Br J clin Pharmac 1993; **36**: 470–473

Biopharmaceutical characterisation of a low-dose (75 mg) controlled-release aspirin formulation

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The release of aspirin from a 75 mg controlled-release formulation, designed to inhibit maximally thromboxane A_2 production while sparing stimulated prostacyclin biosynthesis, was characterised in healthy subjects. The calculated *in vivo* release rate of aspirin matched the design goal of approximately 10 mg h^{-1}. The C_{max} of aspirin associated with the controlled-release formulation was lowered 15-fold relative to a solution formulation of the same dose. The bioavailability of aspirin (based on salicylate concentrations) from the controlled-release formulation was approximately 90% relative to the solution, and drug release was not affected by co-administration of a standard breakfast.

Keywords low-dose aspirin controlled-release food effect cardiovascular

Introduction

Orally administered aspirin has significant potential for reducing mortality associated with unstable angina, myocardial infarction and thrombotic stroke [1, 2]. This therapeutic utility of aspirin is believed to stem from inhibition of the platelet-derived production of thromboxane A_2 [3, 4] which is a potent stimulator of platelet aggregation and vascular smooth muscle contraction [5, 6]. Thromboxane A_2 is produced from arachidonic acid through the sequential action of prostaglandin G/H synthase and thromboxane synthase. Aspirin decreases the formation of thromboxane A_2 by irreversibly inactivating prostaglandin G/H synthase by acetylation of the Ser^{529} residue near the active site of the enzyme [7].

Prostacyclin, which has opposite effects to thromboxane A_2 on vascular tone and platelet function [8], is produced by the vascular endothelium via a prostaglandin G/H synthase-dependent conversion of arachidonic acid. It has been suggested that the anti-thrombotic efficacy of aspirin could be limited by the coincidental inhibition of prostacyclin biosynthesis. To avoid aspirin-induced suppression of vascular prostacyclin biosynthesis while still maintaining maximal inhibition of platelet thromboxane A_2 production, chronic administration of low-dose, conventionally formulated aspirin or alternate day dosing schedules have been evaluated [9, 10]. Unfortunately, depression of basal and stimulated prostacyclin biosynthesis was associated with both chronic administration of conventionally formulated, low-dose aspirin [11,12] and prolonged alternate day administration of a standard 325 mg aspirin formulation [13].

A recent approach to achieving a degree of biochemical selectivity after oral aspirin administration exploits the pre-systemic clearance of aspirin. Thus, by modulating the input rate of aspirin it may be possible to maximise cumulative inhibition of platelet prostaglandin G/H synthase within the prehepatic circulation, with less exposure of the systemic vascular endothelium to aspirin as a consequence of the first-pass hepatic clearance and the subsequent systemic distribution of aspirin [14]. An input rate of aspirin was identified in healthy subjects which afforded biochemical selectivity with respect to administration of a standard low-dose aspirin solution [15]. Based upon this design criterion, a 75 mg controlled-release low-dose aspirin formulation was developed and its effects assessed. Maximal inhibition of platelet-derived thromboxane A_2 was achieved, basal prostacyclin biosynthesis was only marginally depressed relative to control and, importantly, the excretion of prostacyclin metabolites evoked by the systemic infusion of bradykinin (which stimulates endothelial prostacyclin release [16]) was unchanged from placebo control [13].

We now report data from two separate studies undertaken to characterise the release of aspirin from the 75 mg controlled-release dosage form in healthy subjects.

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One study examined the apparent *in vivo* release rate and bioavailability of aspirin, and the second study evaluated the effect of food on drug release.

Methods

Formulation development

The dosage form was a rapidly disintegrating multiparticulate formulation comprising controlled-release aspirin granules compressed (while maintaining their integrity) with inert filler granules to produce standard concave tablets. The reference formulation for the pharmacokinetic studies was an aqueous solution of aspirin (1.5 mg ml^{-1}). The *in vitro* release rate and disintegration time of the tablets were measured as described in the USP XXI.

Clinical studies

Two separate studies were undertaken in healthy male subjects aged between 18 and 45 years of age and with body weights from 63 to 88 kg. The protocols were approved by the local Institutional Review Board and all subjects provided written informed consent prior to participation. All subjects were non-smokers and had abstained from medication for at least 14 days prior to the study. Normal results from physical examination, routine haematological and biochemical screens were a pre-requisite for inclusion. No subject had a prior history of aspirin sensitivity.

