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Influence of adjuvants on the in vitro dissolution of hydrochlorothiazide from hard gelatin capsules

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Summary

The influence of fillers, lubricants and a surfactant on the dissolution of hydrochlorothiazide from hard gelatin capsules was evaluated using a 2^3 factorial design. Measurement of the dissolution efficiency of eight formulations showed that the adjuvants possessing the greatest hydrophilic character had the greatest effect on the release of hydrochlorothiazide from the capsules.

Introduction

Bioavailability, which is a decisive factor in drug efficacy, can be predicted by different in vitro dissolution methods. Bioavailability has been shown to depend on factors such as the nature of the drug, the dosage form and type and the quantity of adjuvants (Aiache and Beyssac, 1991).

Hydrochlorothiazide (HCT) is a widely used diuretic. Because of its limited aqueous solubility, this drug has a potential bioavailability problem (Shah and Needham, 1979; Deppeler, 1981; Shah et al., 1981; Augsburger et al., 1983; Pandit and Khakurel, 1984; Sakr and Sidhom, 1988). The bioavailability and in vitro dissolution (lyoavailability) of HCT have been studied by several authors but with contradictory results, probably due to differences in the dosage form or the adjuvants employed (Alam and Parrot, 1971; McGilveray et al., 1973; Meyer et al., 1975; Marvola et al., 1980; Barbhaya et al., 1982; Patel et al., 1984; Randolph et al., 1985).

Because of its low hydrosolubility, HCT has been used as a model substance to determine the efficacy of disintegrants in solid pharmaceutical dosage forms (Metha and Augsburger, 1981; Botzolakis et al., 1982; Gorman et al., 1982; Henning and Schubert, 1987; Botzolakis and Augsburger, 1988; Herrman et al., 1988). Co-precipitation and solid dispersion methods have been used to enhance HCT solubility in aqueous media (El-Banna

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et al., 1980; Bloch et al., 1982; Pandit and Khakurel, 1984).

The present study was designed to investigate the influence of fillers (lactose or microcrystalline cellulose), lubricants (magnesium stearate or colloidal silicon dioxide) and a surfactant (polysorbate 80) on the in vitro dissolution of HCT from hard gelatin capsules. Eight different hard gelatin capsule formulations containing the adjuvants and 50 mg of HCT were prepared and analyzed according to a 2^3 factorial design (Yates, 1937).

In vitro dissolution release (lyoavailability) of HCT from the capsules was performed using a paddle dissolution apparatus coupled to a spectrophotometer and a computer.

The characteristic measured was the dissolution efficiency (DE); this is defined as the area under the dissolution curve (AUC) up to a certain time t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (Kahn, 1975).

Materials and Methods

Materials

HCT was obtained from Biolab (Sao Paulo, Brazil). Colloidal silicon dioxide (Aerosil 200) was obtained from Degussa (Frankfurt, Germany). Microcrystalline cellulose (Microcel) was obtained from Blanver (Sao Paulo, Brazil). Lactose, magnesium stearate and polysorbate 80 were purchased from Delaware (Porto Alegre, Brazil).

Experimental design

The formulations were prepared according to a 2^3 factorial design, employing the following qualitative factors and levels (Tables 1 and 2).

HCT was mixed with 1% (w/w) polysorbate 80 under manual stirring for 15 min. The drug without surfactant was treated in the same way. The treated and untreated drug (50 mg), filler and 1% lubricant were blended manually for 15 min and the powder mixtures were filled into no. 2 colourless hard gelatin capsules using an Aponorm capsule filling apparatus.

TABLE 1

Factors and levels used for the 2^3 factorial design

Factor	Level
(A) Filler	+ Lactose
	− Microcrystalline cellulose
(B) Lubricant	+ Magnesium stearate
	− Aerosil
(C) Surfactant	+ Polysorbate 80
	− No surfactant

Dissolution studies

Dissolution tests were performed according to the USP method for hard gelatin capsules, using 500 ml of 0.1 N HCl at 37 °C as the dissolution medium. A dissolution apparatus (Erweka DT6R) was coupled to a multiple flow cell spectrophotometer (Perkin-Elmer Lambda 15) and both to an IBM personal computer. Drug dissolution from six capsules was continuously recorded at 272 nm over a 120 min period. The paddle speed was set at 50 rpm. The AUC, dissolution efficiency (DE) and statistical features for each experiment were calculated by a computer program developed by Daniel Gaudy and Gilles Baylac (Laboratoire de Pharmacie Galénique, Pharmacotechnie et Biopharmacie, University of Montpellier I, France).

