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The Dissolution Rate and Bioavailability of Hydrochlorothiazide in Pellet Formulations

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Abstract—The influence of non-active ingredients in the manufacture of pellets on in-vitro dissolution rate and on bioavailability of hydrochlorothiazide has been studied. Pellets were formulated using either microcrystalline cellulose or microcrystalline cellulose-carboxymethylcellulose sodium blends as matrix, and hydrochlorothiazide as the active ingredient. In-vitro drug release from the different pellet formulations was retarded in comparison to a conventional tablet formulation and was dependent on the nature of the non-active ingredient and, for the microcrystalline cellulose-carboxymethylcellulose sodium blend, of the dissolution medium. In-vivo bioavailability of both pellet formulations was low compared with that of the conventional tablet and the plasma concentration-time profiles did not suggest slow release.

The use of pellets for pharmaceutical formulations is of interest for both conventional dosage forms and for controlled release delivery systems. The bioavailability of a drug formulated as a pellet, is influenced by the physicochemical properties of the drug, the composition of the non-active ingredients and the gastrointestinal transit time (Bechgaard 1982; Bechgaard & Christensen 1982; Kaus et al 1984; Bechgaard et al 1985). The aim of the present work was to study the in-vitro dissolution rate and the bioavailability of binary drug-diluent mixtures; hydrochlorothiazide was chosen as the active ingredient. The processing parameters were held constant and two different diluents were used to produce the pellets: microcrystalline cellulose and a microcrystalline cellulose-carboxymethylcellulose sodium blend. As a slow release was expected, these formulations were compared in-vitro and in-vivo with a conventional hydrochlorothiazide tablet.

Materials and Methods

Materials and in-vitro dissolution testing

For pellets type I a mixture of hydrochlorothiazide with microcrystalline cellulose (Avicel PH 101, F.M.C., Philadelphia, USA) was used; for pellets type II a mixture of hydrochlorothiazide with a blend of microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC 581, F.M.C., Philadelphia, USA); for both types 25% hydrochlorothiazide was the active ingredient.

The pellets were prepared using granulation, extrusion and spheronization (O'Connor et al 1985). The Avicel PH 101 and RC 581—hydrochlorothiazide powders were mixed for 3 min in a planetary mixer (Hobart A-200-T, Hobart Co., Hobart, NY, USA) at 50 rev min^{-1} using a 1 kg batch size. Purified water (875 mL in the case of the Avicel PH 101 blend and 1050 mL in the case of the Avicel RC 581 blend) was added to the mixing powders in the same planetary mixer and granulation was for 10 min. The granulated mass was passed through an extruder (Model EXDS-60/Luwa Corporation, Charlotte, NC, USA). The extruder was operated at 50 rev min^{-1} and was fitted with 1·5 mm screens. The extrudate was then processed in a spheronizer (Marumerizer, Model Q-230, Luwa) at a rotational speed of 1000 rev min^{-1} for 1 min. Spheres were dried overnight in an oven at 40°C. All experiments were performed with 0·5–2·5 mm sieve cut.

As conventional hydrochlorothiazide tablets, a commercial preparation (Esidrex tablets—50 mg, batch no. 84K12, Ciba) was used.

Dissolution tests were performed in 900 mL water, simulated gastric fluid and simulated intestinal fluid, using the paddle method (USP XXI, 50 rev min^{-1} 37°C) (Augsburger et al 1983). The release of hydrochlorothiazide was analysed continuously at 273 nm. The geometric variation of the pellets in the various dissolution media was determined using an invert microscope (Wilovert, Wild, Van Hopplynus, Brussels, Belgium).

Bioavailability testing

Six healthy volunteers, 2 males and 4 females, aged 23–25 years, gave informed consent. The study was approved by the Medical School Ethical Committee. Physical examination, electrocardiogram and blood biochemistry did not reveal any abnormalities. The subjects were instructed to take no drugs one week before, or during the study, with the exception of oral contraceptives. Each volunteer was given, in a randomized cross-over design, 50 mg hydrochlorothiazide on 3 occasions, once as a tablet and twice as a hard gelatin capsule filled with pellets (type I or type II). The interval between intakes was 1 week. The drug was administered at 0800 h with 150 mL of water following overnight fasting. A standard breakfast (sandwiches, butter, marmalade, coffee) was given 2 h after intake. No consumption of alcoholic beverages and nicotine was permitted from 12 h before to 36 h after intake.

Venous blood samples (5 mL) were collected into heparinized glass tubes immediately before, and at various times after administration of the drug, as indicated under Results. Plasma was separated by centrifugation at 3000 rev min^{-1}

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and stored at −20°C. Urine was collected before and after intake and samples were stored at −20°C. All the plasma and urine samples were assayed within 10 days of their collection.

