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BIOAVAILABILITY OF HYDROCHLOROTHIAZIDE SUSPENSION

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ABSTRACT

Flocculated and deflocculated suspensions of hydrochlorothiazide stabilized with certain natural stabilizers, some earthy silicates and one member of carbomers were submitted for dissolution studies in simulated gastric juice. Also, the flow rate, PH, sodium and potassium content of urine of five human volunteers administering the drug suspensions were determined as well. The correlation between the dissolution rate and the pharmacologic response of the drug suspensions was declared.

INTRODUCTION

The aqueous suspension as a drug delivery system (1), is second in efficacy only to the solution dosage form. Usually the

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absorption rate of a drug from a suspension is dissolution rate limited. However, a large surface area is presented to the fluids at the absorption site and dissolution may be rapid. Drug contained in a capsule or a tablet may never achieve that state of dispersion in the gastro-intestinal tract that is attainable with a finely subdivided, well formulated suspension. Several studies have demonstrated the superior bioavailability characteristics of suspensions compared to those of solid forms.

Among the more critical factors to consider in formulating suspension dosage forms for maximal bioavailability are particle size, inclusion of wetting agents, formation of insoluble complexes, crystal form and viscosity (2). When a drug is given orally in form of a tablet, capsule or a suspension (3), the rate of absorption is often controlled by how fast the drug dissolves in the fluids at the absorption site. In other words, dissolution rate is often the rate limiting (slowest) step in the sequence:

solid drug dissolution $\longrightarrow$ Drug in solution at absorption site $\longrightarrow$ Drug in systemic circulation.

When dissolution is the controlling step in the overall process, absorption is said to be dissolution rate limited. Since dissolution preceeds absorption, any factor affecting the rate of solution also must affect the rate of absorption. Consequently, dissolution rate may affect the onset, intensity and duration of clinical response.

Hydrochlorothiazide is an inhibitor of the renal tubular reabsorption of sodium. In appropriate doses it causes only a slight increase in chlorine excretion. In low doses, bicarbonate excretion is increased as a result of mild carbonic anhydrase inhibitory action, but this effect is not responsible for the major excretion of sodium and chlorine (4). Hydrochlorothiazide is useful in cardiac oedema as well as oedematous conditions.

The aim of the present work is to investigate the influence of different suspension stabilizers and additives on dissolution and bioavailability of hydrochlorothiazide suspension.

EXPERIMENTAL

Hydrochlorothiazide powder (Bonapace, Melano, Italy), Propylene glycol (Riedel-De Haenag Seelze, Hannover, Germany), Veegum HV (R.T. Vanderbilts Company, Inc. Specialties, U.S.A.), Hydrophilic Aerosil (DeGussa, U.S.A.), Carbopol 934 (Good Rich Chem. Co., U.S.A.), Concentrated hydrochloric acid (PROLABO), Paris, Sodium hydroxide (LAB. Chemical Co. Ltd., Cairo, Egypt), Pure grades of potassium dihydrogen phosphate, and Bentonite; Mechanical stirrer, Spectrophotometer Sp. 600 (Unicam, England), Flame photometer (type carning EEL, England), PH meter (WTW, type D812 LF 39, West Germany).

Methodology:

Preparation of Hydrochlorothiazide Suspension:

Hydrochlorothiazide powder (250 mg of 50 μ average particle

size) was levigated with a suitable volume of propylene glycol equivalent to 30 percent of the total volume of the drug suspension as a wetting agent. Then, the chosen stabilizer was added either in solid form or as magma followed by the flocculating agent (reached in a previous investigation (5) if any in a mortar with thorough trituration.

