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IN VITRO AND INVIVO EVALUATION OF SOME FAST RELEASE DOSAGE FORMS OF HYDROCHLOROTHIAZIDE

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ABSTRACT

The utilization of ternary sugar solid dispersion and solvent deposition systems for increasing the dissolution rate of hydrochlorothiazide (hct) were investigated. The dispersion systems were prepared by the fusion method using various combinations of mannitol and sorbitol, and urea and polyethylene glycol 4000 (peg 4000) were used for comparison. An 1:2 mixture of sorbitol-mannitol was found to be an excellent carrier. The dissolution rate of this sample was closely comparable to that of hct-peg 4000 solid dispersions. Drug-urea eutectic mixtures were inferior to both the sugar and polymer dispersions. Solvent deposition systems of hct with microfine cellulose and potato starch gave higher dissolution rates at the initial sampling times. It is proposed that solid dispersion systems of this drug may prove to be valuable. Tablets fabricated from fast-release hct granules showed better in vivo results than a

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marketed tablet. A linear relationship was observed between in vitro-in vivo data of some of the products.

INTRODUCTION

Hydrochlorothiazide, an important diuretic, has a potential for poor gastro-intestinal absorption due to its limited aqueous solubility. The United States Food and Drugs Administration has recognised its potential for erratic bioavailability (1). A dissolution requirement appears in the U.S.P. - National Formulary (2). Although bioavailability problems have not been definitely documented for this drug, such a probability is indicated by Hossie et al (3). On the premise that hct dissolution in the gastro-intestinal tract controls its absorption, faster dissolution of hct tablets were obtained by controlling formulation factors (4,5). Increased dissolution rates from hct-PVP 11,500 and hct-peg 6000 are also reported (6). Similar results are reported by Monkhouse and Lach (7), who used hct solvent deposited on fumed silica. Recently Deshpande and Agrawal (8,9) have reported better dissolution from solid dispersions of hct using peg 6000, tartaric acid, sorbitol and urea (both solid dispersion and eutectic mixtures). However, the t50% and t75% values reported by them is much higher than required by U.S.P.-N.F. standards. The results of the present investigation could not be reported earlier due to statutory requirements. We now report the results of our investigation on a 1:2 mixture of sorbitol-mannitol and pure mannitol for preparing hct-carrier solid dispersions, and microfine cellulose and potato starch for preparation of solvent deposited systems. No report on the biopharmaceutical aspects of the fast

release dosage forms of hct are available. This prompted us to study the in vivo performance of these preparations in comparison to a marketed tablet from urinary excretion of hct from tablets fabricated from the fast-release granules.

MATERIALS

Hydrochlorothiazide, urea, mannitol, sorbitol, polyethylene glycol 4000, potato starch, microfine cellulose (Elcema P100, Degussa), fumed silica (Cab-O-Sil M-5, Cabot) and all other chemicals were obtained commercially and were of either U.S.P. or analytical reagent grade.

METHODS

Solid dispersions of hct in different carriers were prepared at 1:9 and 1:19 drug-carrier levels by a method already described (10). In all cases except peg 4000 the congealed material was pulverized in a mortar and classified to obtain free-flowing, granular material of size 210-250 μm. The solidified hct-peg 4000 melt was triturated in a cold mortar (cooled by surrounding with broken ice) to obtain material of the previously described size range. All samples were transferred to amber bottles, capped loosely and stored in a vacuum desiccator. Solvent depositions of hct-potato starch and microfine cellulose were prepared by a standard method (11), using acetone as solvent. The samples were made free from solvent vapour, passed through 60 mesh sieve, and stored as before. The preparation and characterization of hct-urea eutectic mixtures were done according to the method described by Goldberg et al (12). A phase diagram of eutectic type was obtained by the

thaw-melt method (13). All samples thus obtained were subjected to a thin layer chromatographic procedure (14) for detecting possible drug decomposition during sample preparation. It was observed that some of the fast-release dosage forms could be compressed directly into tablets. The required quantity of the granules were mixed with potato starch 5%, magnesium stearate 1% and fumed silica 0.1%, and compressed to contain 25 mg of hct in each tablet on a Manesty E2 machine, using a 9/32" or 3/16" die-punch set. The dissolution rates of the fast-release dosage forms and the tablets prepared from them were determined in 1:100 HCl, using the beaker method of Levy and Hayes (15) with slight modification. For studying the solubilizing action of urea, the dissolution of plain hct powder was tested in 1:100 HCl containing various concentrations of urea. Also, physical mixtures of hct and urea in eutectic proportions were prepared and the dissolution rates determined as before. All samples were assayed for hct content spectrophotometrically by a pharmacopoeial method (16).

