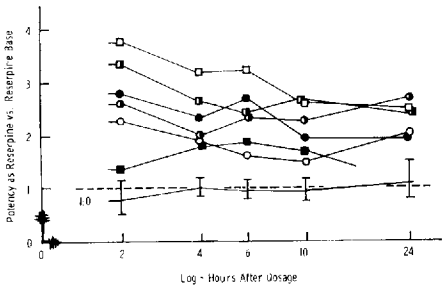

Fig. 2.—Variation with time of the oral potencies of various reserpine–desoxycholic acid molar coprecipitates as compared to reserpine base as a standard. Key: □, 1:16; ◨, 1:32; ●, 1:8; ◑, 1:4; ○, 1:2; ■, 1 + 16; I, 1:0.

tion of reserpine as well as increasing the potency. Considering the 95% confidence limits of potency reported in Table II, reserpine administered as the 1:16 combination behaves equivalent to at least 1.8 mg. of reserpine base (+24 hr.) and possibly equivalent to as much as 5.0 mg. of reserpine (+2 hr.).

A molar equivalent physical mixture of reserpine and desoxycholic acid (1 + 16) produced a slower onset of the period of maximum enhancement (+4–6 hr.), and the potencies were significantly less ($P \leq 0.001$) than those reported for the 1:16 intimate combination. In all cases where calculation was possible, the 1 + 16 mixture was significantly more potent than reserpine base alone (observed P: 0.025–0.05 at +2 hr. and ≤ 0.001 at +4, 6, and 10 hr.).

While there is debate as to whether palpebral ptosis is a peripheral or central manifestation of reserpine-like activity (4–6), this characteristic symptom does indicate absorption of reserpine from the gastrointestinal tract. Coprecipitates of reserpine and desoxycholic acid both increase the potency of reserpine and produce a more rapid onset of reserpine-like activity when administered orally. No attempt has been made here to define the exact physical/chemical nature of the reserpine–desoxycholic acid combination.

REFERENCES

(1) Lach, J. L., and Pauli, W. A., *J. Pharm. Sci.*, **55**, 32 (1966).
(2) Rubin, B., Malone, M. H., Waugh, M. H., and Burke, J. C., *J. Pharmacol. Exptl. Therap.*, **120**, 125(1957).
(3) Bliss, C. I., and Calhoun, D. W., "An Outline of Biometry," Yale Co-Operative Corp., New Haven, Conn., 1954.
(4) Malone, M. H., and Roth, R. H., Jr., *J. Pharm. Sci.*, **51**, 345(1962).
(5) Aceto, M. D., and Harris, L. S., *Toxicol. Appl. Pharmacol.*, **7**, 329(1965).
(6) Fielden, R., and Green, A. L., *J. Pharm. Pharmacol.*, **17**, 185(1965).

Utilization of Hydrophilic Gums for the Control of Drug Release from Tablet Formulations I. Disintegration and Dissolution Behavior

By H. E. HUBER, L. B. DALE*, and G. L. CHRISTENSON

Tablet formulations and data to illustrate rate of drug dissolution and tablet volume decay during *in vitro* disintegration tests are presented. It was found that tablets prepared by compression of hydrophilic gums, excipients, and drug in specified ratios result in prolonged release of drug. Assay of simulated gastric and intestinal fluids from *in vitro* tests show the drug to be released at essentially a uniform rate after an initial hydration phase. The mechanism of prolonged release is proposed as a combination of drug diffusion from, and attrition of, a dynamically changing gel barrier at the tablet periphery.

ORAL CONTROLLED release dosage forms have been recognized as a therapeutically significant advance in dosage form design, whereby a more uniform and prolonged tissue concentration of drug substance may be achieved. The methods used for obtaining prolonged action have been reviewed by Ballard and Nelson (1) and Parrott (2) and various systems are described, whereby an initial therapeutic dose is released followed by a continual release of additional drug substance over a prolonged period of time.

In 1962, a system was developed by The Wm. S. Merrell Co. (3) describing a novel approach for the control of drug substance release rate from tablet formulations. The method described involves mixing a medicinal agent or agents with certain nondigestible, hydrophilic gums and compressing the mixture into tablets. When such a tablet is exposed to water or digestive fluids, a rapid release of drug substance from the dosage form to the dissolution medium is initially observed. However, hydration and gelation of gum at the tablet–liquid interface also occurs to form a viscous gel barrier. The remaining drug substance is then released at a much slower rate that apparently depends on diffusion from and/or attrition of the gel barrier. The nature of the phenomenon is illustrated by Fig. 1, which shows, in cross section, the appearance of such a tablet after exposure to solvent. It can be seen that the intact tablet core is surrounded by a gel barrier layer of significant size.

The present communication is concerned with studies that were conducted to obtain preliminary

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Fig. 1.—A bisected quinidine sulfate tablet after 1 hr. in simulated gastric fluid.

