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Note

Bioavailability of hydrochlorothiazide from isomalt-based moulded tablets

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Abstract

The bioavailability of hydrochlorothiazide (HCT) from moulded isomalt-based tablets was evaluated after oral administration of 50 mg HCT to healthy volunteers as an oral moulded tablet and as a lozenge, in comparison with a conventional tablet formulation (Dichlotride® 50 mg). Moulded tablets had a high relative bioavailability (F_{rel}) as the pharmacokinetic parameters (C_{max}, t_{max}, $t_{1/2}$, $AUC_{0\rightarrow 24\ h}$) determined from HCT plasma concentration versus time profiles were not significantly different ($P > 0.05$; two-way ANOVA) in comparison with the conventional tablet. The relative bioavailability of the moulded tablet administered as a lozenge and as an oral tablet was $106.2 \pm 30.9\%$ and $89.4 \pm 25.9\%$, respectively, in relation to the conventional tablet formulation. Direct moulding of isomalt tablets proved to be a suitable technique to administer a poorly soluble drug either as a conventional tablet or as a lozenge.

Keywords: Isomalt; Hydrochlorothiazide; Direct moulding; Bioavailability

The hot melt moulding technology can offer several technological advantages when used to produce pharmaceutical tablets (Cuff and Raouf, 1999): production of tablets at high drug load, a dust free process, excellent content uniformity of low dose drugs, minimal influence of the drug's compactibility, particle size and particle shape and ease of scale-up. Furthermore, this technique can be used to improve the dissolution rate and solubility of poorly soluble drugs as solid dispersions can be formed and therefore a high oral bioavailability of hydrophobic drugs can be achieved (Chiou and Riegelman, 1971; Chiba et al., 1991; Sheen et al., 1991; Serajuddin, 1999; Leuner and Dressman, 2000). The only limitation of the hot melt moulding technique is its restriction to heat stable products (Cuff and Raouf, 1999; Serajuddin, 1999; Dobetti, 2000).

Recently, Ndindayino et al. (2002) produced by means of the hot melt moulding technique hydrochlorothiazide (HCT) tablets using isomalt (a polyol derived from sucrose) as a carrier; yielding tablets with excellent physical characteristics (hardness, disintegration, etc.) and a rapid in vitro drug release. Due to the sweet taste of the carrier,

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the application of this material is not limited to conventional tablets, but can also be applied to administration as lozenges. The present study reports on the oral bioavailability of HCT (a class IV drug according to the Biopharmaceutics Classification System: low solubility and low permeability) from these isomalt-based moulded tablets administered as a lozenge and as an oral tablet, in comparison with a conventional HCT tablet formulation (Dichlotride® 50 mg, Merck, NJ).

Moulded tablets containing isomalt (Palatinit®) (melting range: 145–150 °C) (Palatinit-Süßungsmittel, Mannheim, Germany), HCT (melting range: 273–275 °C) (Ludeco, Brussels, Belgium) and Explotab® (Pennwest, Patterson, NY) were prepared as previously described by Ndindayino et al. (2002). A mixture of isomalt/HCT/Explotab® (520/50/30; w/w) was melt-extruded at 150 °C using a continuous melt-extruder MP 19 TC 25 (APV Baker, Newcastle-under-Lyme, UK). The resulting molten mass was collected into metal tablet shaped cavities (depth: 4 mm/diameter: 13 mm) to produce 600 mg tablets upon solidification at ambient conditions. A dissolution test was performed as described by Ndindayino et al. (2002).

A HCT human bioavailability study was carried out on five male volunteers (19–45 years, 75–112 kg) after giving informed consent. The subjects had to refrain from taking other drugs for one week and from alcoholic beverages and nicotine for 12 h prior to and during the study. After overnight fasting, each volunteer received at 8 a.m, on three occasions in a randomized cross-over study, an oral dose of 50 mg HCT together with 200 ml of water: once as a moulded tablet administered as a lozenge, once as a moulded tablet orally administered and once as a conventional tablet formulation (Dichlotride®) orally administered. The washout period between sessions was one week (HCT half-life: 10–12 h). All volunteers received a standard breakfast 2 h after administration of the dosage form and a lunch at 12 a.m. Plasma was separated from the venous blood samples and HCT plasma concentrations were determined using a validated HPLC method (Vervaet and Remon, 1997).

The maximum plasma concentration (C_{max}), the time required to reach C_{max} (t_{max}) and the relative bioavailability versus the conventional tablet formulation (F_{rel}) were determined from the individual plasma concentration versus time profiles, while the area under the curve ($AUC_{0\rightarrow 24\ h}$) and plasma elimination half-life ($t_{1/2\beta}$) were calculated using the MW/Pharm software package (v. 3.0, Mediware 1987–1991, Utrecht, The Netherlands). Two-way ANOVA without replicates (Sokal and Rohlf, 1981) was used to statistically evaluate the pharmacokinetic parameters.

The in vitro dissolution results (Fig. 1) showed that the initial release rate of HCT from the moulded tablets was slightly slower in comparison with the conventional formulation due to their different disintegration mechanism: the conventional tablet disintegrating rapidly (<2 min), whereas the moulded tablet released the drug by erosion and dissolution (complete dissolution of the tablet in about 20 min). However, both formulations released their entire drug content within 25 min.

