Bioavailability of Hydrochlorothiazide from Pellets, Made by Extrusion/ Spheronisation, Containing Polyethylene Glycol 400 as a Dissolution Enhancer

Chris Vervaet[1] and Jean Paul Remon[1,2]

Received May 20, 1997; accepted August 5, 1997

KEY WORDS: HCT; hydroflumethiazide; cyclodextrins.

INTRODUCTION

Drugs with limited aqueous solubility such as hydrochlorothiazide (HCT) have a potential for low bioavailability. Several methods which proved to increase the in-vitro release rate of drugs with a low aqueous solubility were tested in-vivo on their ability to increase the bioavailability of the drug. Reduction of the drug particle size (1–3), incorporation of the drug into solid dispersions (4–8) and complexation with cyclodextrins (2,9–10) proved to be suitable methods for increasing the gastrointestinal absorption of drugs with a low aqueous solubility. Vervaet *et al.* (11) demonstrated that the incorporation of a liquid solubiliser into microcrystalline cellulose pellets enabled the enhancement of the in-vitro release rate of HCT. The aim of this study is to evaluate the effect of PEG 400 on the pharmacokinetic parameters of HCT after oral administration of microcrystalline cellulose pellets loaded with HCT and polyethylene glycol 400.

MATERIALS AND METHODS

Materials

Hydrochlorothiazide (HCT)(Ludeco, Brussels, Belgium) was used as a model drug. Polyethylene glycol 400 (PEG 400)(α-Pharma, Vichte, Belgium) was used as a solubilising agent, while microcrystalline cellulose (Avicel PH101®)(FMC Wallington, Little Island, Cork, Ireland) was chosen as a filler and the pellet forming agent. Demineralized water was used as granulation liquid, next to PEG 400.

Formulations

Two pellet formulations were tested in vivo. Type I-pellets consisted of a mixture of HCT and microcrystalline cellulose (ratio: 3.5/96.5; w/w), while PEG 400 was added to form Type I-pellets (HCT/PEG 400/Avicel PH101®—ratio: 3.5/20/76.5; w/w/w). A conventional HCT tablet (Esidrex® 25 mg, Ciba, Basel, Switzerland) was used as the reference formulation.

Preparation of the Pellets

The pellets were prepared using the method described by Vervaet *et al.* (11). The granulation liquid, which was added to the microcrystalline cellulose/HCT mixture, was pure demineralized water in the case of Type I-pellets, while a mixture of demineralized water and PEG 400 was used for Type II-pellets. The batch size of both formulations was 1 kg. After drying the pellets for 48 h at 30°C in a ventilated oven (Heraus, Oberdorf, Germany), the 800–900 μm sieve fraction was isolated.

Dissolution Testing

A dissolution test was performed, using the method described by Vervaet et al. (11), on the HCT tablet and on hard gelatin capsules filled with an amount of Type I- and II-pellets (800–900 μm fraction), equivalent to 25 mg of HCT.

Bioavailability Testing

Eight healthy Caucasian male volunteers, aged 19 to 45 years and weighing between 72 and 112 kg, participated in the study after giving informed consent. The physical state of all volunteers was examined before they were allowed to participate in the study. The subjects had to refrain from taking any other drugs for one week prior to and during the study. Each volunteer was given, in a randomized cross-over study, an oral dose of 50 mg HCT on 3 occasions, once administered as two Esidrex® 25 mg tablets and twice as a two hard gelatin capsule filled with pellets (Type I or II)(800–900 μm fraction). The washout period between the sessions was 1 week (HCT half-life: 5 h). All doses were administered with 200 ml of water at 8 a.m. after overnight fasting. A standard breakfast was given 2 h after administration of the dosage form. A lunch was taken at 12 a.m. No consumption of alcoholic beverages and nicotine was permitted from 12 h before until 24 h after drug intake.

Venous blood samples were collected into glass tubes immediately before and at various time intervals after drug administration. Serum was separated from the blood cells by centrifugation and stored at −20°C until analysis.

