IN VITRO AND *IN VIVO* PROPERTIES OF ALOXIPRIN: A NEW ALUMINIUM DERIVATIVE OF ACETYLSALICYLIC ACID

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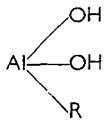
The rates of solution of aspirin from aloxiprin, an aluminium derivative of acetylsalicyclic acid, in buffer solutions of pH 2–8 were found to be lower than those of aspirin B.P., particularly in the more acid buffers.

The excretion of salicylate in the urine of 11 human subjects who received aloxiprin was more delayed than that from a corresponding dose of aspirin B.P. Little difference was found in the total amount of salicylate excreted in 24 hr.

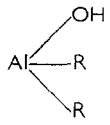
THE name Aloxiprin has recently been selected as the Approved Name to describe a "polymeric condensation product of aluminium oxide and aspirin." This new compound results from the interaction of aluminium isopropoxide and aspirin, and corresponds approximately to the formula $Al_3O_2(C_6H_4(O{\cdot}OCMe){-}COO)_5$.

Aloxiprin has recently been the subject of favourable clinical comment (Wheatley, 1962, and Wood, Harvey-Smith, and Dixon, 1962).

The literature provides many references to various compounds under the general designation, aluminium acetylsalicylate. These compounds have been claimed to approximate in composition to one or other of the structures I, II or III (French Patent 1951, 734,754; U.S. Patent 1951, 2,698,332; 1955, 2,918,485; German Patent 1958, 1,076,703):



I



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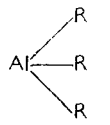
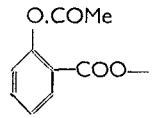


III

where R is



Aluminium acetylsalicylate acid is the subject of a monograph in the National Formulary, U.S.A., and structure II is assigned to this compound Aluminium aspirin (N.F.) possesses a high free salicylic acid content ("not more than 7·5 per cent"), a feature shared by some and probably all other aluminium acetylsalicylates which are prepared in aqueous solution. Such compounds have also generally been observed to be powders of low density which are not readily amenable to the pharmaceutical formulation of acceptable dosage forms.

IN VITRO AND *IN VIVO* PROPERTIES OF ALOXIPRIN

Aloxiprin differs from other aluminium acetylsalicylates hitherto described. It is characterised by a relatively low free salicylic acid content and also by the fact that the powder has a much greater bulk density.

Before aloxiprin was used clinically, it was considered desirable to examine the *in vitro* and the *in vivo* rate or release of aspirin from this compound and also to seek information of the availability of its salicylate content after oral administration.

In the present investigation, the rate of solution of aspirin from aloxiprin in buffer solutions of pH 2–8 at 37° has been compared with that of aspirin B.P. and the rate of excretion of salicylate in human subjects has been estimated after the oral administration of equivalent doses of aloxiprin and aspirin B.P.

EXPERIMENTAL

Materials

Aloxiprin. The material prepared as reported above, was used for the determination of the solution rates after being screened through a No. 120 B.S.S. sieve. This material complied with the specification: total acetylsalicylic acid, not less than 76 per cent; free acetylsalicylic acid, not more than 2·5 per cent; free salicylic acid, not more than 0·4 per cent; aluminium, not less than 7·2 per cent; bulk density, 205–215 ml./100 g.

Tablets containing 400 mg. (±20 mg.) aloxiprin equivalent to 5 grains of aspirin, were used for the excretion studies.

Aspirin. Aspirin B.P. powder passing a No. 120 B.S.S. sieve and aspirin tablets B.P. were used in the corresponding investigations.

Buffer solutions. The buffer solutions were prepared by mixing the following in the proportions given and adjusting to the required pH measured with a glass electrode. A, 0·1M disodium hydrogen citrate; B, 0·1M hydrochloric acid; C, 0·2M disodium hydrogen phosphate; D, 0·1M citric acid.

