimer, D.D., Oral absortion profile of nitrendipine in healthy subjects: a kinetic and dynamic study. *Br. J. Clin. Pharmacol.*, 27 (1989) 179–189.

Torrado, S., Torrado, S. and Cadorniga, R., Comparison of assay methods by second-derivative spectroscopy, colorimetry and fluorescence spectroscopy of salicylic acid in aspirin preparations with a high-performance liquid chromatographic method. *J. Pharm. and Biomed. Anal.*, 12 (1994) 383–387.

Wingstrand, K., Abrahamsson, B. and Edgar, B., Bioavailability from felodipine extended-release tablets with different dissolution properties. *Int. J. Pharm.*, 60 (1990) 151–156.