DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(1), 141-148 (1991)

COMMUNICATION

IN VITRO DISSOLUTION OF TWO ORAL CONTROLLED RELEASE PREPARATIONS OF DICLOFENAC SODIUM.

Ph. Van Wilder, M.R. Detaevernier, Y. Michotte
Laboratory of Pharmaceutical Chemistry and Drug Analysis,
Pharmaceutical Institute, Vrije Universiteit Brussel,
Laarbeeklaan 103, B-1090 Brussels, Belgium

1. INTRODUCTION

The development of controlled release formulations has brought about the need for appropriate quality control methods such as in vitro dissolution testing. Such tests are principally designed to obtain correlation with the in vivo performance of the formulation (1,2,3). If an in vitro test can be defined offering a good correlation the test may serve for routine quality control or may be useful in screening new drug formulations.
Various methods for in vitro dissolution testing have been proposed using different equipments, working conditions and/or dissolution media (1,4,5).

In this contribution we confined to a particular case, i.e. the release of diclofenac sodium, a non-steroidal anti-inflammatory agent, from two oral sustained release formulations : a matrix tablet and a hard gelatin capsule containing coated pellets, each of the formulations containing the same dose of active substance.
These formulations were tested in four media using the stirred vessel - paddle method (U.S.P. XXI and Pharm. Eur. 2nd ed.) and the flow-through method in closed circuit as described in D.A.C. 1979 (5 - 1985).

2. EXPERIMENTAL

2.1. Test material :

The test material consists of two formulations each containing 100 mg of diclofenac sodium :

- formulation 1 is a hydrophobic matrix tablet based on a cetylalcohol skeleton manufactured by Ciba-Geigy (Voltaren retard®). (P1)

- formulation 2 is a hard gelatin capsule containing pellets coated with Eudragit® RL and cellulose acetophtalate. This formulation (P2) is manufactured by Eurand International.

2.2. Equipment :

Two dissolution techniques are used :
- apparatus A1 : vessel with stirred paddle (cfr. USPXXI) obtained from Erweka
- apparatus A2 : continuous flow apparatus obtained from Sotax AG.

Analyte determinations were performed with a Lambda 3 UV-VIS double beam spectrophotometer from Perkin-Elmer Corporation, Analytical Instruments, Norwalk U.S.A..
The statistical calculations are executed on IBM®-PC-XT computer using the SPSS® package (6).

2.3. Dissolution media :

Four dissolution programs are applied over a period of 8 hours, corresponding to media 1 to 4 :
medium M1 : 2 hours at pH 1 followed by 6 hours at pH 6.8
medium M2 : 8 hours at pH 6.8
medium M3 : 2 hours at pH 1 followed by 6 hours at pH 7.5
medium M4 : 8 hours at pH 7.5.

- pH 1 solution consists of 0.1 N hydrochloric acid
- pH 6.8 buffer solution is prepared according to artificial intestinal fluid of Ph. Eur. 2nd. ed. VII.
- pH 7.5 buffer solution is made according to simulated intestinal fluid of USP XXI

All reagents are analytical grade.

TABLE 1
Cumulative fraction as % of label claim liberated after eight hours (= F_8)

Formulation	P1		P2	
Apparatus	A1	A2	A1	A2
Medium M1	24.1	7.7	11.8	10.4
Medium M2	46.7	38.0	55.2	34.2
Medium M3	48.6	43.7	66.0	51.0
Medium M4	59.0	60.3	100.0	100.0

2.4. Procedures :

With apparatus A1 the volume of the dissolution media is 900 ml and the paddle is rotated at 100 rpm.
With apparatus A2 1000 ml of dissolution medium are pumped in a laminar flow mode through the dissolution cell at a flow rate of 1 l/hour.

In both techniques, at fixed time intervals i.e. every hour from 1 to 8 h, 10 ml samples are whithdrawn from the apparatus and immediately replaced by the same volume of fresh medium.
After appropriate dilution with the corresponding medium, samples are determined by U.V. spectrofotometry at λ max in a 1 cm cell. From these data the cumulative fractions of diclofenac sodium released at the times of sampling are calculated.

3. RESULTS AND DISCUSSION

The complete set of experiments is formed by the release of the two formulations tested in the four media using the two techniques resulting in a 2*4*2 experimental design. The raw experimental results are given in Table 1 as the cumulative fraction liberated after 8 hours (= F_8).

