mole. This value along with the predicted transition temperature gave a value for the entropy difference equal to 4.75 e.u.

DISCUSSION

The method developed in this study to determine solubility of rapidly reverting polymorphic states was shown to work very well for sulfathiazole II. Even though the II→I reversion is rapid enough to preclude equilibrium measurement, it is sufficiently slow to allow use of this method. However, it is conceivable that reversions in other systems can be so rapid that this method will not be applicable. Thus, in systems where one form may be 10 times more soluble, the supersaturation obtained in the boundary layer may be such that instantaneous crystallization of less soluble forms will result.

The method has other applications. It can be used to measure rapidly the effect of nucleation and crystallization inhibitors in reverting systems. It can also be used for studying dissolution mechanism for systems that dissolve through acid-base reaction. It may also have value for studying the other factors influencing the dissolution process. More data will be forthcoming to test the general applicability of this method.

CONCLUSIONS

A method suitable for the rapid determination of solubility has been developed and used to obtain solubility and thermodynamic data for sulfathiazole II. The transition temperature predicted from these data was confirmed by an independent experiment.

REFERENCES

(1) Mullins, J. D., and Macek, T. J., THIS JOURNAL, **49**, 245(1960).
(2) Almirante, L., DeCarneri, I., and Coppi, G., *Farmaco Pavia Ed. Prat.*, **15**, 471(1960).
(3) Higuchi, W. I., Lau, P. K., Higuchi, T., and Shell, J. W., THIS JOURNAL, **52**, 150(1963).
(4) Higuchi, T., and Shefter, E., "Problems Related to Increasing Drug Solubility," Symposium, scientific Section, A.PH.A., Las Vegas meeting, 1962.
(5) Niebergall, P. J., and Goyan, J. E., THIS JOURNAL, **52**, 29(1963).
(6) Nernst, W., *Z. Physik. Chem. (Leipzig)*, **47**, 52(1904).
(7) Parrott, E. E., Wurster, D. E., and Higuchi, T., THIS JOURNAL, **44**, 269(1955).
(8) Nelson, E., *ibid.*, **46**, 607(1957).

Sustained-Release Aspirin Tablet Using an Insoluble Matrix

By MAHENDRA S. VORA, ARTHUR J. ZIMMER, and PAUL V. MANEY

The mode of administering drugs in a sustained-release form has recently assumed considerable importance in the pharmaceutical industry. Various resins, plastics, and polymers were investigated in this study. Polyvinyl chloride was selected as the base for the insoluble matrix. Evaluation of the sustained-release aspirin tablet was by *in vitro* and *in vivo* methods. Evidence is presented that the *in vivo* release rates provide a uniform blood level over a predictable period of time.

SUSTAINED-RELEASE tablets may provide the desired release rates by employing one of several techniques (1): (*a*) compressing coated pellets into a soft matrix, (*b*) mixing several granulations (each containing different retarding agents), (*c*) combining different layers of sustained-release granules, (*d*) forming an insoluble complex by ion-exchange methods, and (*e*) distributing medication in fatty bases. Oral sustained-action preparations are described in a Swedish patent (2) which outlines the use of synthetic resins and polymers for the purpose of imparting sustained-release properties to various drugs.

A comprehensive publication "Formulation and Experimental Evaluation of Oral Sustained Release Medication Based on the Principle of Delayed Diffusion," by Simoons (3), has recently been released. This paper advocates the use of several components to obtain the desired release rate.

A recent study by Levy (4) indicated that aspirin is rapidly absorbed from all parts of the gastrointestinal tract. Thus, aspirin can serve as an excellent tracer to assess the effect of certain formulation and dosage form characteristics upon absorption rate. It is understood that other drugs may give different results with these formulations.

Various *in vitro* methods for the evaluation of sustained-release products indicated that the use of radioisotopes could be of value (5). In this work an attempt was made to incorporate aspirin with the resin polyvinyl chloride, then to prepare a two-layer product—one layer to give immediate and the other time-delayed release.

