International Journal of Pharmaceutics, 34 (1987) 259–262
Elsevier

IJP 01168

A new enteric tablet of acetylsalicylic acid. II. Biopharmaceutical aspects

J.-P. Dechesne and L. Delattre

F.N.R.S., School of Pharmacy, University of Liege, Liege (Belgium)

(Received 13 June 1986)
(Accepted 20 August 1986)

Key words: Acetylsalicylic acid; Microdispersed enteric coating; Sustained release; Salicylic acid plasma concentration

Summary

The study compared the in vivo behaviour of two kinds of acetylsalicylic acid (ASA) enteric tablets: a conventional enteric tablet and a "microdispersed" or multiple-unit enteric tablet. The in vivo study showed the advantages of such a microdispersed system, i.e. (a) decreased lag-time and greatest reproducibility of the latter; and (b) mild sustained release effect.

Introduction

In a previous publication (Dechesne, 1986) the technological aspects of the formulation of an acetylsalicylic acid (ASA) "microdispersed" or multiple-unit enteric tablet were studied. Theoretically, compared to a conventional enteric formulation, such multiple-unit dosage forms showed some advantages (Bechgaard, 1977, 1982; Story, 1977), i.e. (a) no decrease of bioavailability; (b) introduction of a mild sustained release effect; (c) side-effects reduction; and (d) less dependency on gastric transit time.

In order to confirm these advantages, two different tablet formulations have been compared by an in vivo study: first, a conventional enteric tablet; and secondly, a "microdispersed" or multiple-unit tablet of ASA.

Correspondence: J.-P. Dechesne, F.N.R.S., School of Pharmacy, University of Liege, Rue Fusch 5, B-4000 Liege, Belgium.

Materials and Methods

Tested tablets

Two tablet formulations of ASA were tested. The characteristics of both tablets are summarized in Table 1.

The conventional tablet corresponded to a core, containing 500 mg of ASA, coated with cellulose acetylphthalate.

The microdispersed tablet corresponded to 500 mg of ASA crystals coated with Eudragit L30D. These crystals were then compressed with microcrystalline cellulose (20%).

In vivo study

Six healthy volunteers (age 23–42 years, height 1.62–1.93 m, weight 50–95 kg) participated in the study on two occasions with informed consent. The study was approved by the relevant Ethics Committee.

The conventional or microdispersed tablets were

TABLE 1

CHARACTERISTICS OF TESTED TABLETS

	Conventional tablet	Microdispersed tablet
Composition	ASA 500 mg starch	ASA crystals 500 mg microcrystalline cellulose
Coating material	Cellulose acetylphthalate	Eudragit L30D
Plasticizer	Diethylphthalate	Propyleneglycol
Disintegration time	11 min 22 s ± 1 min 50 s	22 min ± 2 min
Crushing strength (kg)	> 15	5.3 ± 0.7

Valves are means ± S.E.M.

ingested after a light standard breakfast. Administrations and dosing were conducted every 2 weeks.

Blood samples (= 400 μl) were withdrawn each hour during 8 h after the intake of the medication. Blood samples were withdrawn by making an incision in the tip of the finger with a sterile lancet. Plasma was separated by centrifugation.

Measurement of salicylic acid in plasma

Concentrations of salicylic acid in plasma were measured using a high-performance liquid chromatographic (HPLC) method. Plasma (200 μl) was mixed with phosphoric acid (0.2 ml) and water (0.8 ml), then extracted with freshly distilled ethylacetate (12 ml) for 10 min on a shaker. The phases were separated by centrifugation and 10 ml of the organic phase were removed and evaporated to dryness at 40°C.

The drug residues were dissolved in methanol (0.3 ml) and phosphoric acid (0.3 ml, H_3PO_4, 0.05 M), portions (100 μl) of which were injected into the HPLC system which consisted of an automatic injector (Rheodyne, model 7120) and pump (Pye-Unicam type LC-XPD) fitted with a variable wavelength ultraviolet monitor (Pye-Unicam model 4020) operated at 298 nm. The stainless steel column (25 cm × 0.4 cm i.d.) was prepacked with μBondapak C18 (mean particle size 7 μm).

Chromatography was performed with a mobile phase of methanol (50% v/v) in phosphoric acid (0.05 M) at a flow rate of 1 ml/min. Salicylic acid was eluted with retention time of 7.1 min.

Linear calibration curve of peak height was drawn by analysis of plasma containing salicylic acid over the concentration range 5–50 μg/ml.

Data processing

Mean plasma concentrations at a fixed time had no significance because of the large variations between subjects. Consequently, peak, peak-time and lag-time values have been selected as comparison parameters.

Results and Discussion

Results of salicylic acid plasma concentrations, peaks, peak-times and lag-times are given in Tables 2 and 3 (Figs. 1–6). No side-effects were observed with both formulations.

