substituents should protect better and more effectively preclude interaction with a bioactive macromolecule. Rationalization *c*, because it is a combination of *a* and *b*, also is apparently disputed.

The fact that the *N,N*-dialkylamides are as potent as the *N*-mono-alkylamides could be rationalized as follows: (*a*) better distribution to the receptor because of the increased hydrocarbon content, (*b*) a substantial amount of *N*-dealkylation, (*c*) increased hydrophobic interactions. Upon examination however, rationalizations *a* and *c* must be discarded, for on the basis of these, *N*-monoalkylation should not have decreased activity. It thus appears that *N*-dealkylation may be a factor. If this is the case the three rationalizations previously set forth with respect to the effect upon activity of mono-*N*-alkylation may be valid. These rationalizations are consonant with a sterically accessible amide function interacting with the bioactive macromolecule. The interaction possibly involves hydrogen bonding through the media of an amide hydrogen atom.

CONCLUSIONS

The following compounds: 2-ethyl-2-propylcyanoacetamide[5]; *N*-methyl-2,2-dipropylcyanoacetamide; *N*-methyl-2-ethyl-2-propylcyanoacetamide; *N*-dimethyl-2-ethyl-2-propylcyanoacetamide; 2,2-diethylcyanoacetamide[5]; *N*-methyl-2,2-diethylcyanoacetamide[5]; and *N*-dimethyl-2,2-diethylcyanoacetamide have been found active when subjected to testing by an electroshock method using rats. The median effective dose (ED_{50}, mg./kg.) of each active drug was determined and reported. The least toxic and most active compounds were ($ED_{50}LD_{50}$,[6] TI, respectively): *N*-methyl-2,2-dipropylcyanoacetamide, 70, 450, 6.4; 2-ethyl-2-propylcyanoacetamide, 71, 575, 8.1; 2,2-diethylcyanoacetamide, 170, 1,000, 5.9.

[5] See Footnote *a*, Table I.
[6] Approximate.

Convulsive tendencies and/or lack of activity prevented quantification of the seven drugs: *N*-propyl-2-ethyl-2-propylcyanoacetamide; *N*-propyl-2,2-diethylcyanoacetamide; 1-(2-cyano-2-ethylbutyryl)-piperidine; 1-(2-cyano-2-ethylvaleryl)-piperidine; 1-(2-cyano-2-ethylbutyryl)-pyrrolidine; 1-(2-cyanoethylvaleryl)-pyrrolidine; and 4-(2-cyano-2-ethylbutyryl)-morpholine. Qualitative observations were made and recorded.

REFERENCES

(1) Cunningham, R. W., personal communication.
(2) Schwartz, H. F., Worrell, L. P., and Delgado, J. N., *J. Pharm. Sci.*, **56**, 80(1967).
(3) Johnson, F. H., Eyring, H., and Polissar, M. J., "The Kinetic Basis of Molecular Biology," Wiley, New York, N. Y., 1954, pp. 253, 260, 334, 437, 447.
(4) Close, W. J., and Spielman, M. A., "Medicinal Chemistry," vol. V, Wiley New York, N. Y., 1961, p. 37.
(5) Butler, T. C., *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 367(1955).
(6) Butler, T. C., *J. Pharmacol. Expll. Therap.*, **104**, 229 (1952).
(7) *Ibid.*, **108**, 11(1953).
(8) *Ibid.*, **108**, 474(1953).
(9) *Ibid.*, **109**, 340(1953).
(10) *Ibid.*, **113**, 178(1955).
(11) Butler, T. C., and Waddell, W. J., *Neurology*, **8**, 106 (1958).
(12) Toman, J. E. P., Swinyard, E. A., and Goodman, L. S., *J. Neurophysiol.*, **9**, 231(1946).
(13) Litchfield, J. T., and Wilcoxon, F., *J. Pharmacol. Expll. Therap.*, **96**, 99(1949).
(14) Swinyard, E. A., *J. Am. Pharm. Assoc., Sci. Ed.*, **38**, 201(1949).
(15) Spiegel, A. J., and Noseworthy, M. M., *J. Pharm. Sci.*, **52**, 917(1963).
(16) Albert, A., "Selective Toxicity," 3rd ed., Wiley, New York, N. Y., 1965, pp. 42–67.