The use of *in vitro* methods of testing by de-

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TABLE I.—RELEASE OF ASPIRIN BY ROTATING BOTTLE METHOD[a]

Simulated Fluid	pH	Time	Mean Av., mg.	Mean, % Release	Mean Cumulative
Gastric	1.5	1 hr.	312	31.6	31.6
Intestinal	4.5	1 hr.	155	15.7	47.3
Intestinal	6.9	2 hr.	230	23.4	70.7
Intestinal	6.9	1 hr.	110	11.15	81.85
Intestinal	7.2	2 hr.	122	12.40	94.25
Intestinal	7.5	1 hr.	33	3.35	97.60
Intestinal	7.5	45 min.	8	.810	98.41

[a] Figure 1 and Table I show averages of 10 determinations.

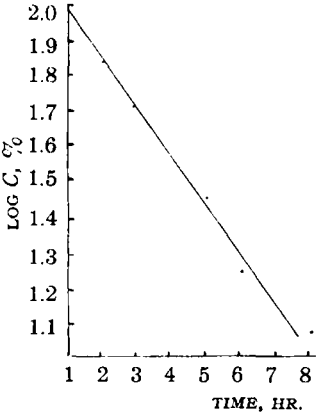

Fig. 1.—Linear relationship between log C (residue) and time.

termining the amount of drug released in simulated gastric juices is of questionable value in correlating actual performance in man. However, the results obtained justify the use of *in vitro* methods as a preliminary study. The value of the *in vitro* tests are considerably enhanced by adequate *in vivo* studies.

In this work we have compared three *in vitro* analytical procedures (one chemical and the other two using radioactive tracers) and determined pH effects before using *in vivo* testing.

In producing a sustained-release product, the objective should be to provide the desirable release rate which is independent of the many aforementioned factors and to develop suitable *in vivo* and *in vitro* procedures.

PHYSIOLOGICAL CONSIDERATIONS

Attempts to explain the physiological factors which determine the attainment of a therapeutic drug level in the blood and tissues have been published (5–8). The rate at which a substance enters the blood stream must be constant and continuous, so that the amount absorbed per unit time would effectively control the concentration level. In Wagner's review and several other papers the various factors affecting absorption in the gastrointestinal tract have been covered (9–12).

In vivo studies conducted in connection with the study of enteric coated tablets have shown that some tablets have remained in the stomach for 8 hours or more before passing into the intestinal tract. On the other hand, it was shown that some tablets passed into the intestinal tract within 15 minutes (13).

The consideration of the many physiological variables that a sustained-release product must encounter while releasing the drug on a predetermined basis presents a problem that may never be completely resolved. Our objective in producing a sustained-release product was to provide a desirable release rate, independent of the environmental conditions of the gastrointestinal tract, and provide suitable testing procedures.

EXPERIMENTAL

Materials.—Polyethylene, ethylcellulose, zein, polyvinyl chloride,[1] aspirin (No. 80 mesh), and isopropyl alcohol.

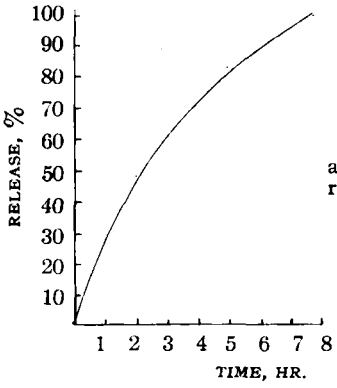

Fig. 2.—Percentage of aspirin tablet released *vs.* time.

TABLE II.—RADIOISOTOPE[a] EVALUATION OF RELEASE RATE[b]

Simulated Fluid	pH	Time, min.	Av. Counts	Total % Released
Gastric	1.5	30	1890	9.95
Gastric	1.5	60	3600	18.95
Intestinal	4.5	30	1575	27.25
Intestinal	4.5	60	3690	38.35
Intestinal	6.9	30	1680	47.20
Intestinal	6.9	60	3810	58.35
Intestinal	6.9	90	5400	66.75
Intestinal	6.9	120	6600	73.05
Intestinal	6.9	30	1230	79.50
Intestinal	6.9	60	2100	84.10
Intestinal	7.2	30	505	86.75
Intestinal	7.2	60	975	89.23
Intestinal	7.2	90	1260	90.75
Intestinal	7.2	120	1950	94.35
Intestinal	7.5	30	225	95.53
Intestinal	7.5	50	450	96.70

[a] Radioisotope used was S^{35}-sodium sulfate. [b] Figure 2 and Table II show averages of 10 determinations.

