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IN VITRO RELEASE OF HYDROCHLOROTHIAZIDE FROM CAPSULE FORMULATIONS

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ABSTRACT

Five different hydrochlorothiazide (50mg. per capsule) capsule formulations were prepared with one of the following diluents: corn starch, dibasic calcium phosphate, lactose, microcrystalline cellulose, or sodium carboxymethyl starch. A comparative dissolution study was conducted using the USP procedure. Significant differences ($p=0.05$) were found among the formulations relative to *in vitro* dissolution rates over a two-hour sampling period. The formulations prepared with lactose consistently ranked near the top (Newman-Keuls multiple range test) while the formulation prepared with sodium carboxymethyl starch ranked last at each sampling time except 3 min.

INTRODUCTION

Hydrochlorothiazide is an important diuretic and antihypertensive drug which is available only in tablets. It is also among those drugs designated by the Food and Drug Administration as potential bioavailability problems (1).

Since 1965 many different dissolution methods have been developed which characterize *in vitro* drug release from solid dosage forms. While these methods cannot always predict *in vivo* availability, the rate at which drugs are released from solid dosage forms is often the rate-limiting factor controlling bioavailability.

Generally, hard gelatin capsule formulations exhibit faster *in vivo* availability as compared to tablets (2). Several reports have evaluated the effect of formulation additives on drug dissolution from capsules (3-5). Diluent effect on hydrochlorothiazide dissolution from capsules has not been reported.

The purposes of this investigation were to develop hydrochlorothiazide capsule dosage forms using various diluents and to compare their dissolution characteristics. Comparison of drug dissolution from capsule formulations may elucidate the performance *in vivo*.

EXPERIMENTAL

Materials - Hydrochlorothiazide powder was used as supplied.[1] Sodium carboxymethyl starch[2], lactose USP,[3] corn starch USP,[3] dibasic calcium phosphate[3], and microcrystalline cellulose[4] were used as purchased.

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1. MSD, Division of Merck and Co., West Point, Pa.
2. Explotab, Edward Mendell Co., Inc., Carmel, N.Y.
3. Fisher Chemicals, Fairlawn, N.J.
4. Avicel PH101, FMC Corp., Philadelphia

Capsule Formulations - Five formulations were developed for this investigation. Each formulation (A-E) was filled into size 4 hard gelatin capsule shells. Formula A contained 50 mg of hydrochlorothiazide and 200 mg of corn starch; Formula B, 50 mg of hydrochlorothiazide and 175 mg of sodium carboxymethyl starch; Formula C, 50 mg of hydrochlorothiazide and 250 mg of dibasic calcium phosphate; Formula D, 50 mg of hydrochlorothiazide and 190 mg of microcrystalline cellulose; and Formula E, 50 mg of hydrochlorothiazide and 200 mg of lactose. To obtain the appropriate capsule fill-weights different amounts of the various diluents were required.

Weight Variation - The USP XIX hard gelatin capsule weight variation test (7) was performed on all five formulations using an analytical balance[5].

Content Uniformity - The USP XIX drug content uniformity test for hydrochlorothiazide tablets (8) was performed on each formulation using a spectophotometer[6] at 273 nm with 1-cm cells. A USP hydrochlorothiazide reference standard was used to prepare standard solutions.

In Vitro Studies - All dissolution studies[7] were carried out

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5. Type 2472, Sartorium balance, Division of Brinkmann Instrument Inc., Westbury, N.Y. 11590
6. Cary Model 219, Varian Associates, Instrument Division, Palo Alto, CA 94303
7. Dissolution test unit, Model 72 RL, Hansen Research Corporation, Northridge, Ca., 91324

at 37 $\pm$ 0.5° in 500 ml of 0.1 N HCl using the USP procedure (6). At various time intervals, 1.0 ml samples were pipetted through a glass wool plug and an equal amount of 0.1 N HCl was added to the dissolution medium to maintain constant volume. The rotational speed was 50 rpm. An electronically controlled stirring motor was used in each experiment. Hydrochlorothiazide concentration was determined at 273 nm against a blank of 0.1 N HCl.

RESULTS AND DISCUSSION

All five hydrochlorothiazide capsule formulations confirmed the USP requirements for weight variation and content uniformity.

The mean cumulative amounts (mg) dissolved at different times are given in Table I and illustrated in Figure 1. A two-way classification analysis of variance (9) was used to compare hydrochlorothiazide release at each sampling time. The calculated F value of 33.66 was significantly higher than the tabular $F_{0.95}$ value, suggesting that there are significant differences ($p=0.05$) among the formulations over all time intervals. To clarify these differences, a one-way analysis of variance at each sampling time was used to determine the times at which significant differences occurred. Except at 3 and 6 min, the calculated F value exceeded the tabular $F_{0.95}$ value of 2.87 which indicates significant differences in dissolution between the formulations at all other sampling times.