Chromatography

HCT serum concentrations were determined using a RP-C18 column (250 × 4 mm − 5 μm)(LiChrospher® 100, Merck, Darmstadt, Germany) equipped with a precolumn (RP-C18 − 4 × 4 mm − 5 μm). Both were kept at a constant temperature of 40°C. The mobile phase was 0.2 M phosphate buffer (pH 7.5)/tetrahydrofuran/acetonitrile (85/10/5; v/v/v). The flow rate was 1 mL/min. The detector wavelength was set at 273 nm.

Hydroflumethiazide (Sigma Chemical Co., St. Louis, MO, USA) was used as the internal standard. 500 μL serum, 100 μL 1.25 μg/ml hydroflumethiazide and 5 mL methyl *tert*-butylether (Sigma Chemical Co., St. Louis, MO, USA) were pipetted into borosilicate glass tubes. After 2 min vortexing and 5 min centrifuging at 2700g, the organic phase was transferred into a new borosilicate glass tube and evaporated until completely dry under a nitrogen stream. The residue was dissolved in 200 μL water, followed by the addition of 3 mL toluene (Vel N.V. Leuven, Belgium). The bulk of the toluene layer was discarded after 2 min of vortexing and 10 min centrifuging at 2700 g.

[1] Laboratory of Pharmaceutical Technology, University of Gent, Harelbekestraat 72, B-9000 Gent, Belgium.

[2] To whom correspondence should be addressed. (e-mail: jeanpaul.remon@rug.ac.be)

0724-8741/97/1100-1644$12.50/0

Another 3 mL toluene was added, this mixture was again vortexed and centrifuged followed by the removal of the toluene layer. After evaporation of the water fraction under a nitrogen stream, the residue was dissolved in 200 μL mobile phase. A 100 μL aliquot of the homogenized solution was injected into the HPLC system.

HPLC Validation

The HCT recovery (10–1000 ng/ml range) varied between 87.5 and 91.5 %, while 93.5% of the internal standard was recovered. The method was linear between 0 and 1000 ng HCT/mL (r^2 = 0.99987 ± 0.00011)(n = 10). The within-day variability was 0.59–5.01% in the 10–1000 ng/ml range, while the intra-day variability for the same concentration range was determined at 0.68–5.89%. The detection and quantification limit in serum were 3.3 and 11.2 ng/ml, respectively.

Pharmacokinetic Analysis

The C_{max} and t_{max} values were determined from the individual serum concentration—time profiles, while the $AUC_{0\rightarrow 24h}$ was calculated using the MW/Pharm software package (v. 3.0; Mediware 1987–1991, Utrecht, The Netherlands). The Wilcoxon signed ranked test for paired observations (12) was used to evaluate the pharmacokinetic parameters.

RESULTS AND DISCUSSION

The bioavailability of three HCT formulations was evaluated: a commercially available tablet (Esidrex® 25 mg) and two hard gelatin capsules, one filled with Type I-pellets containing a mixture of HCT and microcrystalline cellulose, while the other capsule contained microcrystalline cellulose pellets to which 20% (w/w) polyethylene glycol 400 was added (Type II-pellets).

Fig. 1 shows the in-vitro release profiles of the different formulations. The incorporation of PEG 400 into the pellet formulation showed a dramatic increase of the in-vitro release rate ($t_{50\%}$ value of 120 and 7 min for Type I- and II-pellets, respectively) due to the solubilising effect of PEG 400 (11). Both the tablet and the Type II-pellet formulation showed similar dissolution profiles for HCT.