Keyphrases

Cyanoacetamides—synthesis
Structure-activity relationships—cyanoacetamides
Anticonvulsant activity—supramaximal electroshock seizure test
ED_{50} values—cyanoacetamides

Development of a Sustained-Release Aspirin Tablet

By EDWARD H. WISEMAN and N. J. FEDERICI*

Several sustained-release aspirin tablets, some of which are capable of attaining and maintaining plasma salicylate concentrations of about 30 mcg./ml. for 8 hr. after ingestion from a total dose of 975 mg. aspirin are described. The design of the final tablet characteristics was guided by analysis of plasma salicylate concentrations *in vivo*, and the rate of aspirin release *in vitro*.

A SUSTAINED-RELEASE product has been defined as "one in which a drug is initially made available to the body in an amount sufficient to cause the desired pharmacological response as rapidly as is consistent with the properties of the drug determining its intrinsic availability for absorption; and one which provides for maintenance

Received April 12, 1968, from the Medical Research Laboratories, Chas. Pfizer & Co., Inc., Groton, CT 06340
Accepted for publication July 10, 1968.
* Thomas Leeming & Co./Pacquin Divisions, Chas. Pfizer & Co., Inc., Parsippany, N. J.

of activity at the initial level for a desirable number of hours in excess of the activity resulting from the usual dose of drug" (1). The advantages of such a dosage form are chiefly the maintenance of therapeutic drug concentrations without incursions into higher concentrations which may lead to undesirable effects, plus the convenience of less frequent dosage. A further possible advantage is the prolonging of drug action throughout sleeping hours without the necessity to ingest medication.

A convenient way to achieve rapidly and then maintain a desired plasma drug concentration is to combine the active ingredient in a multilayer tablet consisting of a sustained-release core with an outer, instantly available coating. This technique was familiar to the authors in connection with products containing triethanolamine trinitrate biphosphate (2), and it was desired to extend the process to sustaining the action of other therapeutic agents, for example aspirin.

In the design of a prolonged action form of a therapeutic agent, it is important that the aims and limitations of the desired formulation be defined. For an aspirin product, the plasma salicylate level required for analgesia in mild acute pain should be maintained for the maximum possible duration, within the limitation of the amount of aspirin which can be conveniently incorporated into a tablet.

A recent careful study was conducted on the relief of post-partum pain with 650 mg. of aspirin (3). In that investigation, pain relief significantly different from placebo control did not appear earlier than 45 min. after drug administration, and did not increase in intensity after 60 min. as determined either by the number of patients obtaining relief or the magnitude of relief of the individual patient. Four hours after aspirin ingestion, pain relief was no longer significantly different from placebo control. Two earlier studies (4, 5), although less rigorously controlled, reached similar conclusions and suggest analogous pain-relief patterns in a variety of clinical states, including headache.

Following the ingestion of 650 mg. of aspirin, by normal men, average plasma salicylate concentrations reached about 30 mcg./ml. at 45 min., with a maximum of about 40 mcg./ml. at 2 hr., and declined to about 30 mcg./ml. at 4 hr. For the purpose of this study, therefore, these results, viewed in conjunction with the clinical studies, were taken to indicate that pain relief occurred during the time when plasma salicylate levels were above 30 mcg./ml.

The desired characteristics and limitations of the sustained-action aspirin tablet were therefore projected as follows. Plasma levels of 30 mcg./ml. should be attained within 1 hr. after dosage and be maintained for 8 hr. Physical limitations on the tablet size dictated that total aspirin content should be not more than 487.5 mg./tablet. The studies undertaken to design a sustained-release formulation with these characteristics, and to investigate the factors which determine these characteristics, are detailed in this report.

METHODS[1]

Preparation of Tablets—All tablets were double layer in composition, with aspirin incorporated into a restraining matrix in one layer, and aspirin and a cornstarch binder in the second layer. The restraining matrix consisted of a vegetable wax, insoluble extenders, a water-soluble binder, and a fatty-acid salt lubricant. The release rate was governed by the ratio of the sustaining base to active ingredient, as well as tablet hardness. Two restraining matrices were investigated.

Matrix A—Calcium phosphate (tribasic, NF; 175 parts), talcum (USP; 25 parts), and carnauba wax (passing No. 30 mesh sieve; 125 parts) were mixed thoroughly, moistened with glucose (USP; 25 parts) in water, and the granulation dried at 60° for 2 hr. The dried granulation was powdered, and finally screened through a No. 30 sieve.