For the in vivo studies five healthy, adult male volunteers within the age group 23-25 years and weighing 52-63 kgs were dosed, at least two weeks apart, with 25 mg of hct as a) Esidrex tablet (Hindustan Ciba-Geigy), b) 200 ml aqueous solution, c) hct-sorbitol 1:9 solid dispersion tablet, d) hct-mannitol 1:9 solid dispersion tablet, e) hct-urea eutectic mixture tablet, and f) hct- peg 4000 solid dispersion, filled in capsule, in a completely randomized design. No other drugs were taken by the volunteers in the preceding week or during the test. The

volunteers were not in the habit of consuming any intoxicant. All experiments were begun at 8 a.m., when the subjects took the preparation on empty stomach. Tablets or capsules were consumed with 200 ml of tap water, and the solution was drunk as such. Urine samples were collected at 0, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-administration. The volunteers consumed 200 ml of water after each voiding to maintain adequate urine output. No other food or liquid was allowed until 6 hours after dosing, when a standard non-fat, low protein lunch (prepared by the Institute of Technology cafeteria) was eaten by the subjects. The subjects mainly sat or stood during the experiments. Urine samples were analyzed for intact hct by the method of Rehm and Smith (17). Pharmacokinetic parameters were calculated using conventional equations (18, 19).

RESULTS & DISCUSSION

Dissolution rates of hct from its solid dispersions are given in table 1 as the time taken for different percentages of the drug to dissolve. The dissolution rates of hct-peg 4000 dispersions obtained in our experiments are much higher than those reported by Deshpande and Agrawal (8,9), and are closer to those reported by Hoelgaard and Moller (6). From our experiments it seems that the faster dissolution is due to release of hct from the carrier in a minuscular form, with consequent fast dissolution. This assumption is strengthened by the slower dissolution rate of the dispersion containing a higher proportion of the polymer, which is due to two factors : a) the polymer has little solubilizing action on hct, and b) at higher polymer concentration the carrier leach-

TABLE 1

Dissolution Rate of hct from peg 4000 and Sugar Solid Dispersions.

Sample	$t_{25\%}$	$t_{50\%}$	$t_{75\%}$(min)
hct	3.0	10.0	21.5
hct-peg 4000(1:9)	0.5	1.0	2.0
" (1:19)	2.0	3.0	4.0
hct-mannitol(1:9)	0.5	1.0	2.0
" (1:19)	0.75	1.5	5.0
hct-sorbitol(1:9)	2.0	3.5	6.5
" (1:19)	1.0	3.0	6.0
hct-sorbitol-mannitol(1:9) (1 - 2)	1.0	1.5	3.5
" (1:19)	1.0	1.5	16.0

All values are mean of at least 3 readings.

es out during dissolution and forms a concentrated layer of solution around the drug particles, which may either be free or embedded in the carrier; the migration of the released hct particles to the bulk of the dissolution medium is slowed down, and the fall in dissolution rate is due to a viscosity effect. The dissolution rate of hct from solid dispersions containing sorbitol and mannitol or 1:2 mixture of these two are comparable, but mannitol, on overall assessment, gives better results. Sorbitol-hct dispersions were hygroscopic and unsuitable for routine investigations. Plain hct-mannitol dispersions were preferable for tabletting also. It was observed that

hct is only partially miscible with sorbitol and sorbitol-mannitol mixture, but miscible with mannitol in the molten state. Thus hct seems to form either glass dispersions or partial solid solution with these sugars, which explains their fast dissolution.

The sugar solid dispersions demonstrated a fast initial release, followed by a much slower prolonged release. The initial phase is attributed to the release of hct in a minuscular form; there is a probability of the drug being solubilized during preparation by the molten carrier. No wetting of the drug, either by the polymer or the sugar carriers, seems to have contributed to the higher dissolution rates, as hct dissolution is reported to be minimally affected by a surfactant (20), and is not hydrophobic (10).

The effect of urea on hct dissolution is shown in table 2 and figure 1. The increase in dissolution rate is seen to be independent of urea concentration ($p > 0.05$), there being only a small increase in the dissolution rate due to the addition of urea, and an optimal concentration of urea appears to be effective as a solubilizer (figure 2). It was observed that drug urea eutectics of 9:1, 8:2, 7:3,and 6:4 ratios have significantly lower dissolution rates than other samples and the control. In fact the $t_{75\%}$ could not be obtained within 60 minutes for the former group of samples, and also for 1:9 and 1:19 hct-urea solid dispersions. The solid dispersions had very fast initial dissolution rates, and we obtained very small $t_{50\%}$ values than reported (9).