Results and Discussion

To study the influence of adjuvants on the dissolution rate of HCT, substances widely used

TABLE 2

Qualitative composition of the hydrochlorothiazide hard gelatine capsules

Treatment	Formulation	Composition [a]		
		A	B	C
(1)	F7	−	−	−
a	F3	+	−	−
b	F6	−	+	−
ab	F1	+	+	−
c	F8	−	−	+
ac	F4	+	−	+
bc	F5	−	+	+
abc	F2	+	+	+

[a] A, filler; B, lubricant; C, surfactant.

in the pharmaceutical manufacture of drugs were chosen. The dissolution efficiencies (DE) of the eight formulations tested are listed in Table 3.

Formulations F1 and F6 showed the least favorable dissolution with low and depressed release. Both capsules contained magnesium stearate but no surfactant and presented the same disintegration behaviour. After dissolution of the capsule wall, the powder mixture (pharmaceutical complex = PC) remained as a stable agglomerate for a few minutes in the dissolution medium. This compact form was probably due to the difficulty in penetration of the dissolution liquid into the agglomerate. The presence of the hydrophobic lubricant and the absence of surfactant may have caused a decrease in the wettability of the PC. The powder particles were probably held together by hydrophobic binding forces.

The other six formulations showed better release and similar dissolution. The dissolution efficiency values ranged from 51 to 78% (Table 3); the decreasing order of DE of these formulations was F7, F8, F5, F3, F4, F2.

Table 4 shows the results of the evaluation of the factorial design. The ANOVA analysis demonstrated that all effects and interactions were statistically significant ($P \leqslant 0.05$). The most important effect was due to the lubricant, followed by the filler. The change from magnesium stearate to aerosil increased the DE. The hydrophobic property of this lubricant and its ability to form a film surrounding the powder particles are compatible with the result.

TABLE 3

Dissolution efficiency (DE) of the hydrochlorothiazide capsules (t = 120 min)

Formulation	DE	(±S.D.; C.V.)
F1	46.46	(5.03; 10.84)
F2	51.66	(5.83; 11.29)
F3	56.86	(2.14; 3.76)
F4	56.67	(4.05; 7.16)
F5	63.05	(4.40; 6.98)
F6	41.27	(5.57; 13.29)
F7	78.04	(2.67; 3.42)
F8	69.28	(5.95; 9.46)

TABLE 4

Main effects (E) and interactions (I) of the factors on the dissolution efficiency of the capsules ($P \leqslant 0.05$)

E or I	Value
EA	−5.07
EB	−7.23
EC	+2.18
IAB	−1.69
IAC	−0.46
IBC	+2.21
IABC	−1.53

The change from microcrystalline cellulose to lactose decreased the DE value. Both fillers are hydrophilic, but whereas lactose is soluble in aqueous medium, microcrystalline cellulose is insoluble but has a great capacity to incorporate water. The presence of new molecules dissolved in the liquid medium, in this case lactose, could influence the solubility product of the weakly soluble HCT and, as a consequence, cause a decrease in its dissolution rate.

The highly hydrophilic characteristic of microcrystalline cellulose, on the other hand, could increase the contact between water and HCT. The surface activity of this filler and its hydrophilicity probably explain the higher DE values observed.

The effect of polysorbate 80 (EC) and the interaction between lubricant and surfactant (IBC) gave similar values (Table 4). When the effect of B (lubricant), a negative value, the effect of C (surfactant), a positive value, and the interaction of both factors (IBC) are compared, it can be noted that, although the surfactant does not interact directly with HCT, the negative influence of the lubricant, in this case magnesium stearate, was decreased by the simultaneous presence of the surfactant. These results suggest that the surfactant interacted directly with the lubricant to overcome the hydrophobic property of this adjuvant.

The statistical crossover analysis (Table 5) of the primary interactions (IAB, IAC and IBC) showed that the most important interaction took place between the lubricants and the surfactant. The interaction of lactose with both lubricant and

TABLE 5

Crossover analysis of the interactions of the filler with other adjuvants

	Microcrystalline cellulose		Mean DE value	Lactose		Mean DE value
	Aerosil	Magnesium stearate		Aerosil	Magnesium stearate	
Polysorbate 80	69.28	63.05	66.17	56.86	51.66	54.26
No surfactant	78.04	41.27	59.66	56.67	46.46	51.57
Mean DE value	73.66	52.16	62.91 [a]	56.77	49.06	52.91 [a]

[a] Mean of the means.

surfactant was always stronger than the interaction of microcrystalline cellulose with these adjuvants.

Although the adjuvant present at the highest concentration in the formulations was the filler, the most important factor for dissolution of HCT was the lubricant. The presence of surfactant was decisive when the lubricant had hydrophobic properties.

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