Each suspension was diluted with distilled water, transferred to 25 ml glass stoppered measuring cylinder, completed to volume with water. The deflocculated suspension under test are Carbopol 934, agar agar stabilized suspensions and the plain deflocculated one. The flocculated suspension under test are Veegum HV, Carbopol 934, Aerosil, Bentonite stabilized and the plain flocculated systems. These suspensions were examined for:

1. Rate of Dissolution

This was done adopting the following technique (6): In a beaker of 1000 ml capacity, 600 ml of 0.1N hydrochloric acid (PH 1.2) were placed and maintained at 37°C. Then, 25 ml of the suspension under test was added where constant torque stirrer was dipped near the bottom of the container. Samples of the dissolution medium were taken at different time intervals with a pipette whose orifice contained a screen of very fine mesh fabric and replenished with a similar portion of 0.1 N HCL. Then the samples were filtered and the filtrate was neutralized with 1.0 N sodium hydroxide, then rendered alkaline with 0.1 N of sodium hydroxide and measured spectrophotometrically at 273 nm. ($E^{1\%}$1cm of hydroclorothiazide at 723 nm. = 507) (7).

Finally, the percentage of dissolution and $t_{60\%}$ were calculated.

2. Bioavailability of Hydrochlorothiazide Suspension:

This was determined in terms of urine flow rates resulted from the administration of the suspensions under test by human volunteers in comparison with the plain drug. In this technique (8), five healthy, middle aged subjects were chosen for the purpose where they received controlled diet without any factor causing diuresis. A blank experiment was carried out for these five subjects for their urine flow rate, PH, sodium and potassium content of urine.

This was achieved by giving every volunteer 240 ml water and collecting the total combined urine for all subjects after the first hour for the determination of the aforementioned parameters to be considered as a blank. Then, the drug either as a powder or as a suspension was given together with another 240 ml of water and collecting the urine after every half an hour and up to three hours intermitted with the drinking of 240 ml water every one hour. The increase in urine volume, rate of increase of urine, PH, sodium and potassium content of urine (determined as milli-Eq./litre) were estimated.

RESULTS AND DISCUSSION

1. Rate of Dissolution of Hydrochlorothiazide:

A. Table 1 and Table 2 compile the data for the dissolved amount of hydrochlorothiazide (mg/600 ml) in 0.1 N HCL

Table I: Dissolution Rate Profile of Deflocculated Hydrochlorothiazide Suspension at pH 1.2 (Initial = 10 mg/ml).

STABILIZER	CONC. (% W/V)	SAMPLING TIME (MIN.)	DISSOLVED AMOUNT OF DRUG (MG/600 ML)	PERCENTAGE OF DISSOLUTION (W/V)	PREDICTED $t_{60\%}$ (MIN.)
Nil (Plain deflocculated)	-	30	136.3	54.5	57
		60	158.0	63.2	
		90	165.5	66.2	
		120	180.0	72.0	
		150	196.1	78.4	
		180	208.3	83.3	
Agar agar	0.5	30	131.5	52.6	59
		60	153.8	61.5	
		90	171.5	68.6	
		120	190.1	76.0	
		150	203.5	81.4	
		180	219.3	87.7	
Carbopol 934	0.2	30	146.0	58.4	40
		60	165.4	66.2	
		90	180.3	72.1	
		120	194.8	77.9	
		150	210.8	84.3	
		180	222.0	88.8	

Table 2: Dissolution Rate Profile of Flocculated Hydrochlorothiazide Suspension at pH 1.2. (Initial = 10 mg/ml).

STABILIZER	CONC. (% W/V)	SAMPLING TIME (MIN.)	DISSOLVED AMOUNT OF DRUG (MG/600 ML)	PERCENTAGE OF DISSOLUTION (W/V)	PREDICTED $t_{60\%}$ (MIN.)
Nil (Plain flocculated	-	30	155.1	62.0	17
		60	182.5	73.0	
		90	186.4	74.6	
		120	205.1	82.0	
		150	221.3	84.5	
		180	231.5	92.4	
Veegum H.V. 2.0	2.0	30	152.0	60.8	23
		60	178.2	71.3	
		90	180.4	72.2	
		120	187.9	75.2	
		150	198.7	79.5	
		180	211.3	89.5	
Aerosil	4.0	30	154.0	61.6	17
		60	168.1	67.2	
		90	186.4	74.6	
		120	198.8	79.6	
		150	209.1	83.6	
		180	221.7	88.7	
Bentonite	4.0	30	147.1	58.8	35
		60	157.5	63.3	
		90	178.0	71.2	
		120	186.4	74.6	
		150	198.5	79.4	
		180	208.1	83.2	
Carbopol 934	0.4	30	153.0	61.2	23
		60	174.2	69.7	
		90	192.5	77.0	
		120	205.0	82.0	
		150	219.7	87.9	
		180	234.4	93.7	