TABLE 2

Dissolution Rates of hct from Solid Dispersion, Eutectic Mixtures and Physical Mixtures with Urea, and in Urea Solutions.

Sample	t25%		t50%		t75%(min)	
Solid dispersion,						
1:9	1.0		2.0		- *	
1:19	1.0		2.0		-	
Urea Solution,						
5%	1.5		6.0		15.0	
10%	1.5		3.5		8.75	
15%	1.5		4.0		8.0	
20%	1.5		5.75		12.5	
hct:urea	a	b	a	b	a	b
9:1	4.0	4.3	18.0	50.0	-	-
8:2	12.0	15.0	31.0	40.0	-	-
7:3	1.3	6.3	30.0	15.6	-	44.0
6:4	1.6	2.0	9.3	13.0	-	19.0
5:5	1.0	2.3	3.3	6.0	17.0	-
4:6	0.75	1.3	2.0	4.3	12.3	20.0
3:7	0.75	1.0	2.0	2.0	7.3	10.0
2:8	0.75	1.0	2.0	2.0	7.3	8.6
1:9	0.75	0.6	2.0	1.6	7.3	3.6

All values are the average of at least three observations. *, - indicates that the t75% values were not attained within 60 minutes.
a = Physical mixture; b = Eutectic mixture.

This discrepancy could not be explained satisfactorily, due to the reason that the eutectic composition is not mentioned in that report. We had obtained an eutectic composition of 30% by weight of hct and 70% by weight of urea. In the light of an earlier publi-

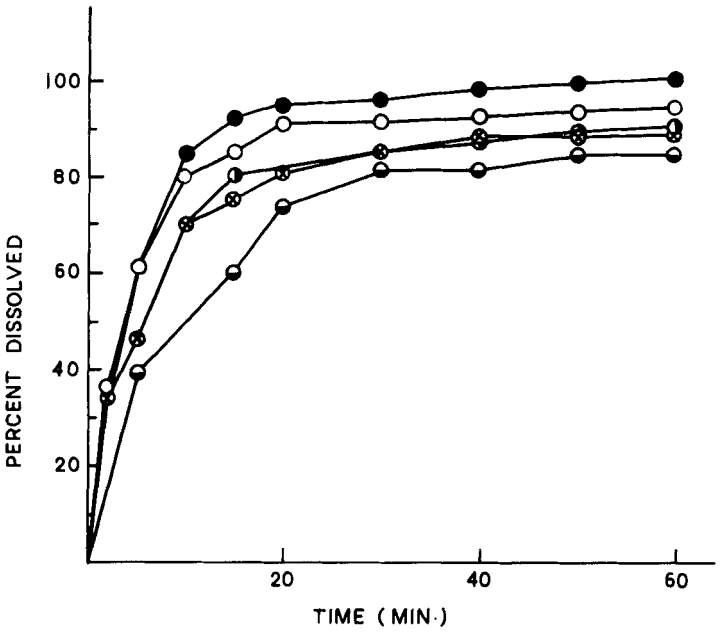

FIG. 1

DISSOLUTION PROFILES OF HYDROCHLOROTHIAZIDE POWDER IN DIFFERENT CONCENTRATION OF UREA IN 1:100 HCl.

⊖- 0% (CONTROL), ⊗- 5% UREA, ○- 10% UREA, ●- 15% UREA, ◑- 20% UREA

cation (21) it seems probable that by increasing the concentration of urea the water bound to hydronium ions would be removed, and this will increase the amount of water available for dissolution of the drug. There is a limit to this interaction, hence the dissolution rate levels off after some time. The addition of the eutectic mixture or the solid solution (10% hct - 90% urea) to water resulted in a quick dispersal of the material, and the microcrystalline hct so released remained in suspension for a long time. These particles were measured microscopically and found to be between 0.5-2 μ, whereas the commercial drug had a size range of 75-87 μ (90% of the

