Table 1. *Release of salicylate from the microcapsules in 0·1 N HCl and at pH 8 in phosphate buffer.*

Time, min	Cumulative % salicylate released* 0·1 N HCl	pH 8
10	34·23 ± 0·08	45·80 ± 0·50
20	49·30 ± 0·05	62·40 ± 0·34
30	60·00 ± 0·20	74·38 ± 0·26
40	68·50 ± 0·08	82·26 ± 0·80
50	75·22 ± 0·50	87·50 ± 0·48
60	80·50 ± 0·40	90·46 ± 0·36
70	84·84 ± 0·35	
80	88·00 ± 0·70	
90	90·60 ± 0·90	
100	93·02 ± 0·84	

* Average of two observations.

that may have migrated to the periphery of the microcapsule wall during the drying stage due to the solvent migration effect. Either one or a combination of both these phenomena would make some drug immediately available.

The drug content of the microcapsules as determined by extraction was 18% w/w compared with the theoretically calculated value of 20% w/w. This 10% difference could have resulted from some of the drug dissolving in the collecting fluid during the preparation of the microcapsules. Possibly because the addition of the alkaline cellulose acetate phthalate-drug dispersion into the acidic, drug-saturated collecting fluid would tend to make the collecting fluid less acidic (and therefore subsaturated with respect to salicylate), some of the drug from the microcapsules would be likely to dissolve in the collecting fluid resulting in a decrease in the drug being encapsulated.

The process of microencapsulation reported gave a remarkable degree of reproducibility. Release rates were within a narrow range, the maximum observed being less than 3% (Table 1). In addition, the process is simple, economical, and amenable to industrial application.

September 26, 1977

REFERENCES

MADAN, P. L., LUZZI, L. A. & PRICE, J. C. (1972). *J. pharm. Sci.*, **61**, 1586–1588.

MADAN, P. L., LUZZI, L. A. & PRICE, J. C. (1974). *Ibid.*, **63**, 280–284.

MADAN, P. L., PRICE, J. C. & LUZZI, L. A. (1974). In: *Microencapsulation: Processes and Applications*, pp. 39–56. Editor: Vandegaer, J. E. New York: Plenum Press.

MADAN, P. L., MADAN, D. K. & PRICE, J. C. (1976). *J. pharm. Sci.*, **65**, 1476–1479.

MADAN, P. L. & MINISCI, M. (1976). *Drug Intell. clin. Pharm.*, **10**, 588–591.

MADAN, P. L. (1977). In vitro *evaluation of drug release from commercial enteric-coated tablets in acidic conditions*, paper presented at A.Ph.A. Academy of Pharmaceutical Sciences, New York, U.S.A., May 17.

LETTER TO THE EDITOR

'Immunogenic impurities' in acetylsalicylic acid

PAUL KALLÓS, H. D. SCHLUMBERGER*, *Villatemtsvägen 12, 5–252 34 Helsingborg, Sweden and *Institute of Immunology and Oncology, Bayer A.G., D–6500 Wupperdal, Germany*

Aspirin has wide use and it is obvious that methods for measuring and determining impurities in it are of importance but the clinical relevance of these impurities should be made clear. In 1976 Bundgaard published a paper entitled 'Colorimetric Analysis of Immunogenic Impurities in Acetylsalicylic Acid' in which he states that 'impurities in acetylsalicylic acid rather than the drug substance itself are held responsible for the appearance of anti-salicyloyl antibodies in patient's treated with acetylsalicylic acid'. The use of the term 'immunogenic impurities' and 'anti-salicyloyl antibodies in patients' is unsatisfactory in that it implies that the immunogenicity of these impurities has some clinical significance. Furthermore, the bibliography is incomplete and some references are quoted in a misleading manner.