and its percentage of dissolution after 30, 60, 90, 120, 150 and 180 minutes. The $t_{60\%}$ for the medicament is predicted from the obtained data since the specifications in U.S.P. (9) states that "not less than 60 percent of the labelled amount of the drug in tablets dissolves in 30 minutes". The obtained data were corrected according to Bates et. al. equation (10).

B. It is evident from Table 1 that, the chosen suspensions under test can be arranged in an ascending order as regards their predicted $t_{60\%}$ as follows: Carbopol 934, plain deflocculated and agar agar stabilized suspensions.

C. The shortest $t_{60\%}$ reached with the deflocculated suspension stabilized with 0.2 percent of carbopol 934 is 40 minutes where as the longest one, 59 minutes, is displayed with the drug suspension stabilized with 0.5 percent of agar agar. Furthermore, the maximum percentage of drug dissolution, 58.4 percent, recorded after 30 minutes is shown by the deflocculated drug suspension stabilized with 0.2 percent of carbopol 934 while the least percentage of dissolution, 52.6 percent, is evidenced with that suspension stabilized with 0.5 percent agar agar.

D. Table 2 declares that the flocculated drug suspensions (except Bentonite stabilized one) exhibit more than 60 percent drug dissolution after the first 30 minutes and hence, comply with the pharmacopoeial limit.

E. Only, the suspension stabilized with 4 percent of Bentonite deviates from pharmacopoeial limits as its $t_{60\%}$

is 35 minutes. On the other hand, the other tested flocculated systems show shorter dissolution time for 60 percent dissolution than that specified.

F. The higher extent of dissolution of the drug formulated in flocculated suspension and stabilized with 0.4 percent of carbopol 934 than the deflocculated one using the same stabilizer could be attributed to the better scattering of the drug floccules on stirring in the dissolution medium than the peptized particles in the deflocculated system. Also, this scattering effect led to a shorter period of dissolution for attaining 60 percent for the flocculated system than the deflocculated one.

G. The deviation from the pharmacopoeial requirement concerning $t_{60\%}$ shown by the flocculated hydrochlorothiazide suspension might be resorted to adsorption of the drug on Bentonite particles obliterating drug dissolution.

H. The flocculated drug suspension stabilized with 4 percent of Aerosil exhibited $t_{60\%}$ of drug after 17 minutes. This was shorter than the pharmacopoeial requirement and than that reached with other stabilizers. This finding might be attributed to the increase in the surface area of the drug in presence of Aerosil as the latter possesses extensive surface area. This is in agreement with Monkhouse et. al. (12) working on the influence of fumed silicon dioxide on the rate of dissolution of hydrochlorothiazide.

I. The shortest $t_{60\%}$ and the highest percentage of dissolution of the drug formulated as plain flocculated suspension after 30 minutes than other tested systems might be mainly due to the building up of hydrogen bonds between the drug and propylene glycol used as wetter. This hydrogen bond formation was slightly suppressed in presence of the tried suspension stabilizers. This finding is in concordance with that reached by Monkhouse et. al. (13) working on the use of adsorbents in enhancing hydrochlorothiazide dissolution.

2. Bioavailability of Hydrochlorothiazide:

A. It is remarkable from Tables 3 and 4 that the powdered drug given to human volunteers produced a greater extent of increase in urine volume than produced by the intake of flocculated drug suspension, although the reverse was noticed for dissolution data. This is in concordance with the results of Hossie et. al. (14) working on the bioavailability of hydrochlorothiazide tablets, who showed that, the dissolution data do not appear to reflect absorption or bioavailability. Furthermore, the deflocculated suspension stabilized with 0.2 percent of Carbopol 934 exhibited a greater increase in the extent and rate of urine than produced by the flocculated suspension stabilized with the same stabilizer.

