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AVAILABILITY OF ANHYDROUS AMPICILLIN AND SULPHADIMIDINE FROM THEIR SUSPENSIONS

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ABSTRACT

Many compounds are adsorbed onto solids from solutions. Clay minerals such as kaolin, bentonite and attapulgite and antacid powders such as aluminium or magnesium hydroxides or silicate have been shown to adsorb such drugs as alkaloids, phenothiazine derivatives and B- vitamins[1]. In such case the rate and even extent of absorption of drugs from the gastrointestinal tract may be considerably reduced.

This report details the effect of presence of kaolin on the in-vitro and in-vivo availability as well as the effect of different additives on the availability of both anhydrous ampicillin and sulphadimidine present together in suspension. It also details the physical characteristics of all formulations. The results of the in-vitro investigation showed that the availability of ampicillin and sulphadimidine was reduced due to their adsorption. The extent

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of availability of either of the medicaments was more when present in combination with kaolin than when present singly.

This study also shows that, most of the additives used, to minimize the adsorption, increased availability of both medicaments and improved sedimentation volume and redispersibility of the suspension.

The t-test for the cummulative amounts of either ampicillin or sulphadimidine excreted in urine, from the considered formulations, after 6 and 24 hours respectively, showed no significant difference ($p<0.05$).

INTRODUCTION

The simultaneous administration of adsorbents such as magnesium silicate, magnesium hydroxide and kaolin with various medicaments may reduce the absorption from the alimentary tract. Sorby [2] studied the effect of attapulgite and charcoal on adsorption of promazine from the gastrointestinal tract. He found that attapulgite retarded the absorption of promazine, but there was little decrease in total bioavailability, while charcoal was found to decrease the rate and extent of absorption.

The extent of adsorption is influenced by the solvent, since this too may be adsorbed, the polar/ non-polar nature of the solute , solvent and substrate all being involved. Studies conducted by Haines and Martin [3-5] of the caking in pharmaceutical suspensions indicated a state of fine deflocculated particles leads to caking. In some cases commonly used suspending agents and electrolytes exaggerate caking. The nature of composite and individual isotherms has been discussed by Gregg[6] and Kippling[7], while Giles et al.[8] have classified composite isotherms relating their shape to orientation of adsorbate and penetration by solvent molecules.

Since redispersibility is one of the major considerations in assessing the acceptability of a suspension, and since sediment formed should be easily dispersed by moderate shaking to yeild a homogenous system, measurement o the sedimentation volume and its ease of redispersion form two of the most common basic evaluative procedure.

The objectives in this work were to study 1) the effect of different additives on availability of ampicillin and sulphadimidine from their suspension, 2) the physical characteristics of suspension in presence of different additives and 3) the in-vivo availability of both medicaments from the chosen formulations .

PROCEDURE

Materials:

The following materials were used : anhydrous ampicillin (Gist - Brocades , Delft , Holland), sulphadimidine (El-Nasr Co. Cairo, Egypt), pure grade of kaolin (200-250 um), glycerin, sorbitol, propylene glycol, polyethylene glycol 600, polyvinylpyrrolidone M.W. 44,000(B.D.H.), gum acacia, gum tragacanth, simple syrup, and Gifford·s buffer[10].

Equipment:

Spectrophotometer (Unicam, England), and Colorimeter (Spekol, Carl Seiss Jeno, DDR).

Formulation:

The following is the proposed formula as used for medicinal treatment :

Anhydrous ampicillin	0.375	gm
Sulphadimidine	1.0	gm
Kaolin	5.0	gm
Water to	100.0	ml

To carry a comparative study for the availability of both ampicillin and sulphadimidine,it was necessary to prepare different formulations containing the two medicaments, singly and in combination, with and without kaolin.

Determination of the Amount of Ampicillin and Sulphadimidine in water:

Ampicillin had been determined in water using spectrophotometric method adopted by Smith et al. [11]. Sulphadimidine had been assayed adopting the colorimetric assay of British Pharmacopeia.

Determination of Ampicillin and Sulphadimidine in Urine:

Urine samples were assayed for ampicillin using a modification of Smith , De Grey and Patel [11] spectrophotometric method. This assay was developed by Smith et al. for determination of ampicillin in pharmaceutical preparations, based on the copper facilitated formation of stable acid degradation products for which the presence of intact ampicillin is essential. Now, the method is adopted to assay ampicillin in blood, bile and urine [12]. Sulphadimidine was assayed adopting Brotton and Marshall [13,14] method.

Oral Absorption Profile of Ampicillin and Sulphadimidine Suspension

a) Administration of Ampicillin and Sulphadimidine Suspension:

Four healthy drug-free male volunteers participated in this study. Their age and weight range were, 26 -35 years and 60-70 kg, respectively. Participants were refrained from any medication during, and at least tow weeks preceding the experiments. The suspensions were given on an empty stomach and no food was allowed for at least 2 hours after administration of the suspensions. Urine was collected quantitatively at suitable time intervals . All four subjects were given the two formulations tested.