Matrix B—Lactose (USP; 125 parts), sucrose (USP; 125 parts), carnauba wax (passing No. 30 mesh sieve; 75 parts), and polyvinylpyrrolidone (12.5% solution; 4.5 parts) were mixed thoroughly. This granulation was then dried, powdered, and screened as for Matrix A.

For preparation of the restraining matrix granulation, appropriate amounts of restraining matrix (A or B) and acetylsalicylic acid (USP) were mixed with small amounts of magnesium stearate (USP) and cornstarch (USP; dried) and the mixture slugged into 1.9-cm. slugs. The slugs were reduced progressively to pass finally through a No. 20 sieve. This granulation, thoroughly mixed with cornstarch (2%), was used for the sustained layer of the final tablet. The instant release layer consisted of acetylsalicylic acid (USP) and cornstarch (10%). The tablets were made in a Stokes BB2 rotary tableting machine, using a capsule-shaped punch [(1.9 cm. × 0.63 cm.) (0.75 in. × 0.25 in.)], thickness 0.71 cm. (0.28 in.), to the appropriate hardness (8–20 kg., Pfizer tester).

In Vitro Studies—The tablet under investigation was placed in one chamber of the basket of a USP disintegration apparatus, and the basket immersed in 0.1 *N* hydrochloric acid (500 ml.) maintained at 37°. Samples (1 ml.) of the hydrochloric acid were removed at varying times, filtered, and the absorbance at 295 mμ, determined in a Beckman DU spectrophotometer. Acetylsalicylic acid concentrations were then determined by reference to a standard curve of absorbance *versus* concentration of known solutions.

In Vivo Studies[2]—Healthy men who had fasted for 12–14 hr. ingested the tablets under investiga-

[1] The authors wish to thank Miss J. Chiaini, Mr. A. Capozza, and Mr. R. Lebel for expert technical assistance.

[2] Carried out in collaboration with Dr. D. G. Iezzoni.

TABLE I—PLASMA SALICYLATE CONCENTRATIONS (mcg./ml.) IN NORMAL HUMAN MALE SUBJECTS AFTER ORAL ADMINISTRATION OF PROPRIETARY ASPIRIN (650 mg.)

Time After Administration, hr.	C.L.	M.O.	W.O.	C.K.	T.H.	Av.
0	0	0	0	0	0	0
0.5	24	27	13	21	5	18
1	30	36	36	45	20	33
2	35	37	40	41	38	39
3	34	40	37	43	37	37
4	—	—	29	35	31	32
5	20	25	24	27	26	25
6	16	24	18	22	21	20
7	—	22	14	20	—	18
7.75	11	20	12	14	14	14

TABLE II—COMPOSITION AND HARDNESS OF EXPERIMENTAL ASPIRIN TABLETS

Formulation No.	Instant Layer: Aspirin, mg. + 10% Cornstarch	Sustained Layer: Matrix Type	Sustained Layer: Carnauba Wax, mg.	Sustained Layer: Aspirin, mg.	Av. Hardness, kg.
I	162	A	90	324	10.5
II	162	A	140	324	10.5
III	162	A	140	324	11.5
IV	162	A	125	324	11.5
V	162	A	110	324	11.5
VI	162	B	130	324	12.5
VII	162	B	75	324	12.5
VIII	162	B	75	324	11.5

tion (total aspirin, 975 mg.) followed by 200 ml. of water. Blood samples were drawn by venipuncture and transferred immediately to heparinized tubes. Plasma samples were separated by centrifugation and assayed for total salicylate by the method of Brodie *et al.* (6).

RESULTS

The plasma salicylate levels attained in normal man after the ingestion of 650 mg. of a commercial aspirin preparation (Bayer) are shown in Table I. Experimental two-layer tablets were formulated as described in *Methods*. Either the ratio of aspirin: restraining matrix was varied, or, at constant composition, the hardness to which the tablets were pressed was changed. All experimental tablets comprised 162.5 mg. of aspirin in the "instant" layer and 325 mg. aspirin in the "restrained" layer (Table II).