In another experiment, the pellet formulation type I was administered to three healthy volunteers and the faeces were collected during 4 days. Intact pellets were isolated with forceps and spatula, counted and the amount of hydrochlorothiazide was determined in the faeces as well as in the collected pellets.

Analytical methods

Concentrations of hydrochlorothiazide in plasma were determined using HPLC, with flumethiazide as the internal standard, as described by Barbhaiya et al (1981).

Hydrochlorothiazide in urine was also assayed with HPLC. Twenty μL of an internal standard solution (650 μg mL^{-1} flumethiazide in methanol, Squibb & Sons, Princeton, NJ, USA), 1 mL 0·01 M acetate buffer (pH 5·0) and 5 mL ethyl acetate were added to 0·5 mL urine. The solution was shaken for 30 s, and separated into the two layers by centrifugation at 3000 rev min^{-1} for 10 min, then 4 mL of the ethyl acetate layer was transferred to a polypropylene tube and evaporated to dryness under nitrogen at room temperature (20°C). The residue was reconstituted in 200 μL of methanol, and 5 μL was then injected into the chromatograph.

For faeces, from each defecation, six 1 g samples were taken, pooled, homogenized and macerated with 300 mL of ethylacetate for 15 min, followed by centrifugation at 3000 rev min^{-1} for 2 min; 250 mL of the supernatant was transferred and evaporated to 100 mL under nitrogen at room temperature. Twenty μL of this solution was injected into the chromatograph. The same method was used to determine the amount of hydrochlorothiazide present in pooled isolated pellets.

Chromatography

The HPLC system consisted of a solvent pump (Waters Associates, M 6000 A), a Valco syringe CV-6-4 MPa-M60 injector (Valco Instr. Corpor., R.S.L., Eke, Belgium), a 5 μm particle size (Rosil C18 H.L.) column (15 cm × 4·6 mm, R.S.L., Eke, Belgium) and a variable wavelength UV detector (Pye Unicam L.C. 3), set at 228 nm. The mobile phase was methanol–water (20:80 v/v). The flow rate was 1·0 mL min^{-1}. All the determinations were at room temperature. The hydrochlorothiazide concentrations were determined from the peak height ratio hydrochlorothiazide/internal standard. The standard curves obtained were (mean ± s.e.m.):

$Y = 4{\cdot}360 \cdot 10^{-3} (\pm 0{\cdot}196 \cdot 10^{-3}) \times + 0{\cdot}022 (\pm 0{\cdot}010)$,
$(r = 0{\cdot}9998 \pm 0{\cdot}0004)$ $(n = 8)$ for plasma;
$Y = 4{\cdot}016 \cdot 10^{-3} (\pm 0{\cdot}121 \cdot 10^{-3}) \times + 0{\cdot}007 (\pm 0{\cdot}013)$,
$(r = 0{\cdot}9996 \pm 0{\cdot}0002)$ $(n = 8)$ for urine and
$Y = 5{\cdot}785 \cdot 10^{-3} (\pm 0{\cdot}596 \cdot 10^{-3}) \times + 0{\cdot}073 (\pm 0{\cdot}064)$,
$(r = 0{\cdot}9998 \pm 0{\cdot}0003)$ $(n = 8)$ for faeces and pellets.

Statistics

In-vivo data were assessed by the Wilcoxon signed ranks test for paired observations. Statistical difference was accepted for $P \leq 0{\cdot}05$.

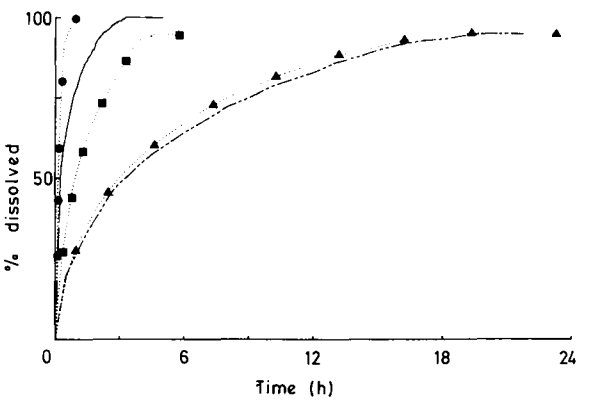

FIG. 1. Release profiles of hydrochlorothiazide tablets, type I pellets and type II pellets, containing 50 mg hydrochlorothiazide. The dissolution tests were performed using the USP paddle method at 50 rev min^{-1} in water, simulated gastric fluid and simulated intestinal fluid. For the tablets and for type I pellets, results in simulated intestinal fluid and in water are not shown, as they were identical as in simulated gastric fluid. —— Tablets (sim. gastric fluid); ··■·· Type II pellets (sim. intestinal fluid); ···▲··· Type II pellets (sim. gastric fluid); ···●··· Type II pellets (water); — - - — Type I pellets (sim. gastric fluid).