In a few patients therapeutic doses of aspirin elicit a syndrome which clinically resembles a systemic allergic (anaphylactic) reaction of the immediate type. Bundgaard and his colleagues (see references quoted by him) claimed this syndrome is in fact anaphylactic and due to an immunogenic impurity in aspirin, namely acetyl-

* Correspondence.

salicylic acid anhydride (ASAN) while, Schlumberger, Löbbecke & Kallós (1974) showed that this side effect of aspirin is not a specific immunologic (allergic) phenomenon and that ASAN plays no causative role. ASAN can be taken by aspirin-intolerant patients with impunity (Juhlin, Michaelson & Zetterström, 1972). Nor can other impurities in aspirin be implicated as causative factors, because, according to Schlumberger & others (1974) 70% of the intolerant cases react with the same syndrome to other chemically unrelated drugs, such as indomethacin, sulfonamides, barbiturates, quinine, quinidine, some antibiotics, and a food additive, tartrazine. Schlumberger & others (1974) showed by passive transfer to rhesus monkeys, that the serum of aspirin-intolerant patients does not contain homocytotropic antibodies of the IgE class with *N*-salicyloyl- or *N*-acetylsalicyloyl-specificity. Such antibodies alone are responsible for allergic reactions of the immediate type. Skin tests in aspirin-intolerant patients with appropriate antigens were also negative. Aspirin-intolerance occurs in about 10–20% of chronic asthmatics and is not infrequently a family-trait. It was concluded by Schlumberger & his colleagues that the syndrome is caused by direct, i.e. not antibody-mediated, liberation of histamine and other mediators by aspirin itself and the other offending drugs, due to an 'inborn error of metabolism' in intolerant patients. The syndrome was denoted as 'drug induced anaphylactoid syndrome'. It was stressed, in accordance with the literature (e.g. Amos, Wilson & others, 1971), that antibodies with anti-salicyloyl specificity, often found in the serum of aspirin-treated patients have no clinical, significance. The results of Schlumberger & others were corroborated by Stevenson, Arroyave & others (1976) and the hereditary nature of aspirin-intolerance has been further documented (e.g. von Maur, Attkinson & others, 1974; Settipane & Pudupakkam, 1975). It has also been shown, that the anaphylactoid syndrome elicited by the therapeutic administration of dextran in some patients (Hedin, Richter & Ring, 1976) and by its experimental use in inbred strains of rats (West, 1959, 1974; Baxter & Adamik, 1976) is also due to a hereditary trait.

Bundgaard refered to Schlumberger (1975) and stated that as well as ASAN other impurities, such as acetylsalicyl salicylic acid (the subject of his paper) 'show similar immunological effects'. He did not refer to the main conclusion of Schlumberger, namely that the derivatives of aspirin investigated, showed immunogenic properties in guinea-pigs *only* when administered parenterally in organic solvents. Since this is never practised in patients the results have no clinical significance.

August 5, 1977

REFERENCES

Amos, H. E., Wilson, D. V., Taussig, M. J. & Carlton, S. J. (1971). *Clin. exp. Immun.* **8**, 563–572.

Baxter, J. H. & Adamik, R. (1976). *Int. Archs Allergy appl. Immun.*, **52**, 196–204.

Bundgaard, H. (1976). *J. Pharm. Pharmac.*, **28**, 544–547.

Hedin, H., Richter, W. & Ring, J. (1976). *Int. Archs Allergy appl. Immum.*, **52**, 145–159.

Juhlin, L., Michaelson, G. & Zetterström, O. (1972). *J. Allergy clin. Immun.*, **50**, 92–98.

Maur, K. Von, Attkinson, S. jnr, Van Metre, Th. E. jnr, Marsh, B. G. & Norman, Ph. S. (1974). *Ibid.*, **54**, 380–395.

Schlumberger, H. D. (1975). *Int. Archs Allergy appl. Immun.*, **48**, 467–474.

Schlumberger, H. D., Löbbecke, E.-A. & Kallós, P. (1974). *Acta med. scand.*, **196**, 451–458.

Settipane, W. A. & Pudupakkam, R. K. (1975). *J. Allergy clin. Immun.*, **56**, 215–221.

Stevenson, D. D., Arroyave, C. M., Bhat, K. N. & Tan, E. M. (1976). *Clin. Allergy*, **6**, 493–506.

West, G. B. (1959). *Int. Archs Allergy appl. Immun.*, **15**, 231–236.

West, G. B. (1974). *Ibid.*, **47**, 297–305.