Buffer pH 2, 3·0 vol. A with 7·0 vol. B; pH 4, 5·5 vol. A with 4·5 vol. B; pH 6, 6·3 vol. C with 3·7 vol. D; pH 8, 9·7 vol. C with 0·3 vol. D.

METHODS

The Rate of Solution of Aspirin B.P. and of the Aspirin from Aloxiprin at 37° in Buffer Solutions of pH 2, 4, 6 and 8, measured as Total Salicylate

The aloxiprin powder (0·5 g.) was weighed directly into each of six plastic bottles of approximately 100 ml. capacity. Buffer solution (100 ml.) at 37° was added to each and after a brief shaking, the bottles were mechanically rotated in a water bath at 37°. Each bottle contained a piece of glass rod to facilitate mixing.

One bottle was removed from the water bath after 15, 30, 45, 60, 90 and 120 min., timed from the moment of the addition of the buffer solution. The solution was rapidly filtered and an aliquot of the filtrate diluted with 4 parts of water. The total salicylate content was determined by adding N NaOH (1 ml.) to the diluted filtrate (1 ml.) in a stoppered tube, heating in a boiling water bath for 30 min., cooling,

acidifying with concentrated HCl and following the procedure described by Brodie, Udenfriend, and Coburn (1944).

The rate of solution of aspirin B.P. (0·4 g.) was measured under identical conditions, except that it was found unnecessary to continue the incubation for more than 30 min.

The Rates of Salicylate Excretion after the Oral Administration of 650 *mg. of Aspirin B.P. and the Equivalent of Aloxiprin*

Eleven healthy male volunteers took part. At 9 a.m. urine was voided and discarded. At 9.30 a.m. each subject took two aspirin tablets B.P. with 100 ml. of water, and urine collections were made after 0, 0·5, 1, 2, 3, 5 and 7 hr. The urine samples collected at each time interval were pooled, the total volume measured and an aliquot was analysed for total salicylate.

The urine (4 ml.) was hydrolysed by boiling with 12N H_2SO_4 (2 ml.) under a reflux condenser for 3 hr. and the hydrolysate diluted to 25 ml. with water. This solution (2–4 ml.) was used for the determination of the "total salicylate" by the method of Brodie and others (1944).

One week later the same procedure was followed with the same 11 individuals except that each received two aloxiprin tablets.

In a separate study the salicylate excretion was followed for 24 hr. after the oral administration of 1 g. of aspirin B.P. and an equivalent dose of aloxiprin to 5 individuals. No restrictions were placed on the diet or fluid intake.

Results

Solution Rate Studies

The rates at which aspirin dissolved from aloxiprin in buffer solutions of pH 2, 4, 6 and 8 respectively at 37°, and the corresponding results obtained with aspirin B.P., are given in Fig. 1.

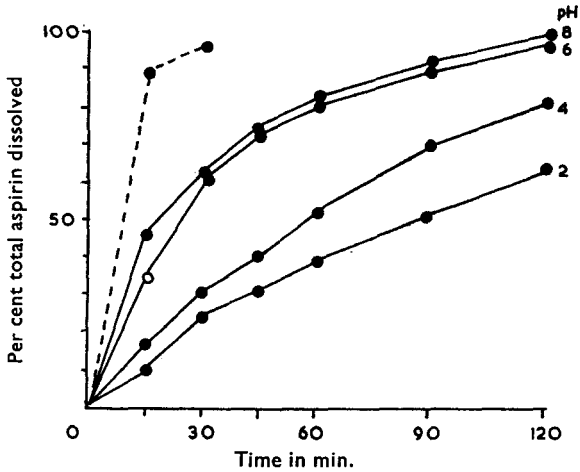


FIG. 1. The rate of solution of aspirin from ●—● aloxiprin (0·5 g.) and ● - - ● aspirin B.P. in 100 ml. of buffer solutions.

The aspirin of aloxiprin dissolves at an appreciably slower rate than aspirin B.P. in all the buffer solutions used. The solution rate of aspirin from aloxiprin increased with increasing pH, so that during the first 60 min. 2–4 times as much aspirin dissolved at pH 8 as at pH 2, whilst changes in pH had little effect upon the solution rate of aspirin powder, under the experimental conditions used.