In Vitro Release Studies—The *in vitro* aspirin release from the experimental tablets is shown in

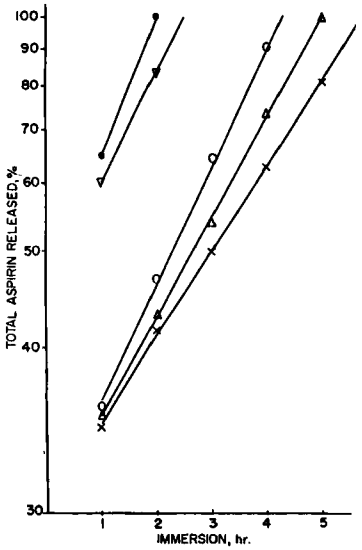

Fig. 1—Rate of aspirin release in vitro *from tablets comprising restraining Matrix A. Each point represents determination on 8–15 tablets. Key: ●, I; ▽, II; ○, V; △, IV; ×, III.*

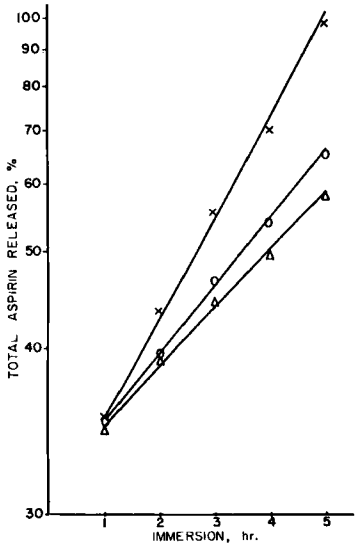

Fig. 2—Rate of aspirin release in vitro *from tablets comprising restraining Matrix B. Each point represents determinations on 8–15 tablets. Key: ×, VIII; ○, VII; △, VI.*