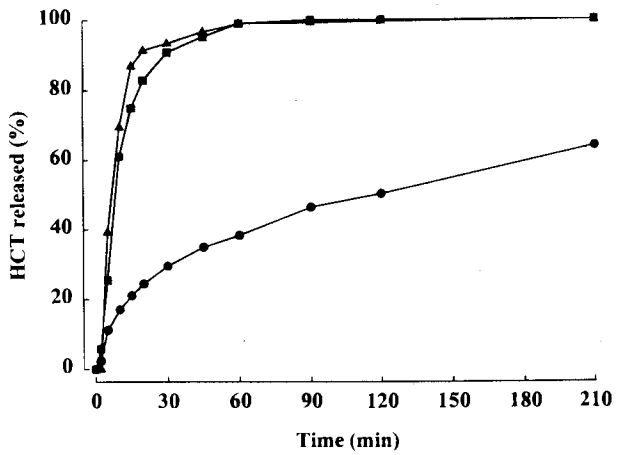

Fig. 1. Dissolution profile of formulations containing 25 mg of HCT. ■: tablet formulation (Esidrex® 25 mg) ●: Type I-pellets (HCT/microcrystalline cellulose 3.5/96.5 (w/w)) ▲: Type II-pellets (HCT/polyethylene glycol 400/microcrystalline cellulose 3.5/20/76.5 (w/w)).

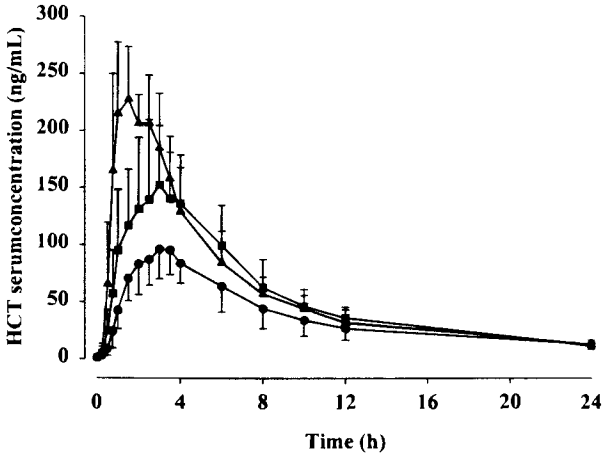

Fig. 2. Mean serum concentration—time profiles (±SD; n = 8) obtained after intake of an oral dose of 50 mg HCT. ■: tablet formulation (Esidrex® 25 mg) ●: Type I-pellets (HCT/microcrystalline cellulose 3.5/96.5 (w/w)) ▲: Type II-pellets (HCT/polyethylene glycol 400/microcrystalline cellulose 3.5/20/76.5 (w/w)).

The mean HCT serum concentration vs. time profiles are presented in Fig. 2. The pharmacokinetic parameters of the different formulations are shown in Table I. The C_{max} values were significantly different ($p \leq 0.01$; Wilcoxon signed ranked test) between all formulations. The t_{max} values of the tablet and the Type I-pellet formulation were not significantly different, while the Type II-pellets showed a significantly shorter t_{max} value ($p \leq 0.01$; Wilcoxon signed ranked test) in comparison to Type I-pellets and the tablet formulation. The calculated $AUC_{0\rightarrow 24h}$ values were significantly higher ($p \leq 0.01$; Wilcoxon signed ranked test) for the tablet compared to Type I-pellets and for Type II-pellets compared to Type I-pellets. The low relative bioavailability (F_{rel}) of the Type I-pellets (70.4%) compared to the HCT tablet is in accordance with previous results (13), where a F_{rel} of 36.4% was found for HCT when administered as microcrystalline cellulose based pellets compared to a 50 mg HCT tablet. The reduced absorption of HCT was due to the absorption window of HCT in the gastro-intestinal tract,

Table I. Mean Bioavailability Parameters (± SD; n = 8) After Administration of an Oral Dose of 50 mg HCT, Once Administered as Two Esidrex® 25 mg Tablets and Twice as a Two Hard Gelatin Capsule Filled with Pellets

	Tablet	Type I-pellets	Type II-pellets
C_{max} (ng/ml)	180.2 ± 42.1	105.9 ± 24.2[a]	254.5 ± 36.0[a,b]
t_{max} (min)	165 ± 64	195 ± 36	83 ± 31[a,b]
$AUC_{0\rightarrow 24h}$ (ng.h/ml)	76.5 ± 15.8	53.0 ± 12.8[a]	86.7 ± 19.5[b]
F_{rel} (%)		70.4 ± 13.8	117.3 ± 34.9

[a] Significantly different from tablet ($p \leq 0.01$; Wilcoxon signed ranked test).