Excretion Rate Studies

The total amounts of salicylate found in the pooled urines of 11 individuals after the ingestion of 0·65 g. aspirin B.P. and an equivalent dose of aloxiprin are given in Table I and Fig. 2. The results show that less

TABLE I

THE MEAN SALICYLATE EXCRETION AFTER THE ORAL ADMINISTRATION OF ASPIRIN B.P. AND ALOXIPRIN TO ELEVEN SUBJECTS (DOSE ≡ 0·648 MG. ASPIRIN)

Period of urine collection hr.	Salicylate excreted*						Ratio A/B
	Aloxiprin			Aspirin B.P.			
	Amount mg. (A)	Cumulative dose per cent	Excretion rate mg./30 min.	Amount mg. (B)	Cumulative dose per cent	Excretion rate mg./30 min.	
0·5	0·6	0·12	0·6	5·0	1·0	5·0	0·12
1	5·0	1·1	5·0	15·5	4·2	15·5	0·32
2	25·0	6·2	12·5	43·0	12·8	21·5	0·58
3	37·5	13·9	18·8	42·0	21·2	21·0	0·89
5	77·0	29·6	19·3	77·0	36·8	19·3	1·00
7	74·5	44·8	18·6	74·0	51·7	18·5	1·01

* Expressed as salicylic acid.

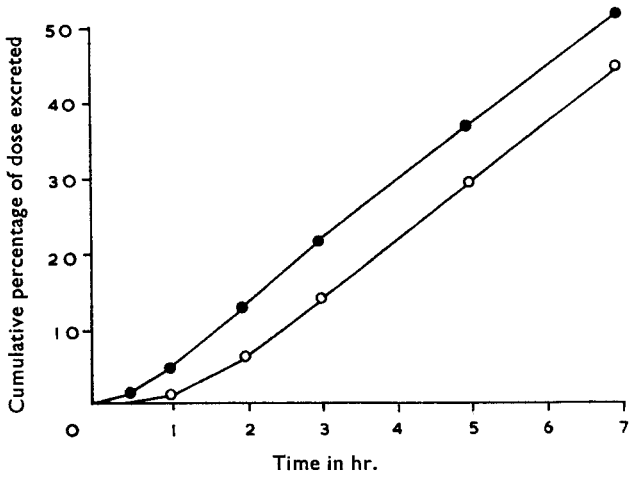


FIG. 2. The mean salicylate excretion after oral administration of 0·65 g. aspirin B.P. (●—●) and the equivalent of aloxiprin (○—○) to 11 subjects.

salicylate is excreted during the first 3 hr. after the administration of aloxiprin than after aspirin B.P., but thereafter the rates of excretion are similar (Fig. 3).

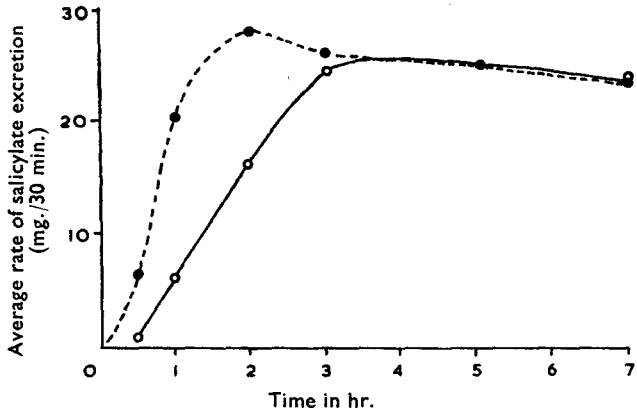


FIG. 3. The average rate of salicylate excretion after the oral administration of 0·65 g. aspirin B.P. (● – – ●) and the equivalent of aloxiprin (○—○) to 11 subjects.

The results obtained by following the salicylate excretion for 24 hr. after the ingestion of 1 g. of aspirin B.P., or the equivalent of aloxiprin in 5 subjects, are given in Table II.