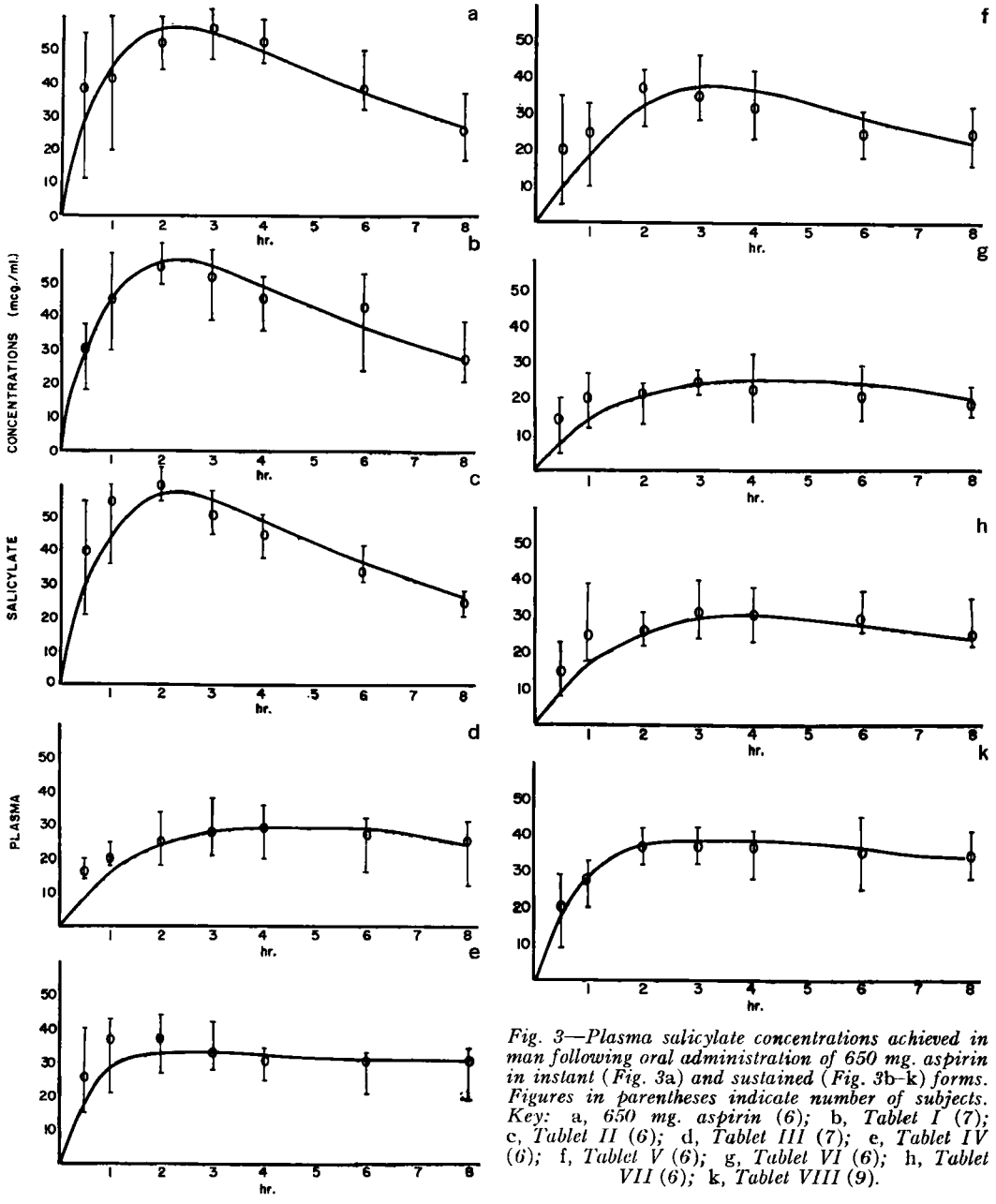

Fig. 3—Plasma salicylate concentrations achieved in man following oral administration of 650 mg. aspirin in instant (Fig. 3a) and sustained (Fig. 3b–k) forms. Figures in parentheses indicate number of subjects. Key: a, 650 mg. aspirin (6); b, Tablet I (7); c, Tablet II (6); d, Tablet III (7); e, Tablet IV (6); f, Tablet V (6); g, Tablet VI (6); h, Tablet VII (6); k, Tablet VIII (9).

Figs. 1 (Matrix A) and 2 (Matrix B). In both series, when tablet hardness was held constant, increasing the ratio of restraining matrix to aspirin content led to a decrease in rate of release of aspirin from the tablet. If the composition of the tablet was held constant, an increase in tablet hardness caused a similar, but less pronounced, decrease in rate of aspirin release.

In Vivo Studies—The plasma salicylate concentrations produced by the experimental tablets are shown in Fig. 3 (*b–k*). Tablets I and II gave no evidence of sustained action ***in vivo***. The time course of plasma salicylate concentrations was indistinguishable from that obtained by oral administration of 975 mg. of nonsustained aspirin (Fig. 3*a*). Tablets III–VIII all exhibited varying degrees of sustained action.

DISCUSSION

For many drugs, it has been shown that the therapeutic effect is proportional to the concentration of drug in the blood (7). The determination of the effective dose of aspirin however, is complicated by the subjective nature of the assay of "pain relief." Nevertheless, the work of investigators skilled in

this type of evaluation parallel in a striking manner the objective plasma salicylate determinations made in this study. Since aspirin has a relatively short plasma half-life (about 4 hr.), "analgesic" plasma salicylate concentrations cannot be maintained much beyond 4 hr. following a single 650-mg. dose. Extended analgesic plasma concentrations may be obtained by giving a second dose 4 hr. after the first, or by giving a larger dose initially. A sustained release form of aspirin would eliminate the frequent dosage required by the first alternative, and eliminate the unnecessarily high plasma drug concentrations in the early hours of the second alternative.

With both of the experimental restraining matrices studies, rate of aspirin release was found to be controlled by the hardness to which the tablet was compressed and the ratio of restraining matrix to aspirin. For example, Tablet II (hardness 10.6 kg.) exhibited no sustained action *in vivo*. Tablet III, of identical composition, but of hardness 11.5 kg., exhibited good sustained properties, but did not exactly conform to the desired specifications. If tablet hardness was kept constant, a reduction in the amount of restraining matrix (Tablets IV and V) led to an increase in both *in vitro* and *in vivo* release rates. Tablet IV had the characteristics desired in a sustained-release preparation, in that it produced plasma salicylate concentrations of about 30 mcg./ml. within 1 hr. of ingestion, and maintained these concentrations for at least 8 hr.

Similar effects were noted with tablets derived from sustaining Matrix B. Tablet VIII performed *in vivo* essentially the same as Tablet IV, while Tablets VI and VII, with higher matrix–aspirin ratios, both displayed slower rates of aspirin release.

