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Detection and determination of salicylic acid impurity in aspirin tablet formulations by high performance liquid chromatography

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Summary

Salicylic acid is a major hydrolytic degradation product of aspirin, responsible especially for gastric irritation during oral aspirin administration. This impurity was investigated in 12 different brands of aspirin formulation readily available in our locality. A simple, rapid and sensitive high performance liquid chromatographic method was adopted for this investigation. The mobile phase was methanol/water (20/80, v/v) adjusted to pH 2.5 with phosphoric acid and was run on a 50 mm reversed-phase column monitored at 240 nm. The limit of detection for salicylic acid was 5ng. Only three of these formulations showed the presence of salicylic acid impurity and all these contained salicylic acid in excess of the USP 1980 limit of 0.3% salicylic acid per tablet.

Résumé

L'acide salicylique est une produit hydrolytique majeur de la dégradation d'aspirin, responsable particulièrement pour les dérangements gastriques, pendant l'administration orale d'aspirin. On a entreprit une étude sur cet impureté dans 12 formulations d'aspirin de marque différent, facilement disponible chez notre environnement locale. On a adopté une méthode chromatographique à liquide simple, rapide et de haute éfficace. La phase mobile était méthanol/l'eau (20/80, v/v) de pH 2.5 et sur une phase colunne envers de 240 nm. L'acide salicylique de concentration aussi bas que 5 ng peut être-détecté, utilisant les montures des sensitivités bas. Seulement trois de ces formulations montraient la présence d'impureté de l'acide salicylique et dans les trois formulations, la quantité de l'acide salicylique était plus que la limite USP 1980 de 0.3% chaque comprimé.

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Introduction

Aspirin (acetyl salicylic acid) is one of the most commonly used and misused anti-pyretic, analgesic and anti-inflammatory agents in this environment. It is within easy reach of any interested individual. It is cheap to buy and various pharmaceutical companies have been encouraged to produce different brands of aspirin preparations for our local market. Some of these brands contain aspirin alone while others include paracetamol (acetaminophen) and caffeine in their formulations for double analgesic, anti-pyretic and stimulant activities.

Aspirin is known to decompose by hydrolysis to salicylic acid not only in solution but also in moist air in the solid state. Most of the adverse effects of aspirin, especially gastric irritation and bleeding, are due to salicylic acid [1,2]. Thus USP [3] prescribes limits for salicylic acid in pharmaceutical dosage forms containing aspirin. The limits are 0.1% for aspirin powder, 0.3% for tablets without buffers, 3.0% for buffered aspirin dosage forms, and 1.0% for suppositories. The presence of salicylic acid in some analgesic products has also been documented [4,5].

A recently developed high performance liquid chromatography (HPLC) procedure for multicomponent analysis of analgesics [6] is

now applied to determine the amounts of salicylic acid impurities in the presence of large amounts of aspirin. The different brands of aspirin formulations investigated were Alabukun®, Anacin®, Aspirin tablet, Bayer aspirin, Cafenol®, Daga®, Dolviran®, Pancemol Co.®, Paracin®, Pengo®, Phensic® and Vitalink aspirin.

Materials and methods

Experimental

Drugs. Pure salicylic acid, aspirin and *m*-hydroxybenzoic acid (the internal standard) were purchased from Sigma Chemicals (Poole, U.K.). The brands of aspirin formulations investigated, all stored at ambient temperatures, were purchased from local chemist shops.

Solvents. Liquid chromatography grade acetonitrile was a gift from Barewa Pharmaceuticals (Lagos, Nigeria) while methanol (liquid chromatography grade) and ethanol (96%) were purchased from May & Baker (Dagenham, U.K.).

Apparatus

The HPLC equipment comprised of a Pye Unicam LC-XPD pump (Cambridge, U.K.) which delivered the eluent onto a reversed-phase stainless steel column (50 × 4.6 mm i.d; Hypersil (5-ODS)). Samples were introduced into the column using a Rheodyne valve system (Cambridge, U.K.) fitted with a 20 µl loop. The eluent was monitored with a Pye Unicam LC-UV variable wavelength detector set at 240 nm and connected to a Pye Unicam PM 8251 potentiometric recorder. The temperature was maintained at 24°C in an air-conditioned room. Also used were a rotamixer and a Jouan bench centrifuge, supplied by Eccles Technical Services Limited, U.K.

Calibration standard

From the stock solutions of 5 mg/ml each of aspirin, salicylic acid and *m*-hydroxybenzoic acid, the concentrations shown in Table 1 were prepared.

Table 1. Calibration concentrations

	Calibration solutions					
Drug	1	2	3	4	5	6
Aspirin (µg/ml)	0	20	40	60	80	100
Salicylic acid (µg/ml)	0	20	40	60	80	100
m-Hydroxybenzoic acid (int. std) (µg/ml)	50	50	50	50	50	50

Assay of the analgesics

Ten tablets of each of the products were randomly selected from a package containing a single batch, weighed and powdered. Twice the average weight of each of the tablets was accurately weighed into a 20 ml volumetric flask and ethanol was added to make up the volume. The solution was shaken on a rotamixer for 1 min and then centrifuged (2500 r.p.m.) for 5 min. Aliquots of the supernatant were diluted to give high concentrations of aspirin, and salicylic acid content was determined. The internal standard was 50 µg/ml *m*-hydroxybenzoic acid.