The following are the two formulations used for estimating the bioavailability of ampicillin and sulphadimidine in humans.

Constituents	Formula I	Formula II
Sulphadimidine	1.0 gm	1.0 gm
Ampicillin	0.375 gm	0.375 gm
Kaolin	5.0 gm	5.0 gm
Water to	100.0 ml	---
Gifford's buffer pH 8.6 to	---	100.0 ml

TABLE 1

Availability of Ampicillin and Sulphadimidine From Their Suspensions

Ampicillin (mg) + Kaolin			Sulphadimidine (mg) + Kaolin		
Added	Retained	Adsorbed	Added	Retained	Adsorbed
375	317.5	575.0	1000.0	200.0	800.0

Ampicillin + Sulphadimidine + Kaolin					
Ampicillin (mg)			Sulphadimidine (mg)		
Added	Retained	Adsorbed	Added	Retained	Adsorbed
375.0	367.5	7.5	1000.0	387.5	612.5

RESULTS

Table 1, report the availability of both ampicillin and sulphadimidine from their suspensions when either medicament or both present with kaolin. From the table, it is to be noted that, kaolin adsorbed both ampicillin and sulphadimidine from their suspension to variable extent. Sulphadimidine was much more adsorbed than ampicillin.

Ampicillin and sulphadimidine each present alone with kaolin in suspension were adsorbed to the extent of 11.5 and 160 mg/gm kaolin respectively. When both medicaments were present with kaolin, both were adsorbed to a lesser extent than when either of them present alone with kaolin. This may be attributed to the competition between the two medicaments for the active sites of adsorption on kaolin. The quantity of ampicillin and sulphadimidine

TABLE 2

Effect of Different Additives on Availability of Ampicillin and Sulphadimidine

Additive	Amount ofAmpicillin and Sulphadimidine (mg/ml)			
	Amp.+Kao.	Sulpha.+Kao.	Amp.+Sulpha.+Kao.	
			Amp.	Sulpha.
Water (control)	317.5	200.0	367.5	387.5
Sorbitol 70%	367.5	450.0	375.0	585.0
Propylene Glycol	260.0	237.5	342.5	687.5
Simple Syrup	375.0	465.0	375.0	480.0
Glycerol	375.0	415.5	375.0	437.5
Absolute Alcohol	375.0	600.0	375.0	775.0
Gum Tragacanth	375.0	897.5	375.0	960.0
Gum Acacia	375.0	860.0	375.0	922.5
P.E.G. 600	330.0	387.5	367.5	637.5
P.V.P.	325.0	767.5	367.5	805.0
Gifford,s Buffer pH 5.2	340.0	675.0	365.0	700.0
Gifford,s Buffer pH 8.6	150.0	1000.0	375.0	1000.0

adsorbed from suspension containing the three components amounts to 1.5 and 122.5 mg/gm kaolin respectively.

The effect of different additives on availability of ampicillin and sulphadimidine from their suspension are shown in Table 2.

As shown in the table, all the additives used with the exception of propylene glycol and Gifford's buffer pH 8.6, increased the availability of ampicillin present singly with kaolin, while all the additives increased the availability of ampicillin present in combination with sulphadimidine,compared to its availability when present singly with kaolin. All the additives increased the

TABLE 3

Physical Characteristics of Ampicillin and Sulphadimidine Suspensions

Formula #	Additive	Conc. (%)	Sedimentation Volume (cm)	# of Shaking
I	Water	to 100.0	6.5	9
II	Sorbitol 70%	10.0	8.5	3
III	Propylene Glycol	10.0	7.5	8
IV	Simple Syrup	10.0	7.5	5
V	Glycerol	10.0	8.0	4
VI	Absolute Alcohol	10.0	8.0	6
VII	Gum Tragacanth	0.2	9.0	9
VIII	Gum Acacia	6.0	8.5	15
IX	P.E.G. 600	10.0	6.5	4
X	P.V.P.	10.0	9.5	7
XI	Gifford,s Buffer pH 5.2	to 100.0	7.5	7
XII	Gifford,s Buffer pH 8.6	to 100.0	7.0	6

amount of available sulphadimidine. The best additive in this regard was Gifford·s buffer pH 8.6. This later result may be due to alkalinity of the medium.

In most cases, the suggested additives, increased the availability of both medicaments compared to the control and to the results when either of the medicaments was present alone in suspension with kaolin.