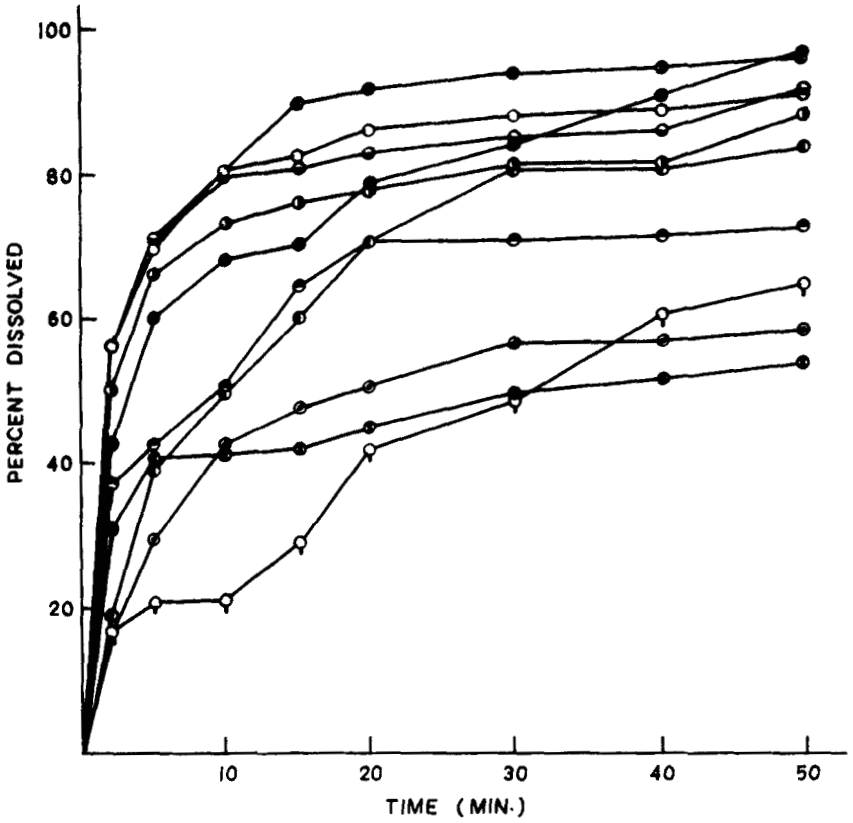

FIG. 2

DISSOLUTION RATE PROFILE OF PHYSICAL MIXTURE OF HYDROCHLOROTHIAZIDE AND UREA.

	●	⊗	◒	○	◑	◐	◓	⚲	◉	◭
DRUG	5	3	1	2	4	10	7	8	9	6
UREA	5	7	9	8	6	0	3	2	1	4

particles); this suggests that the faster dissolution is due mainly to a reduction in particle size to the submicron level, and, to a lesser degree, to the solubilizing effect of urea. The slower dissolution from eutectics prepared with lower proportions of urea may also be due to the hardening effect brought about by heat treatment during sample preparation, or the occ-

TABLE 3

Dissolution Rates of hct Solvent Deposited on Potato Starch and Microfine Cellulose.

Sample	t25%	t50%	t75%(min)
hct-potato starch			
1:9	1.5	3.75	40.0
1:19	1.0	4.0	13.0
1:32	1.25	2.75	13.5
1:49	1.25	2.0	15.0
1:99	1.0	2.0	11.5
hct-microfine cellulose			
1:9	1.0	3.0	-*
1:19	1.25	2.0	9.0
1:99	1.0	1.5	4.0

All values are average of three observations.
* level not reached in 60 minutes.

urence in some cases of supersaturation of urea during cooling process by which effective size reduction will be hindered.

Table 3 lists the dissolution rates of hct solvent deposited on finely subdivided carriers. It is observed that in all cases the dissolution rate is largely affected by the proportion of the carrier. The dissolution rate was quite fast upto the first 20-30 minutes, then either levelled off, or started decreasing. This may possible be due to drug-carrier interaction. The comparatively large time taken to

TABLE 4

Urinary Excretion and pharmacokinetic data* of hct after oral administration of different dosage forms to human volunteers.

Product	Cumulative mg excreted in 24 hr	Cumulative % of dose excreted	Peak excretion (% dose/hr)	Peak excretion rate (mg/hr)	Tmax (hr)	$t_{\frac{1}{2}}$ (hr)	Kel (hr^{-1})	R.B.**%
C	15.21 ±2.10	64.82 ±8.42	15.21 ±1.91	3.80 ±0.48	2.0 ±0.0	3.72 ±0.69	0.190 ±0.033	Control
S	15.01 ±0.91	60.02 ±3.62	13.11 ±2.11	3.27 ±0.54	3.0 ±0.0	5.25 ±0.75	0.134 ±0.099	90.36 ±10.52
M	14.52 ±0.55	59.49 ±2.25	11.01 ±0.94	2.81 ±0.23	3.0 ±0.0	5.27 ±0.69	0.133 ±0.016	90.84 ±14.61
P	16.11 ±1.28	64.45 ±5.14	11.73 ±1.29	2.93 ±0.32	3.33 ±1.15	4.91 ±0.40	0.142 ±0.011	100.86 ± 7.42
U	15.62 ±2.35	62.48 ±9.40	14.01 ±2.91	3.50 ±0.72	3.0 ±0.0	4.70 ±0.83	0.150 ±0.030	96.60 ±10.67
E	13.61 ±0.73	54.45 ±2.92	9.05 ±2.16	2.26 ±0.54	4.33 ±1.53	5.57 ±0.38	0.125 ±0.101	84.59 ± 7.31