Equipment.—Stokes modified BB2 rotary tablet machine, Stokes model F tablet machine, Twin-Shell dry blender, Tracer/Matic scale and gas flow detector model SC73, Beckman model B spectrophotometer, Stokes model 43A oscillating granulator, Day model 71989 mixer, and Strong-Cobb hardness tester.

Preparation of Tablets.—The procedure was to prepare a two-layer tablet which consisted of the A layer and the B layer. The A layer consisted of 640.0 mg. of aspirin and 90.0 mg. of polyvinyl chlo-

[1] Supplied as Opalon by Monsanto Chemical Co., St. Louis, Mo.

TABLE III.—COMPARISON OF CHEMICAL AND S^{35} RADIOISOTOPE METHODS OF RELEASE RATE[a]

Simulated Fluid	pH	Time	Chemical Process Av. in mg.	Chemical Process Cumulative %	Radioisotope Total Av. Counts	Radioisotope Cumulative %
Gastric	1.5	1 hr.	120	18.7	3600	18.9
Intestinal	4.5	1 hr.	125	38.3	3690	38.25
Intestinal	6.9	2 hr.	195	68.7	6600	73.0
Intestinal	6.9	1 hr.	90	82.7	2100	84.2
Intestinal	7.2	2 hr.	72	94.2	1950	94.5
Intestinal	7.5	50 min.	17	96.6	450	96.7

[a] Figure 3 and Table III show averages of 10 determinations.

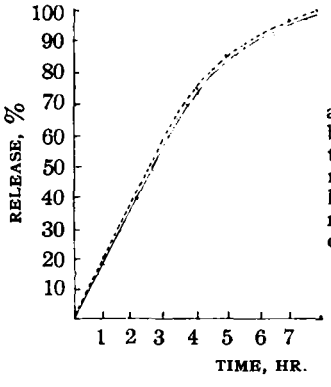

Fig. 3.—Comparative results of Tables II and III with the chemical method (broken line) and the S^{35} radioisotope method (solid line).

ride for the sustained-release portion. For the *B* layer, 320.0 mg. of aspirin (10% starch granulation) was compressed on the *A* layer. The *A* layer granulation was prepared by mixing the polyvinyl chloride and the aspirin in the Twin-Shell dry mixer for 20 minutes, and then granulating in the Day mixer, using 200.0 ml. of isopropyl alcohol for each kilogram of the described mixture. The dry granulation was passed through a No. 12 screen, 0.3% magnesium stearate was added as the lubricant, and the dry granulation was then compressed on a Stokes model BB2 modified tablet machine, using 7/16-in.-diameter punch at a pressure of 6 to 8 Kg.

EVALUATION

In Vitro Evaluation of Release Rate

Equipment.—Rotating bottle apparatus as described by Souder and Ellenbogen (14), 75.0-ml. cylindrical bottles with plastic screw cap, U.S.P. simulated gastric and intestinal fluid, ferric nitrate reagent (1% ferric nitrate in 1% nitric acid), 10% potassium hydroxide solution, 6 *N* hydrochloric acid solution, Beckman model B spectrophotometer, and pH indicator papers were employed.

Procedure.—One tablet with 60.0 ml. of simulated gastric fluid at pH 1.5 was placed in a 75.0-ml. bottle (described above) and rotated in the apparatus at 40 r.p.m. at 37 ± 2° for 1 hour. The liquid was removed (leaving the undissolved core in the bottle), placed in 100.0-ml. volumetric flask; the bottle was rinsed with 15.0 ml. of distilled water which was added to the contents of the flask.

Simulated intestinal fluid (60.0 ml.) at pH 4.5 was placed in the same bottle (containing the core) and rotated for 1 hour. The fluid was collected as described above.

Simulated intestinal fluid (60.0 ml.) at pH 6.9 was placed in the bottle and rotated for 2 hours. The fluid was collected as before.

Simulated intestinal fluid (60.0 ml.) at pH 6.9 was placed in the bottle and rotated for 1 hour. The fluid was collected as before.