TABLE I.—INFLUENCE OF GUM CONTENT ON DISINTEGRATION TIME

Drug/gum ratio	10/1	2/1	1/1	1/4	1/16
Disintegration time, min.	105	250	450	570	650

information on the dissolution and disintegration behavior of such tablets and the influence of formulation variables on their behavior.

EXPERIMENTAL

Influence of Gum Content on Disintegration Behavior.—Six batches of tablets containing nicotinic acid and hydroxypropylmethylcellulose 4000 cps. in the ratio of 10:1, 2:1, 1:1, 1:4, and 1:16 were prepared as follows. The powders were mixed and 1% zinc stearate added as lubricant. The mixes were compressed on a $^3/_8$-in. standard cup punch to yield tablets weighing approximately 250 mg. each. Six tablets from each batch were placed in the basket of a U.S.P. modified Stoll-Gershberg apparatus. The basket was lowered into an 800-ml. beaker containing 600 ml. of simulated gastric fluid maintained at 37° ± 0.5° and the apparatus operated in the manner prescribed by the U.S.P. At the end of 1 hr. the basket was transferred to an 800-ml. beaker containing 600 ml. of simulated intestinal fluid, and the operation was continued until disintegration was complete. The time required for complete disintegration was noted.

In Vitro Drug Release Characteristics.—The *in vitro* release characteristics of two formulations were investigated.

Formula *1*	Per Tablet, mg.
Doxylamine succinate	20
Pheniramine maleate	20
Pyrilamine maleate	20
Sodium carboxymethylcellulose	640
Magnesium trisilicate	40
Stearic acid	10

The sodium carboxymethylcellulose was slugged, granulated, and mixed with the remaining powders. Magnesium trisilicate was added to act as an absorbant for the eutectic formed by the antihistamines. The mixture was compressed into $^7/_{16}$-in. tablets at 750 mg. each and a Stokes (Monsanto) hardness of approximately 16 Kg. These antihistamine tablets[1] were placed in the Stoll-Gershberg apparatus and treated as described, except that simulated intestinal fluids were changed at the end of each 2-hr. period. At various time intervals, aliquots of fluid were withdrawn, treated with sodium hydroxide solution, and extracted with 3 vol. of ether. The combined ether extracts were re-extracted with 0.1 *N* HCl and assayed spectrophotometrically for pyrilamine content. Tablets from two different batches were subjected to this study. Three determinations were made on each batch.

[1] Marketed as Tridecamine tablets, by National Drug Co., Division of Richardson-Merrell, Inc., Philadelphia, Pa.

Formula *2*	Per Tablet, mg.
Quinidine sulfate	300
Hydroxypropylmethylcellulose	150
Magnesium stearate	9

The powders were granulated with water and the granulation was ground to a coarse powder. Lubricant was added and the mix was compressed on $^7/_{16}$-in. punches to yield tablets weighing approximately 459 mg. each and a Pfizer hardness of approximately 12 Kg.

Five of these tablets were individually subjected to the release test described for antihistamine tablets. Here, however, the baskets were transferred to fresh solution at the end of each hour. An aliquot of each solution was pipeted into a volumetric flask and made to volume with 0.1 *N* HCl. The solutions were filtered and assayed spectrophotometrically for quinidine sulfate content.

Volume Decay of Tablets.—In order to demonstrate the change in volume during disintegration, quinidine sulfate tablets (disk shaped) were measured, prior to disintegration, with an Ames micrometer gauge. They were disintegrated as previously described for 1, 2, 3, 4, and 5-hr., respectively, removed from the fluids, allowed to dry, and again measured. Tablet volumes were calculated from the formula $\pi r^2 h$. A displacement method for volume determination was also done to verify the micrometer procedure. Volumes were in close agreement with the micrometer procedure.

RESULTS

Influence of Gum Content on Disintegration Behavior.—Tablets made with hydroxypropylmethylcellulose and nicotinic acid had disintegration times proportional to the per cent gum. As the gum content was increased, the disintegration time was extended. The results are given in Table I.

In Vitro Drug Release Characteristics.—Drug substance release patterns from the antihistamine tablets and quinidine sulfate tablets are shown in Figs. 2 and 3. It can be seen that in both cases, an initial rapid release of drug substance occurred. For example, approximately 26% of the pyrilamine content was released from the antihistamine formulation in 1 hr., while approximately 32% of the quinidine sulfate was released in the same time period. After the initial rapid release phase, a much slower constant rate of release occurred until about the 7th hour. It was observed at this time that the tablets were completely hydrated and proceeded to dissolve.