B. The lower bioavailability of flocculated drug suspension

Table 3: Influence of Stabilizers on Urine Flow Rate of Deflocculated Hydrochlorothiazide Suspension

STABILIZER	CONC. (% W/V)	TIME (MIN.)	TOTAL VOLUME OF URINE OF 5 VOLUNTEERS (ML)	THE EXTENT OF INCREASE OF URINE VOLUME (ML)	RATE OF INCREASE OF URINE VOLUME (ML/MIN.)	SODIUM CONTENT (M.EQ.)	POTASSIUM CONTENT (M.EQ.)	pH
Nil (Powdered drug only)	-	BLANK	200	-	-	93.6	48.6	5.9
		30	225	25	0.83	99.1	48.6	6.5
		60	300	100	1.66	103.2	50.4	6.7
		90	370	170	1.88	126.0	51.0	6.7
		120	475	275	2.29	144.0	51.0	6.7
		150	625	425	2.83	228.0	52.2	6.7
		180	720	520	2.88	228.0	53.4	6.8
Agar-agar	0.5	BLANK	290	-	-	102.0	54.0	6.3
		30	330	40	1.33	142.5	54.0	6.5
		60	410	120	2.00	152.5	54.9	6.8
		90	440	150	1.66	195.0	56.7	7.0
		120	490	200	1.66	215.0	56.7	7.0
		150	530	240	1.60	215.0	56.9	7.1
		180	575	285	1.58	232.5	59.2	7.2
Carbopol 934	0.2	BLANK	260	-	-	107.5	52.2	6.2
		30	320	60	2.00	130.0	52.2	6.8
		60	400	140	2.33	152.5	53.1	6.9
		90	560	300	3.33	162.5	54.0	7.1
		120	665	405	3.37	175.0	54.9	7.3
		150	800	540	3.60	175.0	56.1	7.8
		180	975	715	3.97	215.0	57.0	7.8

Table 4: Influence of Stabilizers on Urine Flow Rate of Flocculated Hydrochlorothiazide Suspension

STABILIZER	CONC. (% W/V)	TIME (MIN.)	TOTAL VOLUME OF URINE OF 5 VOLUNTEERS (ML)	THE EXTENT OF INCREASE OF URINE VOLUME (ML)	RATE OF INCREASE OF URINE VOLUME (ML/MIN.)	SODIUM CONTENT (M.EQ.)	POTASSIUM CONTENT (M.EQ.)	pH
		Blank	200	-	-	97.5	52.2	6.0
		30	290	90	3.00	112.5	52.3	6.1
Nil		60	395	195	3.25	120.0	54.0	6.25
(Plain		90	510	310	3.44	142.5	54.9	6.3
Flocculated		120	550	350	2.92	175.0	56.7	6.4
suspension)	-	150	590	390	2.60	232.5	56.7	6.4
		180	615	415	2.30	280.0	60.3	6.6
		BLANK	210	-	-	102.5	54.0	6.1
		30	265	55	1.83	130.0	54.0	7.0
		60	360	150	2.50	152.5	55.8	7.1
Veegum H.V.	2.0	90	550	340	3.77	170.0	57.6	7.1
		120	600	390	3.25	185.0	59.4	7.1
		150	660	450	3.00	215.0	60.3	7.12
		180	700	490	2.72	250.0	60.8	7.3
		BLANK	310	-	-	97.5	50.4	6.2
		30	510	200	6.60	97.5	50.4	6.6
		60	680	370	6.16	107.5	51.3	7.1
Aerosil	4.0	90	730	420	4.66	120.0	54.0	7.1
		120	765	455	3.79	125.0	54.9	7.2
		150	860	550	3.66	135.0	54.9	7.5
		180	950	640	3.55	200.0	57.6	7.5

TABLE 4 (COND.)