In vivo *release rate study* Twelve subjects who had fasted for 8–16 h prior to dosing were randomised to receive either the 75 mg controlled-release aspirin tablet ingested with 200 ml tap water or 75 mg aspirin solution (50 ml of a 1.5 mg ml^{-1} solution) followed by 150 ml tap water. The washout period between treatments was 4 days. At approximately 4 h and 8 h after drug administration, each subject received a standard meal. Blood samples (3 ml) for measurement of aspirin and salicylate concentrations were taken by individual venepuncture prior to aspirin administration and at 5, 10, 15, 20, 30, 40, 60, 90, 120 and 150 min and 3, 4, 6 and 8 h after administration of the solution formulation, and before and 0.5, 1, 2, 3, 4, 6, 8, 10 and 14 h after administration of the controlled-release formulation. All blood samples were transferred rapidly to pre-cooled vials containing potassium fluoride (30 μl of a 10% w/v solution) and heparin (30 μl of a 1000 iu ml^{-1} solution), which were immediately centrifuged at 4° C. The plasma was separated and stored at −70° C prior to analysis within the subsequent 7 day period.

Fed-fasted study The effect of food on the controlled-release dosage form was assessed by administering it to subjects in either a fed or fasted state. The total volume of fluid ingested was 200 ml as described above. Eight subjects were assigned randomly to either treatment in a simple cross-over design with a 4 day washout period. Fasted subjects had avoided food intake for 8–16 h prior to drug administration. Subjects who received the controlled-release formulation in the fed state consumed the following 860 calorie breakfast approximately 30 min prior to drug administration: 6 ounces orange juice, two strips of bacon, 8 ounces of whole milk, 2 slices of toast or bread with 2 pats of butter and 1 tablespoon of jelly. Blood samples (3 ml) for measurement of aspirin and salicylate concentrations were collected as described above.

Pharmacokinetic parameters

C_{max} and t_{max} values for aspirin and salicylate were noted directly from the plasma drug concentration-time data. The elimination rate constant after administration of the solution formulation was determined by linear regression of the terminal phase of each log plasma drug concentration-time plot. In both the release rate and fed-fasted studies, AUC values for aspirin and salicylate were calculated by the linear trapezoidal method from zero to the last measured plasma drug concentration. In the release rate study, the extrapolated salicylate AUC value following administration of both the solution and controlled release formulations was obtained by division of the last measured plasma salicylate concentration by the individual elimination rate constant determined after administration of the solution. The extent of drug release was calculated for each subject from the ratio of the salicylate AUC for the controlled-release formulation to that for the solution formulation, and the rate of drug absorption was calculated using a modified Wagner-Nelson equation [17, 18] as described below:

$$\text{CRFA} = \frac{[C_{SA}(t)]_{CR} + k_{soln} \times \text{AUC}(0,t)_{CR}}{k_{soln} \times \text{AUC}_{soln}} \quad (1)$$

where CRFA is the cumulative relative fraction absorbed, $[C_{SA}(t)]_{CR}$ is the plasma salicylate concentration at time t after administration of the controlled-release dosage form, $\text{AUC}(0,t)_{CR}$ is the AUC value for salicylate to time t calculated using the linear trapezoidal rule for the controlled-release formulation, k_{soln} is the first-order terminal elimination rate constant for salicylate calculated from the solution data, and AUC_{soln} is the total AUC for salicylate after administration of the solution. The CRFA calculations were based upon plasma salicylate rather than aspirin concentrations to avoid any effects of non-linearity in the pre-systemic clearance of asiprin which could have arisen from the different input rates of aspirin from the solution and controlled-release formulations. This approach assumes that the rate of aspirin absorption and conversion to salicylate is rapid compared with the rate of salicylate elimination [18], which is reasonable considering the differences in the rate constants describing these processes [19, 20].

Drug analysis

Aspirin and salicylate were measured by gas chromatography/mass spectrometry as described by FitzGerald *et al.* [15]. The assay was linear up to at least 100 μg ml^{-1}, the limit of determination of each analyte was approximately 500 pg ml^{-1}, and the inter-assay coefficient of variation was typically less than 5% at the limit of determination.

Statistical methods

Student's paired two-tailed *t*-test was used to evaluate differences between sets of data and a 5% significance level was assumed.

Results and discussion

In vitro *drug release*

The controlled-release tablets disintegrated rapidly within 5 min. The release of aspirin was essentially zero-order, being complete within 8 h. In the first hour of dissolution 10–15 mg aspirin was released reflecting a small amount of granule rupture during tablet compression. However, this initial release did not perturb the early phase of the plasma aspirin concentration-time profile.

In vivo *drug release*

Mean plasma aspirin and salicylate concentrations after administration of the controlled-release and solution formulations are shown in Figure 1. The mean C_{max} value of aspirin after administration of the controlled-release formulation was 15-fold lower than after administration of the solution (96 ± 22 ng ml^{-1} *vs* 1317 ± 374 ng ml^{-1}, mean ± s.d.). Plots of the CRFA indicated rapid drug absorption from the solution formulation and that the rate of drug release from the controlled-release dose form was approximately zero-order up to 8 h (Figure 2). The extent of release of aspirin from the controlled-release formulation was 88 ± 27% (mean ± s.d.) relative to the solution. The mean (± s.d.) AUC values for salicylate from the controlled-release and solution formulations were 4024 ± 1108 ng ml^{-1} h and 4750 ± 1218 ng ml^{-1} h, respectively; and the corresponding aspirin AUC values were 494 ± 116 ng ml^{-1} h and 650 ± 82 ng ml^{-1} h.