The mean HCT plasma concentration versus time profiles are shown in Fig. 2. The mean pharmacokinetic parameters calculated from individual plasma HCT concentration versus time profile are summarized in Table 1. Based on these data no significant differences ($P > 0.05$; two-way ANOVA) in C_{max}, t_{max}, and $AUC_{0\rightarrow 24\ h}$ values

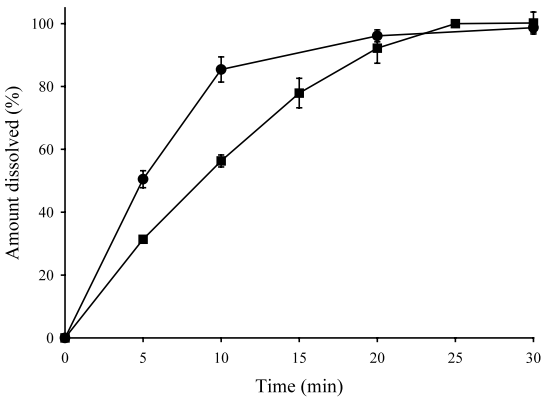

Fig. 1. Dissolution profiles of HCT from the moulded tablet formulated with a mixture of isomalt/HCT/Explotab® (520/50/30; w/w) (■) in comparison with a conventional tablet (Dichlotride® 50 mg) (●).

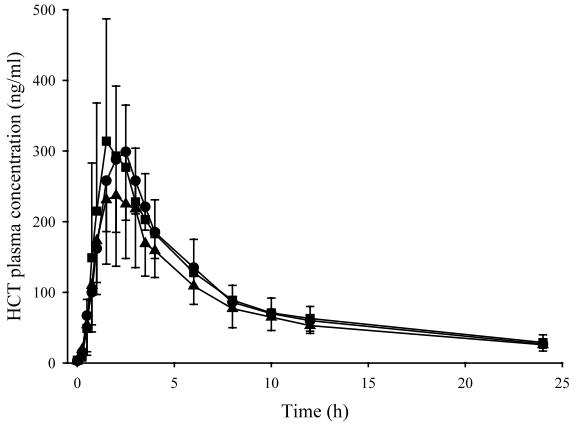

Fig. 2. HCT plasma concentration versus time profiles (±SD, $n = 5$) after administration of an oral dose of 50 mg HCT to human volunteers: moulded tablets (isomalt/HCT/Explotab®, 520/50/30, w/w) administered as a lozenge (●) and as an oral tablet (▲); conventional HCT tablet formulation (Dichlotride® 50 mg) (■).

Table 1
Pharmacokinetic parameters of HCT after oral administration to human volunteers ($n = 5$) of isomalt-based moulded tablets containing 50 mg HCT (in comparison with a conventional Dichlotride® tablet)

Parameters	Moulded tablets		Dichlotride®
	Oral administration	Lozenge	
C_{max} (ng/ml)	270±88	302±100	350±136
t_{max} (h)	2.2±0.6	2.2±0.6	1.9±0.5
$AUC_{0\rightarrow 24\ h}$ (ng h/ml)	1867±337	2168±255	2197±671
$t_{1/2\beta}$ (h)	9.0±1.1	8.8±1.0	8.9±0.9
F_{rel} (%)	89.4±25.9	106.2±30.9	–

were observed between the moulded tablets and Dichlotride®, neither when the moulded tablet was administered as an oral tablet nor as lozenge.

The plasma elimination half-life ($t_{1/2\beta}$) values ranging between 8.8±1.0 and 9.0±1.1 h were not significantly different ($P > 0.05$; two-way ANOVA) for both formulations and were in accordance with the values (8.2–12.3 h) reported by Redalieu et al. (1985) after oral administration of 50 mg HCT. The high inter-individual variability of plasma HCT half-life (0.86–14.81 h) reported by Beermann and Groschinsky-Grind (1977) during their study on pharmacokinetics of HCT in man was not observed.

Next to the formulation of traditional oral tablets, the hot melt direct moulding proved to be a suitable alternative technique to formulate intraoral isomalt-based tablets, which is an important advantage for geriatric and pediatric patients who have swallowing difficulties (Liang and Chen, 2001). Furthermore, these tablets were produced simply and efficiently at an industrial scale and showed a good taste and a better mechanical resistance (Dobetti, 2000; Ndindayino et al., 2002) when compared to the commonly used techniques to produce intraoral systems such as freeze-drying, spray-drying or sublimation (Jaccard and Leyder, 1985; Corveleyn and Remon, 1998; Liang and Chen, 2001; Chang et al., 2000). Nevertheless, the moulded tablets can not achieve disintegration times similar to the above mentioned techniques.

From these results, it can be concluded that the bioavailability of HCT from moulded tablets formulated with isomalt as a carrier was similar to the in vivo availability of the commercial HCT tablet. However, the isomalt-based moulded tablets have the additional advantage that they can be administered as a conventional tablet as well as a lozenge.

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