This increase in availability as a result of the presence of the proposed additives may be explained as stated by Nasipuri et al.[15] working on suspension by the following three mechanisms: 1) Formation of a protective film at the adsorption surface. 2) Decreased diffusion of the adsorbate due to

TABLE 4

Cumulative Amount of Ampicillin Excreted in Urine (Formula I)

Subject	Cumulative Amount of Ampicillin (mg)							
Time (hrs)	0.5	1.0	2.0	3.0	4.0	5.0	6.0	24.0
A	--	0.14	0.80	1.58	2.09	2.33	2.47	3.90
B	--	0.16	1.23	1.96	2.42	2.67	3.09	4.49
C	--	0.09	0.40	0.80	1.16	1.39	1.65	2.51
D	--	0.57	1.94	2.77	3.16	3.34	3.58	5.93
Mean	--	0.24	1.09	1.78	2.21	2.43	2.70	4.21
S.D.	--	0.22	0.66	0.82	0.83	0.81	0.83	1.41

an increase in the bulk viscosity and environmental viscosity around the particles. 3) Possible interaction between the additives and the adsorbates.

The physical characteristics of ampicillin and sulphadimidine suspension containing different additives are shown in Table 3.

All additives, with the exception of gum acacia, improved the physical properties of the suspensions. Gum acacia produced a cemented cake which was difficult to redisperse and required 15 shakings for complete redispersion. All other additives showed no caking in their suspensions. As regard to the sedimentation volume and redispersibility of the suspensions, sorbitol 70 % was the best additives as its suspension required only 3 shakings to redisperse completely compared to 9 shakings in case of control.

The results of in-vivo availability of ampicillin and sulphadimidine from the two formulations tested are shown in Tables 4-7.

TABLE 5

Cumulative Amount of Ampicillin Excreted in Urine (Formula II)

Subject	Cumulative Amount of Ampicillin (mg)							
Time (hrs)	0.50	1.0	2.0	3.0	4.0	5.0	6.0	24.0
A	0.04	0.20	0.86	1.72	2.69	3.05	3.18	3.59
B	0.26	0.69	1.24	1.64	1.89	2.08	2.19	2.40
C	0.06	0.21	0.63	0.92	1.17	1.44	1.59	2.32
D	0.04	0.35	1.03	1.70	2.05	2.44	2.55	4.84
Mean	0.10	0.36	0.94	1.50	1.95	2.25	2.38	3.29
S.D.	0.11	0.23	0.26	0.38	0.62	0.67	0.66	1.19

TABLE 6

Cumulative Amount of Sulphadimidine Excreted in Urine(Formula I)

Subject	Cumulative Amount of Sulphadimidine (mg)							
Time (hrs)	0.50	1.0	2.0	3.0	4.0	5.0	6.0	24.0
A	1.53	3.77	18.25	39.71	75.51	115.83	158.45	568.85
B	0.69	3.69	9.21	19.39	42.72	75.84	98.69	380.09
C	1.09	2.60	8.52	20.15	59.08	95.33	147.75	712.83
D	2.35	5.95	18.91	34.99	58.39	101.81	133.13	493.13
Mean	1.41	4.00	13.72	28.56	58.92	97.20	134.50	538.72
S.D.	0.71	1.40	5.62	10.34	13.39	16.61	26.03	139.60

TABLE 7

Cumulative Amount of Sulphadimidine Excreted in Urine (Formula II)

Subject	Cumulative Amount of Sulphadimidine (mg)							
Time (hrs)	0.50	1.0	2.0	3.0	4.0	5.0	6.0	24.0
A	1.20	4.09	20.90	47.43	78.21	115.83	145.49	686.05
B	4.42	8.89	25.79	58.72	103.00	151.96	206.77	467.17
C	4.87	10.87	42.06	86.66	141.11	221.91	290.35	744.43
D	6.70	16.28	68.32	162.72	225.65	304.71	388.18	879.32
Mean	4.50	10.03	39.27	88.88	136.99	198.60	257.70	694.24
S.D.	2.30	5.04	21.38	51.91	64.52	83.32	105.32	171.66

The t- test for the cummulative amounts of either ampicillin or sulphadimidine excreted in urine, from the two formulations considered, after 6 and 24 hours respectively showed no significant difference ($p<0.05$). Comparing the 24 hours cumulative amount of ampicillin excreted in urine from both formulations indicated that, formula I exhibited greater bioavailability than formula II. This may be due to the fact that ampicillin in formula II will be in alkaline medium in which ampicillin exists in an ionized state which is not highly absorbed.

Sulphadimidine in formula II showed greater bioavailability than in formula I. This may be due to the fact that in formula II, sulphadimidine being present in alkaline medium, form its soluble salt which is readily absorbed, while in formula I sulphadimidine remains mainly in an insoluble form. This results show that, there is a clear correlation between the in-vitro and in-vivo availability of sulphadimidine, but no such correlation exist for ampicillin.

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