TABLE IV.—COMPARISON OF CHEMICAL AND C^{14} ISOTOPE METHODS OF RELEASE RATE[a]

Simulated Fluid	pH	Time	Chemical Process Av. mg.	Chemical Process Cumulative %	Radioisotope Total Av. Counts	Radioisotope Cumulative %
Gastric	1.5	1 hr.	103	16.1	8000	16.6
Intestinal	4.5	1 hr.	100	31.7	7000	31.2
Intestinal	6.9	2 hr.	167	57.8	12000	56.4
Intestinal	6.9	1 hr.	75	69.5	5200	67.0
Intestinal	7.2	2 hr.	112	87.0	7900	83.5
Intestinal	7.5	1 hr.	32	92.0	2600	89.0
Intestinal	7.5	45 min.	34	97.2	2800	95.0

[a] Table IV and Fig. 4 show averages of 10 determinations.

Experimentally, 1.0% ethylcellulose in acetone solution for granulating the materials in the *A* layer, instead of the isopropyl alcohol, provided a release rate of longer duration in the tablet described above. The use of 15% zein solution in isopropyl alcohol as the granulating agent in the preparation of the *A* layer provided a release rate of shorter duration than the ethylcellulose granulation. Substituting polyethylene (No. 80 mesh) for the polyvinyl chloride in the same proportion in the matrix provided a sustained-release tablet with the desired release rate when tested *in vitro*. The scope of this study permitted only detailed experiments on the formulation containing the polyvinyl chloride as the insoluble matrix.

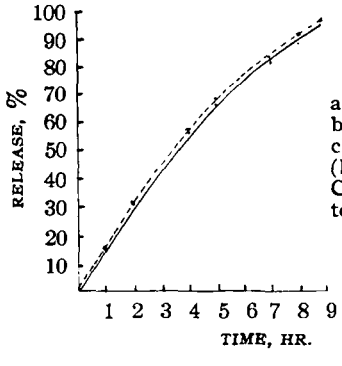

Fig. 4.—Comparative results of Table IV with the chemical process (broken line) and C^{14} aspirin radioisotope (solid line).

Simulated intestinal fluid (60.0 ml.) at pH 7.2 was placed in the bottle and rotated for 2 hours. The fluid was collected as before.

Simulated intestinal fluid (60.0 ml.) at pH 7.5 was placed in the bottle and rotated for 1 hour. The fluid was collected as before.

Simulated intestinal fluid (60.0 ml.) at pH 7.5 was placed in the bottle and rotated for 45 minutes. The fluid was collected as before.

The total salicylate of each volumetric flask was determined by the method of Pankratz and Bandelin (15).

Table I shows the *in vitro* release of the aspirin in the simulated gastric and intestinal fluid. Figure 1 explains the linear relationship between the percentage log *C versus* time. Figure 2 represents percentage release *versus* time.

In Vitro Evaluation Using Soluble Isotope S^{35}

Equipment.—Tracer Laboratories, Inc., Versamatic II scale with a Geiger-Müller tube end window detector, 1-in. stainless-steel planchets, infrared lamp, and Stokes model F single punch tablet machine.

Procedure.—Sixty-four grams of No. 80 mesh aspirin powder was mixed thoroughly with S^{35} radioisotope solution containing 1,900,000 total counts. The mixture was dried under an infrared lamp and mixed with 8.0 Gm. of polyvinyl chloride. It was then granulated with isopropyl alcohol, passed through a No. 12 mesh screen again, lubricated with 0.3 Gm. magnesium stearate, and compressed on a Stokes model F single punch tablet machine using 7/16-in. diameter punch at a pressure of 6 to 8 Kg. The tablets were compressed to 720 mg., giving approximately 19,000 counts per tablet.

Evaluation.—As stated in the chemical process, this core was rotated with 60.0 ml. of simulated gastric and intestinal fluid. The fluid was changed at the intervals shown in the chemical process (13). Every 30 minutes, 0.4 ml. fluid was withdrawn and the same amount of the fluid was replaced. Samples were mounted on stainless-steel planchets and a drop of 2% sodium sulfosuccinate solution was used to spread them evenly. Drying of the samples was carried out under the infrared lamp. The counts per 10 minutes were determined using the Tracer/-Matic scale with the Geiger-Müller tube detector.

Table II shows the average count based on 30-minute intervals and the total percentage released over a period of 8 hours. Table III represents the comparison of the described chemical determination and the S^{35} radioisotope experiment. Each experiment shows the cumulative percentage release in the simulated gastric and intestinal fluid over the period of approximately 8 hours. Figure 3 represents the comparative results of Tables II and III.