TABLE II

THE SALICYLATE EXCRETION IN 24 hr. AFTER AN ORAL DOSE* OF ASPIRIN B.P. AND ALOXIPRIN IN 5 SUBJECTS

	Salicylate excreted‡			
	Aloxiprin		Aspirin B.P.	
	Total mg.	Dose per cent	Total mg.	Dose per cent
A	603	81·7	598	80·2
B	650	88·5	595	80·0
C	556	75·5	595	80·0
D	552	75·0	660	88·5
E	603	81·7	—	—
Mean	593	80·5	612	81·2

* Dose administered: Aspirin B.P. = 972 mg. (±50 mg.); Aloxiprin = 960 mg. (±50 mg.) Aspirin.
‡ Expressed as salicylic acid.

Thus, while the salicylate excretion after the administration of aloxiprin is initially lower than that after aspirin B.P. there is little difference in the total amount of salicylate excreted in 24 hr.

DISCUSSION

The results in Table I show that comparable quantities of the two salicylate preparations were excreted at different time intervals. Amounts of total salicylate in the urine corresponding to approximately 1, 5 and 13 per cent of the ingested doses were excreted during periods of 30 min., 1 hr. and 2 hr. after the oral administration of aspirin and during 1, 2 and 3 hr. after aloxiprin. Urinary excretion of salicylate after aloxiprin

therefore shows a time lag of between 30 min. and 1 hr. This lag in excretion could be due to comparatively little of the aspirin of aloxiprin being absorbed whilst it remains in the acid environment of the stomach.

This supposition is supported by the results of the solution rate investigations (Fig. 1) which show that the aspirin of aloxiprin dissolves appreciably more slowly in acid solution (pH 2) than aspirin B.P. and thus would be expected to dissolve less readily in gastric fluid. It has been previously reported that the rate of absorption of aspirin from the gastrointestinal tract is limited by its rate of solution (Edwards (1951), Nelson and Schaldemose (1959), Levy (1961), Levy, Gumtow, and Rutowski (1961)).

The results further suggest that in the intestinal tract, aspirin is absorbed at comparable rates from the two formulations. If this were not so, the plots of the respective amounts of salicylate excreted against time (Fig. 2) would give diverging lines; in fact, two parallel lines are obtained, which are separated by an interval corresponding to approximately 45 min.

It has been demonstrated (Table II) that the total amount of salicylate excreted over 24 hr. from aspirin and from aloxiprin does not differ appreciably, thus indicating that the whole of the aspirin of aloxiprin becomes available.

Thus, aloxiprin may provide a form of aspirin suitable for clinical conditions requiring the prolonged administration of relatively large doses of aspirin. Since it would seem that, as the aspirin of aloxiprin is relatively slowly released in the stomach, this compound could well cause fewer gastric disturbances than aspirin B.P., a view which is supported by the recent work of Wood and others (1962).

The excretion rates of the two preparations have been compared on the basis of the salicylate content of the pooled urines from a number of subjects. In view of the fact that a cross-over design was employed and that information of variation between subjects was not specifically required, analysis of the pooled urines, rather than of individual urines, was considered adequate. A consequence of this procedure is that the excretion characteristics revealed by the mean of several individuals, may well exhibit a pattern which is quite atypical of that for any individual. If, for example, the subjects show peak levels at different times, then the peak of the mean will be lower than that of most of the individuals and will be sustained over a longer period, so as to show a plateau effect as an artefact. The shape of the salicylate excretion curve as plotted from the mean values will not therefore necessarily portray the excretion pattern normally encountered in an individual.

Levy and Sahli (1962) have recently compared the gastrointestinal absorption of aluminium aspirin (National Formulary) and of aspirin (U.S.P.). They reported that the total apparent salicylate excretion from aluminium aspirin (N.F.) is markedly less than that from aspirin (U.S.P.), and concluded that the aluminium aspirin in the form which they used, was incompletely absorbed.

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