STABILIZER	CONC. (% W/V)	TIME (MIN.)	TOTAL VOLUME OF URINE OF 5 VOLUNTEERS (ML)	THE EXTENT OF INCREASE OF URINE VOLUME (ML)	RATE OF INCREASE OF URINE VOLUME (ML/MIN.)	SODIUM CONTENT (M.EQ.)	POTASSIUM CONTENT (M.EQ.)	pH
		BLANK	265	-	-	112.5	48.6	6.55
		30	380	115	3.83	142.5	48.6	6.55
		60	500	235	3.91	142.5	49.5	6.60
Bentonite	4.0	90	560	295	3.27	150.0	54.0	6.65
		120	635	370	3.08	157.5	54.9	6.70
		150	680	415	2.76	215.0	54.9	6.70
		180	730	465	2.58	265.0	56.7	6.70
		BLANK	210	-	-	115.0	55.8	6.50
		30	260	50	1.60	162.5	55.8	6.50
		60	340	130	2.10	195.0	55.8	6.70
Carbopol		90	425	215	2.38	215.0	57.6	6.90
934	0.4	120	540	330	2.75	222.5	58.5	7.10
		150	650	440	2.93	250.0	59.4	7.10
		180	710	500	2.77	275.0	61.2	7.20

stabilized with either 2 percent of Veegum HV or 4 percent of Bentonite magma than other tested stabilized flocculated suspensions might be attributed to alkalinity of these earthy silicates causing partial hydrolysis of hydrochlorothiazide to inactive disulphonamide. This finding is in agreement with the results of Dobrecky et. al. (15) working on the stability of thiazides and anthranilic acid derivatives used as diuretics.

C. It is evident that there is a diminution in the extent and rate of increase in urine volume shown by the deflocculated suspension stabilized with agar agar relative to that produced by the powdered drug. This might be due to the protective action of agar agar or due to partial flocculation of the drug in presence of the negative charges on agar agar, thereby, hindering drug absorption.

D. The flocculated drug suspension stabilized with 4 percent of Aerosil exhibits the greatest increase in extent and rate of urine volume comparable to the plain flocculated one and the other tested flocculated suspensions. This might be attributable to the scattering effect of fine particles of Aerosil that increased the surface area of the drug and hence, increased its bioavailability. The latter assumption is in agreement with Monkhouse et. al (12) working on the use of adsorbents in enchancement of drug dissolution.

E. The decrease in total urine volume with about 20 percent produced by the administration of plain flocculated drug suspension than that reached with powdered drug after 180 minutes might be due to size enlargement of hydrochlorothiazide particles by flocculation. However, the smaller change in urine PH noticed with plain flocculated drug suspension than that achieved by the powdered drug after 3 hours might be attributed to the acidic nature of potassium dihydrogen phosphate, used as flocculating agent. Furthermore, it might be the reason for the increase of excretion of potassium ion via urine.

CONCLUSION

From the aforementioned arguments, the following can be concluded:

1. The deflocculated hydrochlorothiazide suspension stabilized with 0.2 percent of Carbopol 934 exhibited both the shortest $t_{60\%}$ and the maximal percentage of drug dissolution than the other tested deflocculated suspensions. Also, this suspension was shown to be more biologically available than the flocculated one stabilized with the same stabilizer.
2. Flocculated hydrochlorothiazie suspension stabilized with 4 percent of Aerosil declared the shortest $t_{60\%}$ and the maximal bioavailability comparable to the other tested earthy silicates stabilized suspensions and the plain flocculated suspension.

3. There is a direct relationship between the dissolution rate and the bioavailability of hydrochlorothiazide in deflocculated suspensions. The deflocculated drug suspension stabilized with 0.2 percent of Carbopol 934 showed both maximum dissolution and maximum bioavailability of drug after 180 minutes.
4. No correlation exists between the dissolution rate and the bioavailability of hydroclorothiazide in flocculated suspensions as the plain flocculated one exhibited maximum dissolution but not with a maximum bioavailability.

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