Results

In-vitro dissolution

The in-vitro release of hydrochlorothiazide from both pellet formulations was slow, compared with the release from conventional tablets (Fig. 1). The release profiles for the conventional tablet and for the type I pellets were not dependent on the composition of the dissolution medium. A 100% release was obtained after 220 min for the conventional tablets and after 21 h for the type I pellets. No change in dimensions was observed in the different dissolution media for type I pellets.

The release rate of hydrochlorothiazide from type II pellets was affected by the composition of the dissolution medium: 100% of the drug was released in 22 h for simulated gastric fluid and in 4·5 h for simulated intestinal fluid, compared with 80 min in water (Fig. 1). The change in dimension of type II pellets was strongly dependent on the composition of the dissolution medium and was much less pronounced in gastric fluid.

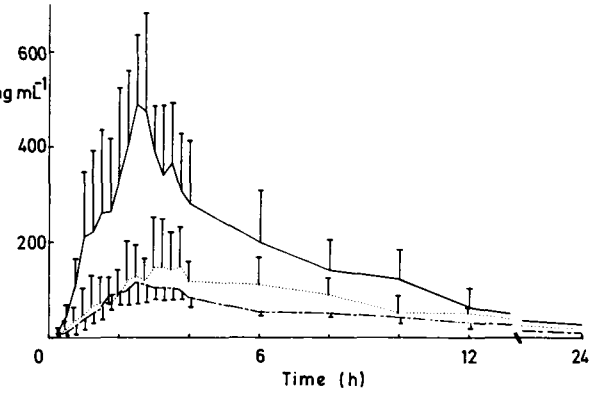

FIG. 2. Mean plasma concentration-time profiles (± s.e.m.) obtained after intake of 50 mg hydrochlorothiazide as tablets (——), type I pellets (— · —) and type II pellets (. . . . .) (n = 6).

Table 1. Plasma peak concentration, t_{max}, area under the curve and urinary recovery after administration of 50 mg hydrochlorothiazide as a conventional tablet and as two pellet formulations to six subjects. Means (±s.e.m.) are shown.

	Tablets	Pellets type I	Pellets type II
C_{pmax} (ng mL^{-1})*	489 (±147)	116 (±34)	148 (±78)
t_{max} (min)	148 (±18)	140 (±24)	207 (±46)
AUC_p (ng h mL^{-1})*	3137 (±659) (100%)	1144 (±183) (36%)	1579 (±431) (50%)
Urinary recovery (mg/24 h)*	33·9 (±3·5) (100%)	13·2 (±3·6) (39%)	18·4 (±5·9) (54%)
Total amount of HCT excreted as % of dose	67·9 (±6·4)	26·4 (±6·5)	36·9 (±9·2)

* $P \leq 0{\cdot}05$ (Wilcoxon test) (tablets vs pellets type II)
$P \leq 0{\cdot}05$ (Wilcoxon test) (tablets vs pellets type I)
N.S. (Wilcoxon test) (pellets type I vs pellets type II)

In-vivo studies

The mean plasma hydrochlorothiazide concentration-time profiles after administration of 50 mg hydrochlorothiazide, as a conventional tablet or as a capsule containing type I and type II pellets, are shown in Fig. 2. C_{max}, t_{max} and AUC are shown in Table 1. C_{max} and AUC were significantly ($P < 0{\cdot}05$) higher for the tablet formulation than for the pellet formulations, but between the pellets no significant difference was observed. The urinary excretion followed a similar pattern (Fig. 3). Overall recovery of hydrochlorothiazide in urine over 24 h was 67·9, 26·4 and 36·9% of the dose after treatment with conventional tablets, type I pellets and type II pellets, respectively. The relative bioavailability data calculated from the urinary analysis are in close agreement with the results of the plasma concentration-time profiles (Table 1).

After administration of type I pellets, more than 95 percent of the pellets were recovered from the faeces. The residual amount of hydrochlorothiazide in the pellets was 13% (±0·3; mean±s.e.m.; n=3) of the dose administered. The total amount of hydrochlorothiazide excreted in the faeces, as a percentage of the administered dose (50 mg) was 48% (±8%, n=3), 61% (±2%, n=3) and 67% (±2%, n=3) after 36, 60 and 76 h, respectively.