One can observe a large variation of the F_8-values; from 8 to 60% for P1 and from 10 to 100% for P2. Only for P2, in

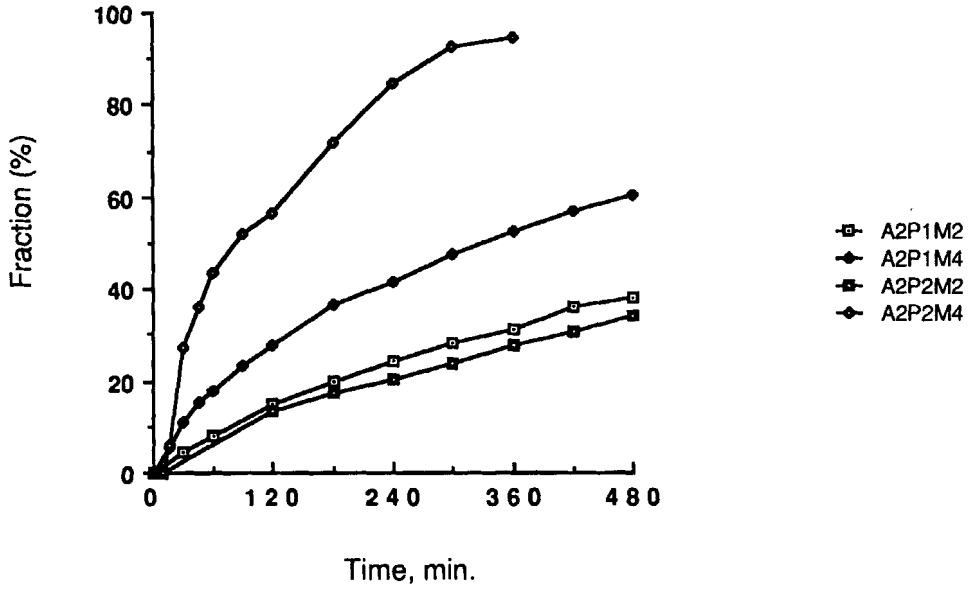

FIGURE 1

In vitro release of formulations P1 and P2 in the apparatus A2 in medium M2 and M4

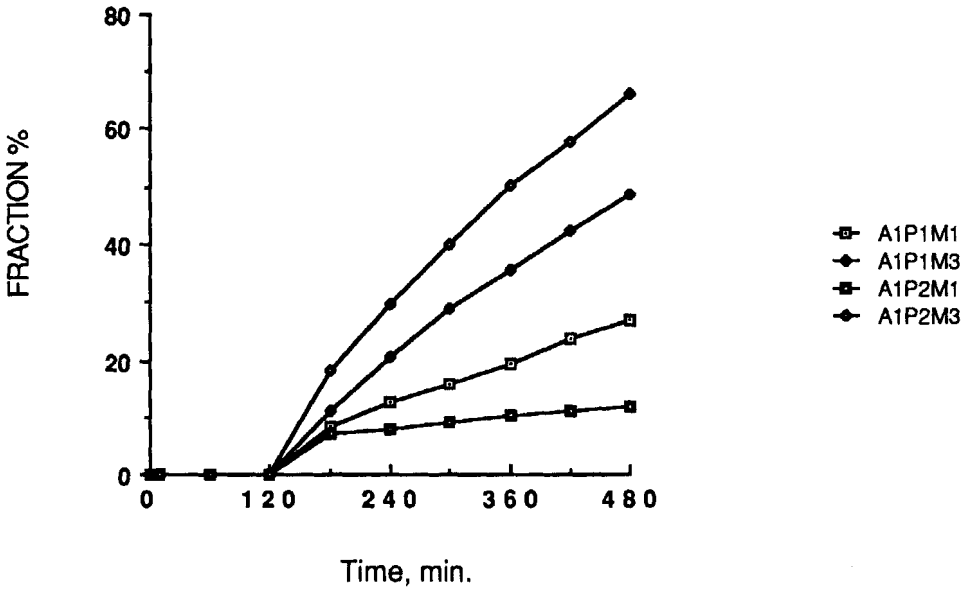

FIGURE 2

In vitro release of formulations P1 and P2 in the apparatus A1 in medium M1 and M3

TABLE 2
$\ln t_a$ -values obtained after RRSW-transformation of experimental data.

Apparatus	Formulation P1 A1	Formulation P1 A2	Formulation P2 A1	Formulation P2 A2
Medium M1	8.13	8.52	13.22	12.85
Medium M2	7.00	6.99	6.69	7.46
Medium M3	6.49	6.56	6.12	6.61
Medium M4	6.38	6.26	3.87	4.67

medium M4, total release is obtained after 8 hours. Two typical dissolution curves are presented in figures 1 and 2.

In order to obtain some more statistically founded information on parameter effects, i.e. formulation, medium and apparatus effects, the dissolution curves are linearized according to the Rosin - Rammler - Sperling - Weibull transformation (RRSW) (7).

$$F = F_\infty \left[1 - e^{-\left(\frac{t - t_o}{t_a}\right)^B}\right] \qquad \text{eq. 1}$$

F = cumulative fraction liberated at time t
F_∞ = cumulative fraction liberated at infinity ($F_\infty = 1$ in all cases)
t = time in minutes
t_o = lag time in minutes
t_a = time for 63.2% release in minutes
B = shape parameter