[b] Significantly different from Type I-pellets ($p \leq 0.01$; Wilcoxon signed ranked test).

the major part being absorbed in the duodenum and the upper part of the jejunum (14). As the slow in-vitro dissolution rate from Type I-pellets indicated (Fig. 1) only part of the HCT was made available for absorption in the upper parts of the gastro-intestinal tract. This was confirmed by Herman *et al.* (13) who found a high fecal HCT concentration and little of the total dose remaining in the excreted intact pellets, indicating that most of the drug was released from the microcrystalline cellulose pellets in the lower parts of the gastro-intestinal tract.

The higher bioavailability after administration of the tablet, compared to the Type I-pellets, was due to the tablet disintegration, exposing the HCT-crystals to the gastro-intestinal liquids, whereas these liquids had to penetrate the inert microcrystalline cellulose matrix (15) of Type I-pellets to wet and dissolve the drug crystals.

The improvement of the absorption parameters from Type II-pellet compared to the tablet formulation (the mean C_{max} value increased from 180.2 to 254.5 ng/ml, while the mean t_{max} shifted from 165 to 83 min) is to be attributed to the fact that HCT was solubilised in the pellets (11) whereas the drug crystals still had to dissolve when a tablet was administered.

From the results presented it can be concluded that—when formulating a drug with a low aqueous solubility—microcrystalline cellulose pellets loaded with polyethylene glycol 400 yielded a higher bioavailability compared to pellets without PEG 400. The PEG 400 loaded pellets showed only a significantly higher absorption rate in comparison to a disintegrating tablet formulation.

ACKNOWLEDGMENTS

C. Vervaet is a research assistant of the National Fund of Scientific Research (Brussels, Belgium). The authors wish to thank FMC for the generous supply of Avicel®.

REFERENCES

1. N. Kondo, T. Iwao, H. Masuda, K. Yamanouchi, Y. Ishihara, N. Yamada, T. Haga, Y. Ogawa, and K. Yokoyama. *Chem. Pharm. Bull.* **41**:737–740 (1993).
2. G. G. Liversidge and K. C. Cundy. *Int. J. Pharm.* **125**:91–97 (1995).
3. P. Kanaujia, N. Venkatesan, V. Jaitely, and S. P. Vyas. *East Pharm.* **38**:49–50 (1995).
4. C. Doherty and P. York. *J. Pharm. Pharmacol.* **41**:73–78 (1988).
5. A. T. Serajuddin, P. C. Sheen, and M. A. Augustine. *J. Pharm. Sci.* **79**:463–464 (1990).
6. Y. Chiba, N. Kohri, K. Iseki, and K. Miyazaki. *Chem. Pharm. Bull.* **39**:2158–2160 (1991).
7. S. L. Law, W. Y. Lo, F. M. Fin, and C. H. Chaing. *Int. J. Pharm.* **84**:161–166 (1992).
8. K. P. Chowdary and K. V. Suresh-Babu. *Drug Dev. Ind. Pharm.* **20**:799–813 (1994).
9. K. Uekama, S. Narisawa, F. Hirayama, and M. Otagiri. *Int. J. Pharm.* **16**:327–338 (1983).
10. T. Tokumura, Y. Tsushima, M. Kayano, Y. Machida, and T. Nagai. *J. Pharm. Sci.* **74**:496–497 (1985).
11. C. Vervaet, L. Baert, and J. P. Remon. *Int. J. Pharm.* **108**:207–212 (1994).
12. S. Siegel and N. J. Castellan. In: McGraw-Hill International Eds, 2nd edition, Statistical series, 1988, p. 87–95.
13. J. Herman, J. P. Remon, R. Lefebvre, M. Bogaert, G. H. Klinger, and J. B. Schwartz. *J. Pharm. Pharmacol.* **40**:157–160 (1988).
14. B. Beermann, M. Groschinsky-Grind, and A. Rosén. *Clin. Pharmacol. Ther.* **19**:531–537 (1976).
15. R. E. O'Connor and J. B. Schwartz. *Pharm. Res.* **10**:608–611 (1993).