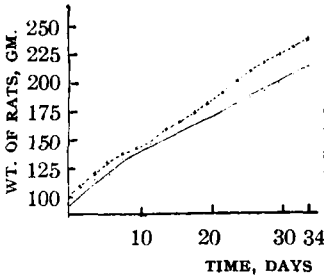

Fig. 5.—Toxicity study showing comparative growth rate of test animals (solid line) and control animals. Average polyvinyl chlorine consumed 9.9 Gm./2 days.

TABLE V.—SALICYLATE CONTENT (MCG./ML.) OF PLASMA WITH SUSTAINED-RELEASE TABLET

Subject	Age	Wt.	Blood Samples at Intervals of Hr. 1	4	7	10	24
1	31	160	36	52.2	69.6	69.6	6
2	30	150	89.6	85.2	67.2	67	9.6
3	31	170	65	81.6	70	67	...
4	45	188	55.2	42	30	24	18
5	28	160	50.2	52.8	66	60	46
6	29	140	65	69.6	72	72	36
7	32	150	40	60	66	...	23
8	30	150	60	72	70	50	37
9	29	165	41	41	39	45	12
10	30	160	55	62.4	64.8	64.8	...

TABLE VI.—SALICYLATE CONTENT (MCG./ML.) OF PLASMA WITH REGULAR ASPIRIN TABLET

Subject	Age	Wt.	Blood Samples at Intervals of Hr. 1	4	7
1	27	160	42	32.4	24
2	26	140	55.2	48.0	24
3	30	180	32.4	48.0	16.8
4	31	160	48.0	37.2	24.0
5	30	163	48.0	50.4	42.0
6	23	115	67.2	48.0	22.0

In Vitro Evaluation Using Insoluble Isotope Aspirin C^{14}

Procedure.—Aspirin radioisotope (activated at carboxyl group C^{14}) was dissolved in 90.0 ml. of isopropyl alcohol which contained 5.0 Gm. aspirin. The alcohol was evaporated with the infrared lamp. The triturate represents 1400 counts per minute/mg.

A 2570-mg. quantity of the triturate was mixed with 45.730 Gm. of aspirin. Enough of the alcohol was added to make a thin slurry. It was mixed thoroughly, 6.75 Gm. of polyvinyl chloride added, and the triturate was mixed again; the alcohol evaporated.

This material was then granulated and prepared into tablets as described in the first step of this experiment.

Evaluation.—The procedure for evaluation was identical to the one described using the soluble isotope, except the gas flow counter was used and the counting time was measured as shown in Table IV and Fig. 4. Table IV presents a comparison of the percentage release of the described chemical process and that released from C^{14} isotope. Plotting these results (Fig. 4) shows nearly identical curves.

Toxicity Study on Rats

Although there are reasons to believe that high molecular weight compounds, such as polyvinyl chloride, are physiologically inert, we considered it advisable to investigate the toxicity of the polyvinyl chloride used in this study.

A group of 16 Sprague-Dawley rats was maintained for 34 days on a diet of laboratory chow.[2] Nine of the rats were on a diet of polyvinyl chloride and seven were fed the regular laboratory chow. They were weighed every other day, and a record of the food consumed was recorded. There were no significant effects, either on the growth rate or the appetite, of the rats being fed the polyvinyl chloride.

Upon completion of the feeding tests, five of the

[2] Ralston-Purina Co., St. Louis, Mo.

TABLE VII.—SALICYLATE CONTENT (MCG./ML.) OF PLASMA WITH SIX 0.32-GM. REGULAR ASPIRIN TABLETS

Subject	Age	Wt.	Blood Samples at Intervals of Hr. 1	4	6	7	10.5	13.5	24
1	30	160	126	100	100	174	175	153	90
2	29	140	156	105	100	...	185	186	95
3	29	165	102	84	80	125	156	140	82
4	30	150	110	108	90	145	168	140	...

rats receiving polyvinyl chloride were sacrificed, and a gross pathological examination was made on the liver, kidneys, G. I. tract, heart, spleen, and lungs. No abnormalities were observed

These data correspond with a much more detailed study on the toxicity of a mixture of 95% polyvinyl chloride and 5% polyvinyl acetate. The scope included feeding tests on 150 rats over a period of 400 days (16).

Figure 5 illustrates the growth rate and the average consumption of polyvinyl chloride in the test animals.