A Newman-Keuls multiple range test (10) was performed to determine the relative rank of the formulations with regard to dissolution. Ranking is shown in Table II. The formulation (E) prepared with lactose consistently ranked near the top at each time while

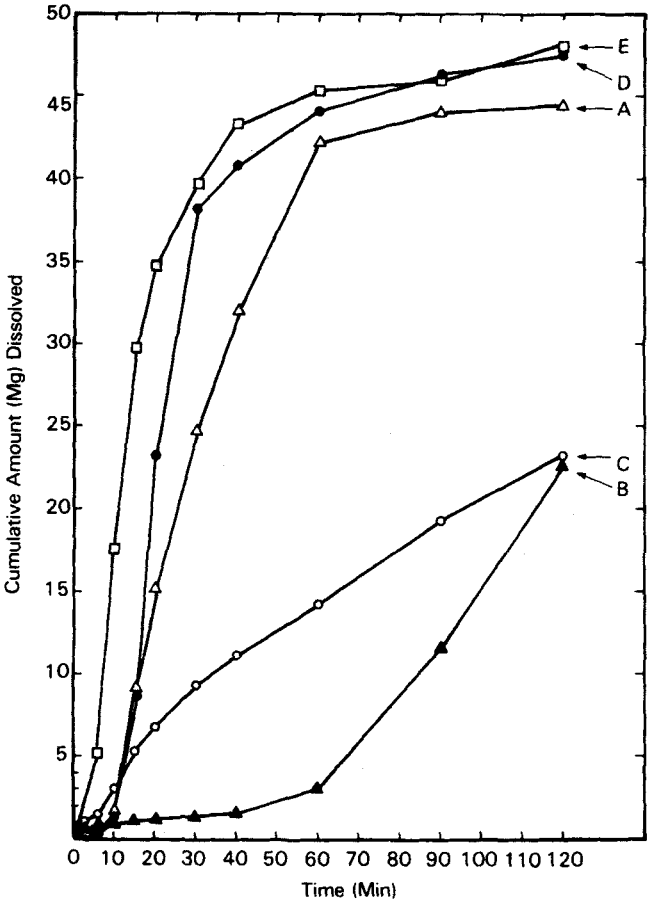

Figure 1- Effect of diluents on the dissolution rate of hydrochlorothiazide *from capsule formulations* in 0.1N HCL. KEY: A, corn starch as diluent (△) B, sodium carboxymethly starch as diluent (▲) C, dibasic calcium phosphate as diluent (○) D, microcrystalline cellulose as diluent (●) E, lactose as diluent (□).

the formulation prepared with sodium carboxymethyl starch (B) ranked last at each time except 3 min. Formulations prepared with microcrystalline cellulose (D), corn starch (A), and dibasic calcium phosphate (C) ranked second, third and fourth respectively for all sampling times beginning at the 20 min data.

TABLE I - Cumulative Amount of Hydrochlorothiazide Dissolved at Various Times[a] from Five Capsule Formulations

	Capsule Formulations[b]				
Time(min.)	A(mg.)	B(mg.)	C(mg.)	D(mg.)	E(mg.)
3	0.33(0.19)	0.46(0.01)	0.81(0.40)	0.31(0.30)	0.44(0.29)
6	0.77(0.10)	0.67(0.05)	1.59(1.31)	0.67(0.13)	5.40(6.54)
10	1.90(1.36)	0.93(0.08)	3.01(1.49)	1.51(1.25)	17.76(6.97)
15	9.23(1.45)	1.06(0.13)	5.22(1.23)	8.95(4.83)	29.61(3.75)
20	15.71(1.20)	1.20(0.10)	6.90(1.23)	23.16(3.63)	34.98(4.14)
30	24.82(1.28)	1.45(0.08)	9.32(1.05)	38.12(3.34)	39.83(1.15)
40	32.11(1.56)	1.66(0.09)	11.05(0.94)	40.84(0.80)	43.09(1.80)
60	42.57(1.40)	3.25(0.40)	14.42(0.81)	44.81(0.50)	45.36(0.88)
90	44.10(0.47)	11.67(0.65)	19.21(0.77)	46.34(0.17)	46.26(0.28)
120	44.67(0.48)	22.69(0.52)	22.86(1.38)	47.58(1.38)	47.64(0.24)

[a]Each value represents an average of five determinations. Standard deviation in parenthesis.

[b]Diluents: A, corn starch; B, sodium carboxymehtyl starch; C,dibasic calcium phosphate; D, microcrystalline cellulose; E,lactose.

TABLE II - Newman - Keuls Multiple Range Test Ranking (from highest to lowest) of Cumulative Dissolution Data at Various Times from Five Hydrochlorothiazide Capsule Formulations.

Sampling Times (min.)	Formulation[b] Ranking (highest to lowest)
3	C B E A D [a]
6	E C A D B
10	E C A D B
15	E A D C B
20	E D A C B
30	E D A C B
40	E D A C B
60	E D A C B
90	E D A C B
120	E D A C B

[a]Products underlined indicate statistical similarity.

[b]Diluents: A, corn starch,; B, sodium carboxymehtyl starch; C, dibasic calcium phosphate; D, microcrystalline cellulose; E, lactose.

The excellent dissolution of hydrochlorothiazide from the lactose formulation is attributable to the hydrophilic nature of lactose which rapidly disperses hydrophobic drug particles and increases the permeation rate of the dissolution medium (11). Microcrystalline cellulose has a fast wicking rate for water (12) and thus readily draws dissolution medium into the capsule mass. This effect explains its high ranking as shown in Table II.

Starch also ranks favorably with lactose and microcrystalline cellulose, however it produces a somewhat slower dissolution rate. Starch granules are known to swell in dissolution medium, therefore in capsule formulation it apparently forms a viscous matrix which slows hydrochlorothiazide dissolution. Dibasic calcium phosphate is a hydrophobic diluent and, as expected, prevents rapid dispersion of drug particles and subsequent dissolution.

The formulation containing sodium carboxymehtyl starch produced the slowest hydrochlorothiazide dissolution rate. Sodium carboxymethyl starch concentrations above 8% in tablet formulations increase disintegration times, possibly due to viscosity-producing effects (13). Apparently sodium carboxymethyl starch forms a viscous, gelatinous mass which entraps hydrochlorothiazide particles and slows dissolution.

This investigation shows the dramatic effect capsule diluents can have on the dissolution of a hydrophobic drug.

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