Effect of food

Plasma aspirin and salicylate concentrations were similar in the fed and fasted states with the only statistically significant effect being a doubling of the t_{max} of aspirin from 1.1 h (range 0.5–3.0 h) to 2.6 h (range 1.0–3.0 h). The C_{max} values were similar (aspirin: 62 ± 21 (fasted) *vs* 76 ± 20 ng ml^{-1} (fed); salicylate: 676 ± 187 (fasted) *vs* 671 ± 343 ng ml^{-1} (fed)) as were the AUC values (aspirin: 253 ± 116 (fasted) *vs* 390 ± 126 ng ml^{-1} h (fed); salicylate: 5518 ± 1346 (fasted) *vs* 5962 ± 2889 ng ml^{-1} h (fed)). Although food has been shown to affect the plasma concentrations of salicylate (and presumably aspirin) after administration of some granule-based and monolithic enteric coated aspirin preparations [21, 22], co-administration of the controlled-release formulation with food in this study had a negligible effect on drug release from the formulation. The lack of a food effect may reflect the number and small size of the controlled-release aspirin granules (0.5–1.5 mm) in the rapidly disintegrating tablet.

The results of this investigation indicate that the controlled-release aspirin formulation reasonably meets the criteria for a robust dosage form which can be used as a probe for assessing the clinical importance of preserving prostacyclin biosynthesis during aspirin-based inhibition of platelet-derived thromboxane A_2 production.

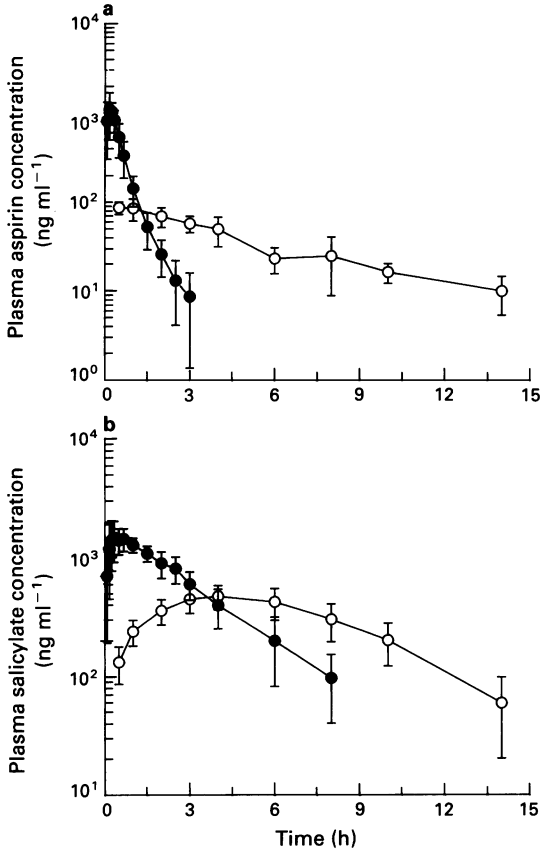

Figure 1 Mean (± s.d., n = 12) plasma concentrations of aspirin (a) and salicylate (b) after administration of 75 mg aspirin as either a solution (•) or controlled-release dosage form (○).

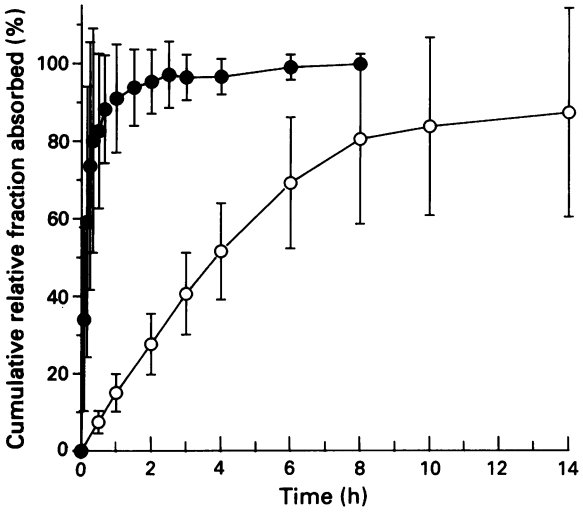

Figure 2 The mean (± s.d., n = 12) cumulative relative fraction of drug absorbed (CRFA) as a function of time after administration of 75 mg aspirin as a solution (•) or controlled release dosage form (○).

We thank Ms Phoebe Tribble who provided expert support for these studies.

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(Received 28 October 1992, accepted 13 July 1993)