*Mean ± S.D.(n=5), **Relative Bioavailability.

TABLE 5

Significance of Difference in the Cumulative Amount of hct Excreted at Different Sampling Times.

Hour	Product					
	C	M	P	S	E	U
1	-	NS	NS	NS	NS	NS
2	-	S*	S*	NS	S*	S*
3	-	S*@	S*	S@	S*	S*
4	-	NS	NS	NS	S*	NS
5	-	NS	NS	NS	S*	NS
6	-	NS	NS	NS	S*	NS

C=Control Solution; M=Drug-mannitol solid dispersion tab.; P=Drug-peg 4000 solid dispersion capsule; S=Drug-sorbitol solid dispersion tab.; E=Commercial tab. (Esidrex); U=Drug-urea eutectic mixture tab. S=Significant difference ($p < 0.05$); NS=No significant difference ($p > 0.05$); *=Significantly lower than control; @=Significantly higher than E.

attain t75% values for potato starch could be explained satisfactorily on the basis of adsorption playing an important role : the outermost layer of the deposited hct crystals dissolve out rapidly, leaving behind a layer of crystals weekly bound to the carrier, hence the larger t75% values.

The total urinary recovery of hct and other pertinent data are listed in table 4. The mean cumulative percent of hct excreted in 24 hours varied from 54.5% to 64.5% of the administered dose. This is in close approximity to the value reported (22). Statistical analysis (Student's paired t-test) of the data

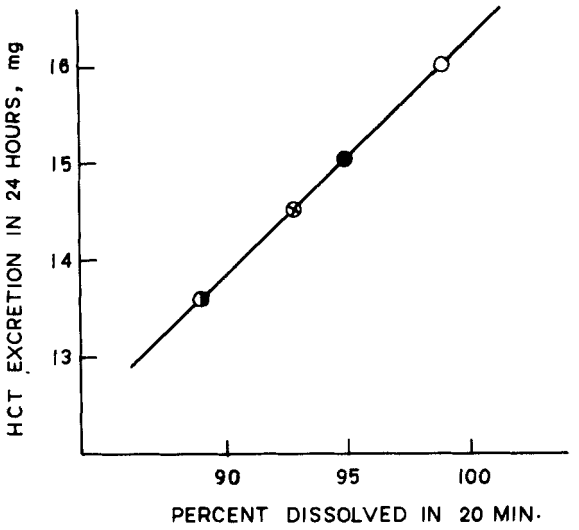

FIG. 3

CORRELATION BETWEEN DISSOLUTION RATE AND TOTAL HYDROCHLOROTHIAZIDE EXCRETION IN 24 HOURS

○ - DISPERSED, HCT-PEG 4000
● - DISPERSED, HCT-SORBITOL
⊗ - DISPERSED, HCT-MANNITOL
◑ - COMMERCIAL TABLET (ESIDREX)

indicated no significant difference ($p > 0.05$) between any of the six preparations tested. Statistical analysis of the cumulative per cent of hct excreted between 1-6 hours are shown in table 5 : it is observed that the cumulative amount of hct excreted from the commercial tablet was significantly lower than the drug solution, drug-sorbitol and drug-sorbitol-mannitol tablets. The total urine voided by the subjects in 24 hours did not differ significantly ($p > 0.05$). Large inter-subject variations were observed in the time for maximum excretion following the administration of the commercial tablet. The eutectic

composition in tablet form showed a relatively low in vitro dissolution rate, but its bioavailability was not lower than the control solution. A linear correlation between the cumulative hct excreted in 24 hours and dissolution at 20 minutes is observed for some of the preparations, and is shown in figure 3.

The present study brings out the usefulness of some fast-release preparations of hct in augmenting its therapeutic efficacy. Moreover, the suggestion of Beerman et al (22) that urinary recovery studies are preferable for assessing the performance of hct preparations is supported by the in vitro-in vivo correlation obtained in our studies.

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