If $F_\infty = 1$: equation 1 can be written as

$$\ln \ln \frac{1}{1 - F} = B \cdot \ln (t - t_o) - B \cdot \ln t_a$$

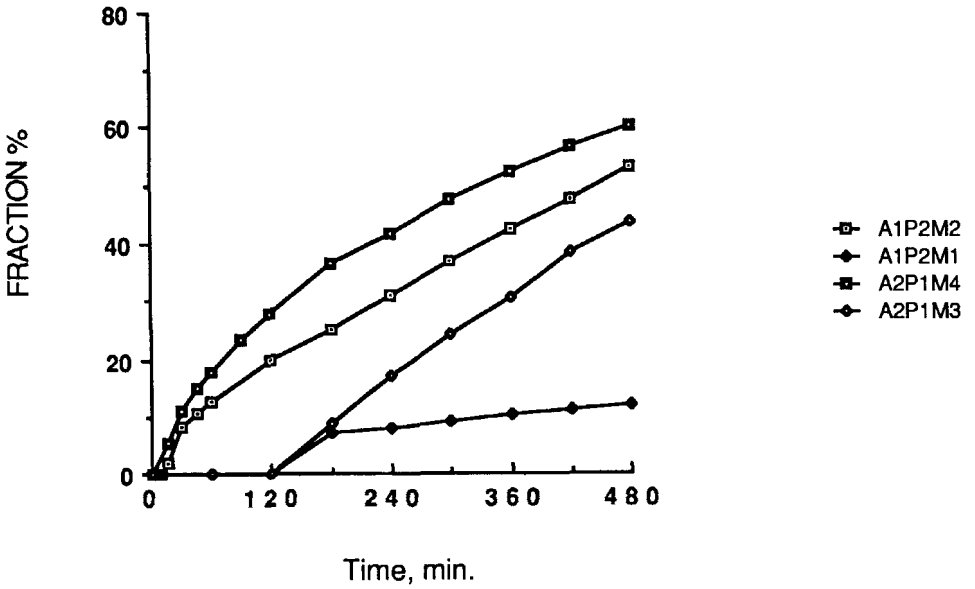

FIGURE 3

Delay effect in the dissolution curve of formulation P1 in medium M3 compared to medium M4 and of formulation P2 in medium M1 compared to medium M2

In order to evaluate possible effects of the apparatus, formulation, or medium on the release profile of diclofenac sodium salt, an analysis of variance is performed on lnt_d. The 2*2*4 factorial design is shown in table 2.

For the curve parameter lnt_d (rate of release) significance is obtained for the medium effect ($P < 0.002$), for the interaction effect medium-formulation ($P < 0.005$) and for the formulation effect ($P < 0.05$).
A significant formulation effect is expected since we are dealing with two completely different formulations.
The interaction factor medium-formulation results from a slower release of P2 compared to P1 in medium 1, mainly similar release properties of both formulations in M2 and M3, and a faster release of P2 in medium M4.
For both formulations, tested with either dissolution apparatus a faster release is observed changing the media from M1 to M3 and M2 to M4, which corresponds to a raise in

pH from 6.8 to 7.5. Since at both pH values (in media M2 and M4) sink conditions were observed (as verified by the dissolution in these media of a trituration of 100 mg of diclofenac sodium with lactose) the medium effect has to be attributed to the excipient composition.
Probably the different swelling capacity and permeability of the celluloseacetophtalate and Eudragit RL filmcoating may explain these phenomena for the coated pellets (P2)(8) while for the matrix tablet a different erosion pattern of the cetylalcohol skeleton might be responsable.
As diclofenac sodium is practically insoluble in acidic solutions (9) no dissolution occurs in 0,1 N hydrochloric acid.
Moreover the acidic digestion in M1 and M3 delays the further release at pH 6.8 and 7.5 in media M1 and M3 compared to the release in the respective media M2 and M4 (figure 3). This delay may be explained by a lower micro pH environment in the formulations due to the acidic soaking stage.

Summary

The release of diclofenac sodium from the two controlled-release formulations tested is strongly medium dependent : faster dissolution is obtained in media without acidic stage or with higher pH-values. An acidic digestion generates some slower release afterwards when compared to media without acidic stage. There is also a strong formulation effect and the pellets are more sensitive to changes in dissolution parameters. Further investigations will be undertaken to evaluate more specifically the influence of pH and buffer composition.

ACKNOWLEDGEMENTS

The authors wish to thank Mrs. C. De Ryck for excellent technical assistence.

REFERENCES

1. Joint report of the Section for Control Laboratories and the Section of Industrial Pharmacists of the F.I.P., Guidelines for dissolution testing of solid oral products Pharm. Ind., 43 (4), 334 (1981).

2. Langenbucher F. and Möller H., Pharm. Ind., 45 (6), 623 (1983).

3. Joint report of the Section for Control Laboratories and the Section of Industrial Pharmacists of the F.I.P., Correlation of Drug Availability In Vitro and In Vivo : Recommanded Methods, Pharm. Ind., 46 (9), 941 (1984).

4. Möller H., Pharm. Ind., 48 (5), 514 (1986).

5. Möller H., Pharm. Ind., 45 (6), 617 (1983).

6. SPSS Inc. Chicago, Il., U.S.A.

7. Langenbucher F., J. Pharm. Pharmac., 24, 979 (1972).

8. Brossard C., Labo-Pharma-Probl.Techn., 30 (317).

9. Herzfeldt D. and Kummel R., Drug Dev. Ind. Pharm., 9 (5), 767 (1983).