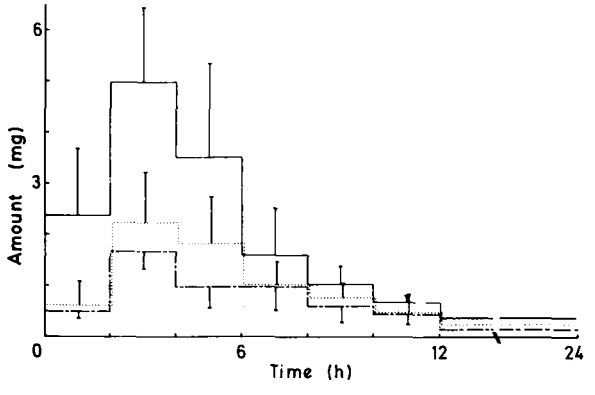

FIG. 3. Mean urinary excretion of hydrochlorothiazide (±s.e.m.) after intake of 50 mg hydrochlorothiazide, as tablets (——), type I pellets (— · —) and type II pellets (· · · ·) (n=6).

Discussion

The formulation of hydrochlorothiazide as pellets made of a binary mixture of drug with microcrystalline cellulose or of drug with microcrystalline cellulose-carboxymethylcellulose sodium lowered the release rate of the drug. Earlier communications (O'Connor & Schwartz 1984a,b; O'Connor et al 1984, 1985) have reported the varying degrees of slowing of in-vitro dissolution for pellets consisting of theophylline or quinidine sulphate and microcrystalline cellulose and carboxymethylcellulose sodium.

The release rate of hydrochlorothiazide, formulated as a conventional tablet and as type I pellets, was not dependent on the dissolution medium used. For the type II pellets the dissolution rate was faster in water and slower in simulated intestinal fluid, compared with the conventional tablet. The dissolution rate of type II pellets in simulated gastric fluid was identical to that of type I pellets.

That the dissolution rate of type II pellets depends on the dissolution medium can be explained by the hydrophilization of hydrochlorothiazide due to carboxymethylcellulose sodium. The viscosity and solubility of carboxymethylcellulose sodium are strongly dependent on the pH. The viscosity is maximal between pH 6 and 9 and declines abruptly below pH 2·5 (Brown & Houghton 1941). Moreover the ionic strength profoundly influences the physicochemical properties of carboxymethylcellulose sodium; the release rate decreases with an increase in ionic strength (O'Connor et al 1985). Observation of type II pellets in the different dissolution media revealed a variation in degree of swelling with the geometric variations being in close agreement with the differences in release rate. Swelling of the pellets was pronounced in artificial intestinal fluid and in water, while the geometry remained unchanged in artificial gastric fluid.

The plasma concentration-time profile and the urinary excretion pattern obtained after administration of the conventional tablet are in good agreement with the data of Barbhaiya et al (1982).

The plasma concentrations after intake of pellet formulations were low compared with those after intake of the conventional tablet; urinary excretion patterns correlated well with these results and the calculated relative bioavailability data based on AUC and on urinary recovery were in close agreement. Several studies have demonstrated that the main uptake of hydrochlorothiazide takes place in the duodenum and the first part of the jejunum and to a small extent in the stomach (Beerman et al 1976; Backman et al 1979). Due to the fast release of hydrochlorothiazide from the conventional tablet, even in gastric fluid, most of the drug is probably available for absorption at the appropriate sites. Both pellet formulations have a very slow release rate in simulated gastric fluid in-vitro; it could be that in-vivo only a small amount of the drug is released before the formulation has passed the region where absorption is optimal. In this regard it is worth mentioning that Redalieu et al (1985) found for normal release hydrochlorothiazide, zero-order absorption kinetics, suggesting an unusual absorption mechanism. Inspection of the plasma concentration profiles after intake of the pellet did not allow any conclusions to be made about the slow release characteristics of these formulations.

The low levels of hydrochlorothiazide in the excreted

intact type I pellets (13·4% of the dose) together with the high faecal levels of the drug, prove that most of the drug is released from the pellets during the gastrointestinal transit. The slightly higher bioavailability of type II pellets as compared to type I pellets, could be due to faster release from type II pellets once the intestine is reached.

Conclusion

The bioavailability of hydrochlorothiazide formulated as pellets containing microcrystalline cellulose or microcrystalline cellulose-carboxymethylcellulose sodium is low compared with a conventional tablet formulation. The correlation between the in-vitro dissolution profiles and the in-vivo data is poor. This is perhaps due to the fact that hydrochlorothiazide absorption seems to be restricted to the upper part of the intestine.

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