The alliance of *in vitro* and *in vivo* techniques proved to be a powerful combination in this investigation. Although *in vitro* studies were unable to provide absolute values for *in vivo* performance, the qualitative picture was maintained. Those tablets which released their aspirin swiftly *in vitro* (I and II) proved, *in vivo*, to be indistinguishable from nonsustained aspirin. As the rate of aspirin release *in vitro* was decreased, either by increasing the amount of restraining matrix or by increasing tablet hardness, the tablets exhibited sustained release over longer periods *in vivo*. Most interestingly, Tablets IV and VIII, although of different restraining matrices, had essentially identical rates of aspirin release *in vitro*, and the time course of plasma salicylate concentrations from these tablets was virtually identical. The entirely artificial *in vitro* rate of release of aspirin from the tablet into dilute hydrochloric acid thus proved to be a reliable guide to tablet performance *in vivo*. *In vitro* release rates were therefore used in the selection of tablets for *in vivo* studies, and finally in the quality control of the production in quantity of Tablets IV and VIII.

Tablets IV and VIII represented the successful attainment of the goal of this study. Both of these tablets, in a single dose of 975 mg., rapidly achieved plasma salicylate concentrations of about 30 mcg./ml., and maintained those concentrations for a period of 8 hr. Either formulation eliminated the need for frequent aspirin ingestion, or of plasma salicylate concentrations above those required for therapeutic effects. The individual plasma salicylate concentrations in subjects receiving Tablet VIII [the tablet in which aspirin showed excellent stability (8)] are shown in Fig. 4. Chronic administration of Tablet VIII (2 tablets = 975 mg. aspirin, every 8 hr. for 56 hr.) resulted in relatively constant plasma salicylate concentrations at all times during treatment. These findings will be reported in detail in a subsequent paper (8).

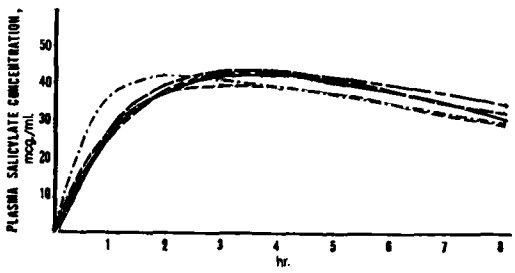

Fig. 4—Individual plasma salicylate concentrations achieved following oral administration of 650 mg. aspirin as sustained Tablet VIII.

SUMMARY

The development of several sustained-release aspirin tablets, which rapidly achieve and maintain constant plasma salicylate concentrations over 8 hr., is described. The tablets are two-layered, consisting of 162.5 mg. aspirin in a rapid-release layer, together with 325 mg. aspirin in a sustained-release layer. Carnauba wax, in combination with soluble extenders, was used as the restraining agent. It was found that the *in vitro* rates of aspirin release into acid media showed excellent correlation with the observed *in vivo* sustained characteristics. One of the experimental sustained-release aspirin tablet gave constant plasma salicylate concentrations on chronic administration.

REFERENCES

(1) Nelson, E., "Remington's Practice of Pharmacy," 12th ed., Mack Publishing Co., Easton, Pa., 1961, Chap. 38.
(2) Fuller, H. L., and Kassel, L. E., *Antibiot. Med. Clin. Therapy*, **3**, 322(1956).
(3) De Kornfield, T. J., Lasagna, L., and Frazier, T. M., *J. Am. Med. Assoc.*, **182**, 1315(1962).
(4) Cronk, G. A., *New Engl. J. Med.*, **258**, 219(1958).
(5) Sadove, M. S., and Schwartz, L., *Postgrad. Med.*, **24**, 183(1958).
(6) Brodie, B. B., Udenfriend, S., and Coburn, A. F., *J. Pharmacol. Exptl. Therap.*, **80**, 114(1944).
(7) Wagner, J. G., *J. Pharm. Sci.*, **50**, 359(1961), and references therein.
(8) Wiseman, E. H., in preparation.

Keyphrases

Aspirin—sustained-release tablets
Sustained-release tablets—double layer
Plasma concentration—aspirin, sustained release
Dissolution—aspirin, sustained release
UV spectrophotometry—analysis