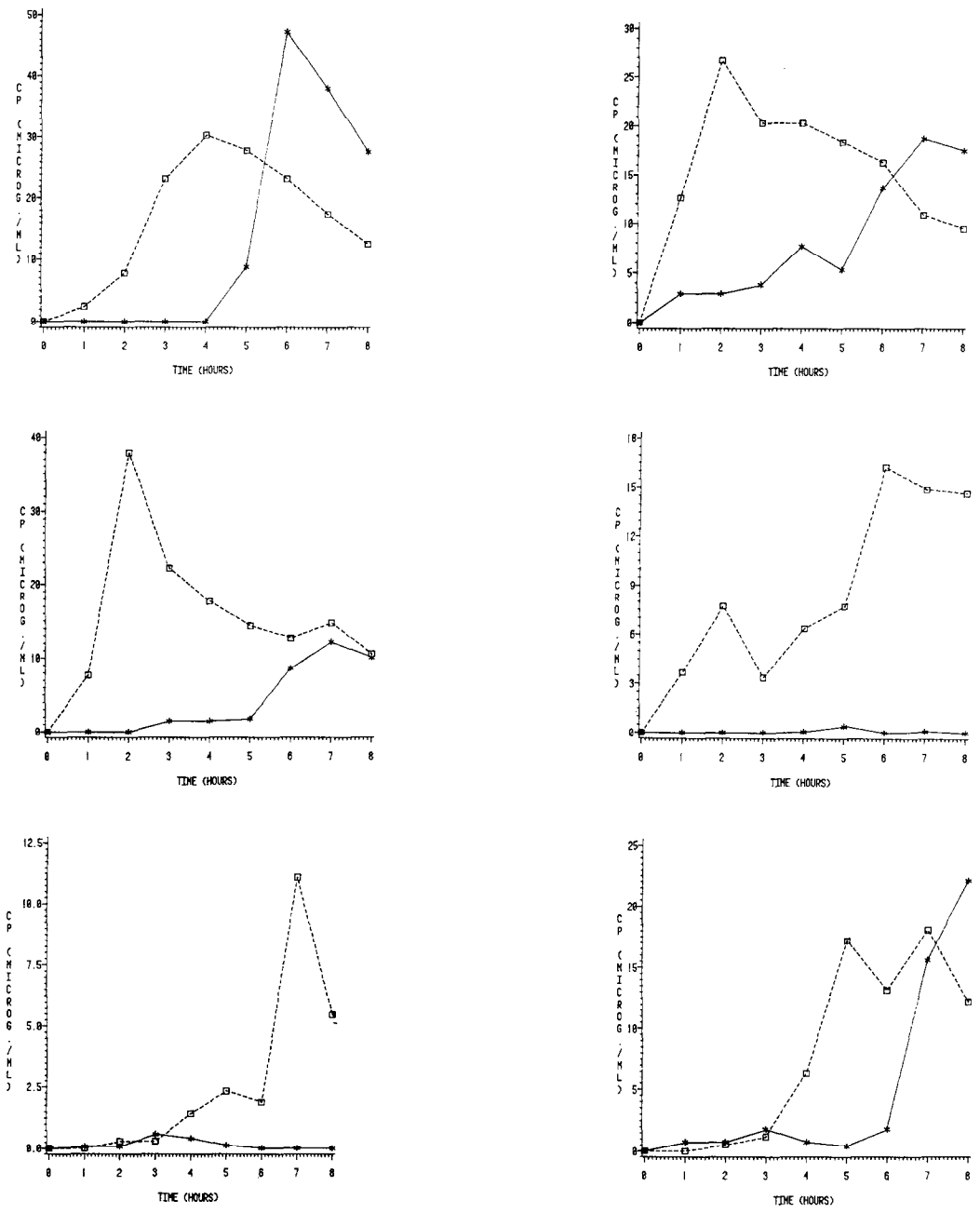
Examination of Tables 2 and 3 leads to some conclusions: (a) peak-time is always greater with conventional tablets; (b) except for subject 1, the peak value of the microdispersed tablet is close to or higher compared to conventional tablet and plasma concentrations decrease more slowly (mild sustained release effect); (c) lag-times are always higher for conventional tablets; and (d) results

TABLE 2

VALUES OF LEADING PEAK AND TIME TO REACH IT

Subject	Conventional tablet		Microdispersed tablet	
	Conc. (μg/ml)	Time (h)	Conc. (μg/ml)	Time (h)
1	47.3	6	27.8	4
2	18.7	7	26.7	2
3	12.1	7	37.9	2
4	*	*	16.3	6
5	*	*	11.1	7
6	22.1	8	17.2	5

* = not detected.



Figs. 1–6. Salicylic acid plasma concentrations for individual volunteers. * = conventional enteric tablet; □ = multiple-unit enteric tablet.

obtained with the microdispersed tablets stand within a more narrow range.

These results are in agreement with those published by Bechgaard (1977). This means that the use of multiple-unit dosage forms mainly eliminates the dependency of the release on gastric

TABLE 3

VALUES OF LAG-TIME (h)

Subject	Conventional tablet	Microdispersed tablet
1	5	1
2	6	1
3	6	1
4	8	1
5	8	7
6	7	4

emptying, since pellets (or crystals) pass the pylorus even when the sphincter is closed and, as described earlier (Story, 1977), the use of such microdispersed formulation maintains bioavailability compared to conventional enteric tablets.

In conclusion, the results of the present study clearly demonstrate the importance of the galenical form of enteric tablets on the in vivo release. Following the administration of a conventional tablet, we observe large variations between subjects and highest lag-time. Following the administration of a microdispersed enteric tablet we observe a decrease of both lag-time and inter-subject variations.

Acknowledgements

The author wishes to thank the National Fund for Scientific Research of Belgium for financial assistance.

References

Bechgaard, H., Entero-coated pellets. En biofarmaceutisk vurdering. *Arch. Pharm. Chemi.*, 84 (1977) 296–300.

Bechgaard, H., Critical factors influencing gastrointestinal absorption. What is the role of pellets? *Pharm. Acta Helv.*, 28 (1982) 149–157.

Dechesne, J.-P., A new enteric tablet of acetylsalicylic acid. I. Technological aspects. *Int. J. Pharm.*, (1986) in press.

Story, M.J., Enteric-coated pellets: theoretical analysis of effect-of dispersion in the stomach on blood level profiles. *J. Pharm. Sci.*, 66 (1977) 1495–1496.