Evaluation In Vivo

Sixteen healthy adult males served as test subjects. Their weight and ages are listed in Tables V, VI, and VII. The subjects were divided into three groups *A*, *B*, and *C*. In group *C*, the subjects participated in both the *A* and *C* groups.

The protocol for group *A* was: (*a*) 10 subjects selected had no salicylates for 48 hours, (*b*) overnight urine was emptied from the bladder and determined for the presence of salicylates, (*c*) two 960-mg. sustained-release aspirin tablets were swallowed with 100 ml. of water, and (*d*) blood and urine samples were collected at 1, 4, 7, 10, and 24 hours (Table V).

The protocol for group *B* was: (*a*) six different subjects were selected and followed the procedure as above, (*b*) same as above, (*c*) each subject swallowed two 0.32-Gm. aspirin tablets whole with 100 ml. of water, and (*d*) blood samples were collected (Table VI) at 1, 4, and 7 hours.

The protocol for group *C* was: (*a*) four subjects were selected and followed the procedure as above, (*b*) same as above, (*c*) each subject swallowed six 0.32-Gm. whole aspirin tablets with 200 ml. of water, (*d*) blood samples were collected at 1, 4, 6, 7, 10.5, 13.5, and 24 hours. (*e*) At the end of 6 hours, a second dose of six 0.32-Gm. aspirin tablets was taken with 200 ml. of water (Table VII).

Each of the above tests was conducted 4 days apart. All subjects were denied food but permitted water for 2 hours after initiation of tests.

Analytical Methods

Salicylates in the urine and blood were determined by methods outlined by Trinder (17). Figure 6

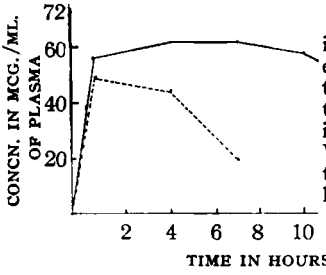

Fig. 6—Comparison of plasma levels (Table V) obtained with sustained-release (solid line) and (Table VI) regular aspirin tablets (broken line).

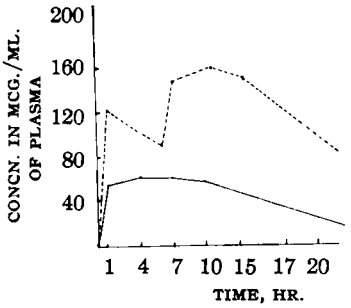

Fig. 7—Comparison of plasma levels (Table V) obtained with sustained - release (solid line) and (Table VII) regular aspirin tablets (broken line).

illustrates graphically a comparison of the micrograms per milliliter plasma level interpreted from results of groups *A* and *B*. Table VII outlines the results from group *C*. Figure 7 shows the comparative results interpreted from groups *A* and *C*.

RESULTS AND DISCUSSION

The use of polyvinyl chloride as described in the preparation of sustained-release tablets appears to have desirable characteristics. A method for the tableting is presented that will give reproducible results when tested *in vitro*. In the development of this sustained-release aspirin, our experiments included the use of polyethylene, ethylcellulose, zein, and polyvinyl chloride[1] with varying degrees of success. The scope of this project permitted only a detailed study of the agent polyvinyl chloride. The information obtained from this work confirms reports (18) of earlier investigations to the extent that physical and chemical properties of each drug require a particular type of matrix in order to provide the desired sustained-release characteristics. The amount of pressure exerted in the compression of the tablets was important.

The salicylate plasma level, according to the data presented with the sustained-release tablet, was uniform for over 10 hours. There was a significant amount of salicylate in the plasma after 24 hours. On the other hand, the urine excretion studies indicated a significant amount of salicylates present after 36 hours.

In vivo studies indicated that with the regular commercial aspirin tablets a peak level was reached within 1 hour and then dropped rapidly. When a massive dose (1.92 Gm.) was administered, the blood plasma level reached a high concentration within 1 hour, then dropped rapidly. A second identical dose was given at the end of 6 hours, and the plasma level showed the cumulative effect for a period of 6 hours, then gradually dropped. Figure 7 shows the comparative effect on plasma level by the 1.92 Gm. of aspirin in sustained-release form and the same dose with commercial aspirin tablets.

SUMMARY

A method for the preparation of a sustained-re-

lease aspirin tablet was developed. The tablets were evaluated by three methods *in vitro*. Absorption studies were made comparing the salicylate plasma level from the sustained-release tablets with that obtained from the regular commercial aspirin tablets.