Results and discussion

This study was initiated because of the high level of salicylic acid observed in a product during our routine analytical services. Based on the column selectivity and a mobile phase of methanol/water (20/80, v/v), adjusted to pH 2.5 with phosphoric acid, the limit of detection of salicylic acid was 5 ng, the optimum detection wavelength was found to be 240 nm. Figure 1 shows a typical analytical chromatogram. Figure 2 shows the chromatogram obtained from a product, indicating the presence of salicylic acid. There was a linear relationship between the peak:height ratios and the concentrations of aspirin (20–100 µg/ml) and salicylic acid (20–100 µg/ml) with correlation coefficient values > 0.999 for each compound.

The results of the assay of aspirin and salicylic acid in the 12 aspirin-containing formulations are shown in Table 2. These results could be analysed as follows.

(a) Three (1–3) of the 12 products contained

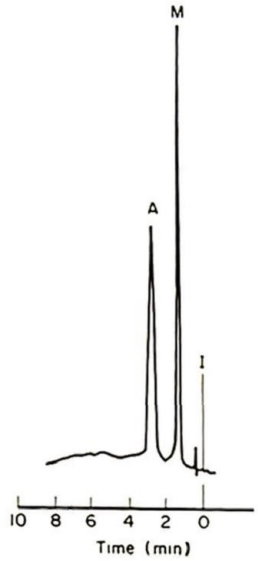

Fig. 1. A typical analytical chromatogram of aspirin, using a Hypersil 5-ODS column (50 × 45 mm i.d.) with a mobile phase of methanol/water (20/80, v/v) pH 2.5 with detection at 240 nm. I = injection, M = internal standard and A = aspirin.

aspirin alone in their formulations. Two out of these had aspirin contents between 95% and 105% of the limit while the third had 90% of the stated aspirin content.

(b) Six (4–9) products contained both aspirin and caffeine. Of these, one product (No. 4) had an extremely low aspirin content (76%) and another (No. 6) had 132% of the stated aspirin content.

(c) Three (10–12) products included both paracetamol and caffeine in their aspirin formulations. The results showed that they contained 1.19%, 5.20% and 16.96% of salicyclic acid respectively (expressed as a percentage of total salicylate).

This study illustrates that not all available aspirin products are chemically equivalent. Since no hydrolytic degradation product was detected in products 2 and 4 (Table 2) the low aspirin content could only be attributed to poor product quality. However, products 10–12 (Table 2) showed the presence of salicylic acid impurities. Analyses of products 10, 11 and 12 (Table 2) were repeated five times to confirm their salicylic acid contents. The physical examination of tablets of product 12 showed

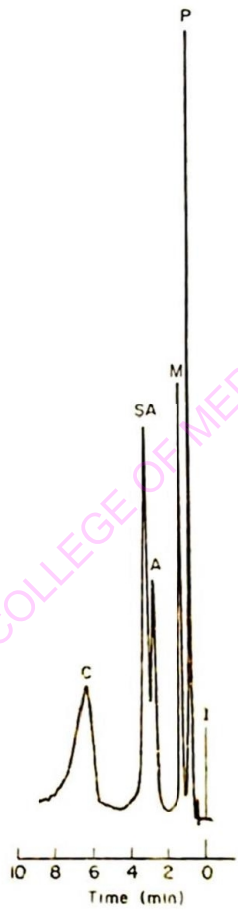

Fig. 2. Chromatogram of a product showing the presence of salicylic acid, paracetamol and caffeine. Chromatographic details as for Fig. 1. I = injection, P = paracetamol, M = internal standard, A = aspirin, SA = salicylic acid and C = caffeine.

that they had varying shades of colour, ranging from the original white colour to deep brown depending on the stage of decomposition. A smell characteristic of acetic acid was detected from this sample.

These samples were purchased from local drug stores at different locations in Lagos with an average relative humidity of 71%, consequently the possibility exists of trans-acetylation producing diacetyl-*p*-aminophenol from a combination of acetylsalicylic acid and acetaminophen [7]. This could also account for the fact that the total salicylate content obtained

Table 2. Concentrations of aspirin and salicylic acid in the formulations

Product no.	Aspirin content (% of that stated on bottle)	Salicylic acid	
		mg/tablet	Percentage of total salicylate
1	94.81	—	—
2	89.88	—	—
3	102.33	—	—
4	76.00	—	—
5	93.72	—	—
6	132.41	—	—
7	97.89	—	—
8	94.50	—	—
9	99.49	—	—
10	97.98	2.73	1.19
11	88.28	8.82	5.12
12	64.42	19.50	16.96

from each tablet is < 100% for each of the three products.

These observations confirm earlier studies [7] and also the notion that aspirin and paracetamol combinations are not stable in humid environments.

Rapid hydrolysis of aspirin in solution during analysis was minimised by the use of pH 2.5 for the mobile phase, almost the optimum pH for aspirin stability, and also, the samples were assayed within 10 min of preparation.

Conclusion

This simple, rapid, sensitive and selective method of determination of salicylic acid impurities in aspirin-containing tablet formulations can be routinely applied to the quality control of these formulations. The results clearly support earlier studies which found that combined aspirin and paracetamol formulations are fairly unstable in ambient humidities such as those in Nigeria. Consequently, this high concentration of salicylic acid in these oral formulations is a cause for concern.

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