Volume Decay of Tablets.—Tablet volume decay data, obtained for quinidine sulfate tablets, are shown in Fig. 4. An initial rapid decay is noted during the initial period of tablet hydration in gastric fluid followed by an interim change in rate of decay when transferred to intestinal fluid. Linear decay of the dry tablet core takes place

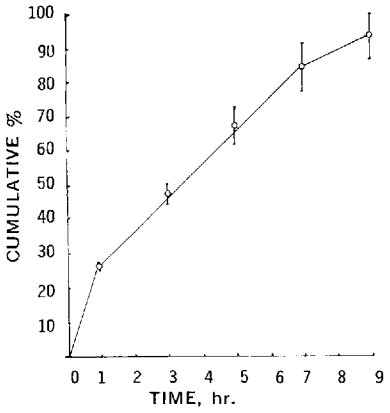

Fig. 2.—*In vitro* dissolution rate for antihistamine tablets. Average and standard deviation of cumulative per cent drug released for six baskets of six tablets.

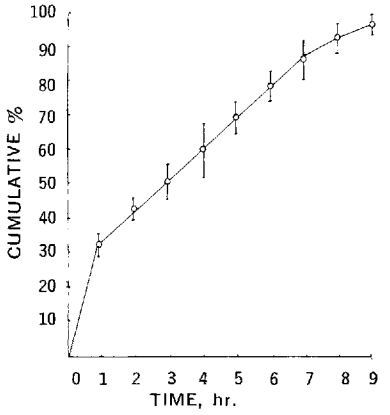

Fig. 3.—*In vitro* dissolution rate for quinidine sulfate tablets. Average and standard deviation of cumulative per cent drug released for five individual tablets.

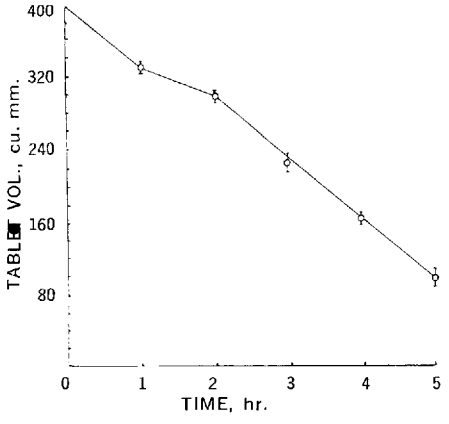

Fig. 4.—*In vitro* volume decay for quinidine sulfate tablets. Average and standard deviations for each of five baskets of six tablets run 1, 2, 3, 4, and 5 hr., respectively.

over the remaining time period until hydration is complete at approximately 7 hr. The 5-hr. sample was the last point at which a large enough dry core was available for accurate measurement.

DISCUSSION

The studies which have been described do not permit a complete elucidation of the exact mechanism involved in this approach to control of drug substance release from tablet formulations. However, the data do support the theory that hydration and gelation of the gum at the tablet–liquid interface constitute an important step in the mechanism. The existence of a gel barrier would be expected to retard drug substance release by limiting the exposure of solid drug to the dissolution liquid. Attrition of and/or diffusion from the gel barrier with concomitant formation of fresh gel could explain the constancy of release rate observed over a considerable time period.

As illustrated by the experiments with the nicotinic acid formulations, the percentage of gum in the formulation has a marked influence on the disintegration and dissolution behavior of the tablet. It should be recognized, however, that this behavior will differ, in quantitative terms, with different drugs and different gums. It has been the author's experience that the most useful gums are those which hydrate readily and rapidly at body temperature. Two examples are sodium carboxymethylcellulose and hydroxypropylmethylcellulose. The antihistamine and quinidine formulations illustrate the type of behavior observed when these gums are used. The dissolution rate patterns here are especially interesting in that a constant rate of release occurred over a considerable time period. This is in contrast to many other systems designed for controlled release where it has been found that release rate decreases as the drug substance content in the dosage form reservoir decreases.

Although no direct correlations between *in vitro* and *in vivo* behaviors of specific formulations have been attempted, it is interesting to note that Halpin (4) in his clinical investigation of the antihistamine formulation reported that the clinical response extended over a 12-hr. period. He also reported a rapid onset of activity. His observations were confirmed by Hansel (5), who reported an antihistaminic effect lasting for 12 hr. Jones *et al.* (6) using an intradermal wheal test, found that the preparation suppressed wheal size for a 12- to 14-hr. period.

The approach that has been described appears to offer attractive possibilities for sustaining the release of drug substances administered orally. The availability of many different gums, the utilization of other excipients, and the application of techniques such as multiple compression of tablets offer the possibility of varying qualitative and quantitative aspects of release rate patterns over a wide range.

REFERENCES

(1) "Remington's Pharmaceutical Sciences," 13th ed., Martin, E. W., ed., Mack Publishing Co., Easton, Pa., 1965, Chap. 41.
(2) Sprowls, J. B., Jr., "Prescription Pharmacy," 1st ed., J. B. Lippincott Co., Philadelphia, Pa., 1963, Chap. 3.
(3) U. S. pat. 3,065,143.
(4) Halpin, L. J., *Ann. Allergy*, **17**, 602(1959).
(5) Hansel, F. K., *Laryngoscope*, **69**, 1219(1959).
(6) Jones, T. L., Dale, L. B., and Christenson, G. L., *Ann. Allergy*, **17**, 878(1959).