The base polyvinyl chloride appears to be nontoxic according to extensive data available. Further *in vivo* evaluation by a double blind technique would be valuable in predicting the clinical efficacy of the developed sustained-release tablet.

REFERENCES

(1) "Remington's Practice of Pharmacy," 12th ed., Mack Printing Co., Easton, Pa., 1961, p. 499.
(2) Swedish patent 808,014.
(3) Simoons, J. R. A., "Oral Sustained Release Medication," Drukkerij Wed. G. Van Soest N. V., Amsterdam, 1962.
(4) Levy, G., THIS JOURNAL, **50**, 388(1961).
(5) Lazarus, J., and Cooper, J., *ibid.*, **50**, 716(1961).
(6) Teorell, T., *Arch. Intern. Pharmacodyn.*, **57**, 205(1937).
(7) Boxer, G. E., and Jelinek, V. C., *J. Pharmacol. Expll. Therap.*, **92**, 226(1948).
(8) Swintosky, J. V., Bondi, A., Jr., and Robinson, M. J., THIS JOURNAL, **47**, 753(1958).
(9) Wagner, J. G., *ibid.*, **50**, 359(1960).
(10) Hogben, C. A. M., Shanker, L. S., Tocco, D. J., and Brodie, B. B., *J. Pharmacol. Expll. Therap.*, **120**, 540(1957).
(11) Truitt, E. B., Jr., and Morgan, A. M., *Toxicol. Appl. Pharmacol.*, **2**, 237(1960).
(12) Weikel, J. H., Jr., and Lish, P. M., *Arch. Intern. Pharmacodyn.*, **119**, 398(1959).
(13) Maney, P. V., and Kuever, R. A., THIS JOURNAL, **30**, 276(1941).
(14) Souder, J. C., and Ellenbogen, W. C., *Drug Stds.*, **26**, 77(1958).
(15) Pankratz, R. E., and Bandelin, F. J., THIS JOURNAL **41**, 267(1952).
(16) Mellon Institute, Special Report "Vinylite" Resin VYNU to Rats (1947).
(17) Trinder, T., *Biochem. J.*, **57**, 30(1954).
(18) Lazarus, J., and Cooper, J., *J. Pharm. Pharmacol.*, **11**, 275(1959).

Rheology and Suspension Activity of Pseudoplastic Polymers I

Quantification of Pseudoplastic Viscosity as a Second Order Function of the Rheogram and the Relationship of This Parameter to Concentration

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The apparent viscosity (pseudoplastic viscosity) was determined for a number of natural and synthetic gums in aqueous solution, based on flow curves obtained with a multiple point instrument. The power expression $F^N = n'G$ was used to calculate the apparent viscosity from the rheograms. The relationship between the resulting apparent viscosities and the concentrations of the suspending agents studied which were required to produce these viscosities was determined and reduced to the mathematical expression, $n' = e^{KC+b}$, where n' is apparent viscosity, C is concentration, and K and b are material constants. The usefulness of the concentration–apparent viscosity relationship to formulation and product development is discussed.

TWO APPROACHES to the attainment of suspension stability have been discussed recently. Martin and Haines (1) have suggested that controlled flocculation is an approach to the problem of suspension stability, and Samyn (2) suggests that suspensions may be stabilized by preventing phase separation through the careful selection of the rheological properties desired in the suspension media. To achieve this latter goal, Samyn advocated the use of a combination of pseudoplastic and plastic suspending agents in the formulation of suspensions.

A knowledge of the flow properties and rheological parameters of pharmaceutical suspending media is of interest from at least three stand points: (*a*) effect on suspension stability, *i.e.*, ability to retain insoluble particles in a suspended or substantially suspended easily redispersed state; (*b*) effect on the flow, pourability, and measurability of the final product required for pharmaceutical use; and (*c*) effect on process design and methods of manufacture in large scale production.

In practically all industrially made pharmaceutical suspensions, including flocculated systems, suspending agents of some type are used to stabilize the suspension product. The mucilages of natural and synthetic gums, which include a large majority of suspending agents, are pseudoplastic. However, for reasons of convenience, cost, or due to a lack of knowledge of a better approach, these mucilages are very often evaluated in pharmaceutical practice using a single

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