acetate degrades significantly in the absence of water. When 0.5% water is added, the stability picture remains essentially the same, indicating that the water's contribution to degradation is offset by the partial protection it affords against solid-state oxidation. As more water is added, however, the degradation rate increases linearly with water concentration, indicating that the contribution of solid-state oxidation has plateaued and the effects of hydrolysis are becoming more evident.

The vitamin A acetate report (5) provides another example of the usefulness of the concepts and models presented in this paper. In discussing the theory behind their presentation, the authors (5) stated: "If vitamin A degrades by functional dependence of water content, then a $(1 + a)$ order reaction may be expressed as $dC_a/dt = -K \cdot C_A \cdot C^a_{H_2O}$ [their Eq. 1] where C denotes concentration and the subscripts denote vitamin A acetate and water." From their data, they reached the conclusion that the apparent value of a is 2–3, a relatively high order.

If one assumes that zero-order kinetics prevail for the water-dependent degradation (a reasonable assumption, since vitamin A acetate is relatively water insoluble), then their Eq. 1 reduces to our Eq. 1 when the value of a is unity. A slightly different interpretation of their data yields values of a that are close to unity and confirm the validity of the model in Fig. 3. That interpretation is as follows.

From the sharp break in the slope in Fig. 8, it is evident that the 0–0.5% range of water concentration is atypical. That is, their Eq. 1 assumes a continuous function and, for their system, the function can be considered continuous only between 0.5 and 2.0% added water. Therefore, the "water added" concept should, in our opinion, start from their 0.5% mark. Thus, their 0.5, 1.0, 1.5, and 2.0 values for "percent water added" should (more correctly) be taken as 0, 0.5, 1.0, and 1.5%, respectively. For example, their 1.5% is, more correctly, 1.0% (*i.e.*, 1.5 − 0.5). Recalculating their data using the corrected values of water added yields the following values for a: 85°, 0.90; 70°, 0.87; 55°, 1.45; 25°, 1.46; and 5°, 1.42. Considering the complexity of the system, experimental values of 0.87–1.46 (average = 1.2) against a theoretical value of unity is good confirmation of the validity of the model in Fig. 3.

CONCLUSION

Stability data for solid dosage forms, gathered under suitably controlled conditions, can often be successfully interpreted using the schematic models presented in Figs. 1–3.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 10, 1973, from the *Development and Control Division, Endo Laboratories, Inc., Subsidiary of E. I. du Pont de Nemours and Company, Inc., Garden City, NY 11530*

Accepted for publication June 28, 1973.

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Sodium-Ion Electrode: Continuous Monitoring of Tablet Dissolution *via* Flowing Streams

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Abstract □ The use of a continuous flowing stream apparatus to follow tablet dissolution was studied. A dissolution chamber using a commercially available filter unit was designed to follow tablet dissolution through use of either a sodium-ion electrode or a spectrophotometric analytical module. The effect of variation of flow rate on the dissolution profile and the ability of the apparatus to differentiate between the common tablet parameters of hardness and drug potency were shown.

Keyphrases □ Tablet dissolution—determination in continuous-flow equipment using sodium-ion electrode or UV spectrophotometry differentiation between parameters of hardness and drug potency □ Dissolution equipment, tablets—continuous-flow system using sodium-ion electrode or UV spectrophotometry, differentiation between parameters of hardness and drug potency □ Sodium-ion electrode system—used to determine tablet dissolution in continuous-flow system

The importance of *in vitro* testing of tablet and capsule dissolution and its relationship to drug availability are accepted facts. The correlation of *in vitro* to *in vivo* data shows the need for a versatile and flexible apparatus which, through adjustment of its parameters to the variance in dissolution profiles of different tablets, can succeed in matching such data. A second but equally important consideration is a reduction in the time and labor required for such *in vitro* analysis. By using the technique of continuous analysis in flowing streams to monitor dissolution, the entire profile can be recorded and experimental error can be reduced to a minimum.

In recent years, equipment for studying the dissolution of solid dosage forms under conditions of continuous flow has been presented. The arguments for using a continuous-flow method and the theoretical considerations involved have been documented (1, 2). These authors suggested that the continuous-flow

methodology should have sufficient flexibility to be useful in studying intrinsic dissolution characteristics of a sample while maintaining reproducibility and the ability to detect small differences in formulation.

The described apparatus differs from previously presented systems in that it allows a choice of analytical module using an inexpensive, universally available dissolution cell. A sodium-ion electrode may be mounted in a flow cell and employed as a sensor in addition to a spectrophotometric sensor as used previously. The sodium-ion electrode has limitations, some of which were documented in these laboratories (5).

The reproducibility of the apparatus, as well as its ability to detect differences in tablet hardness and to analyze and differentiate between tablets of different drug potency, is evaluated in this report.

EXPERIMENTAL

Materials—Both commercial and specially manufactured tablets were used. Only one batch number each of sodium warfarin[1], sodium butabarbital[2], and sodium bicarbonate[3] tablets was used. The sodium salicylate tablets were manufactured in these laboratories using a 16-station rotary tablet press[4] equipped with an induced die feeder. Standard concave punches [0.95 cm. (0.375 in.)] were used. These tablets were compressed from the following formulation: sodium salicylate[5], 50 mg.; fast flow lactose[6], 216.5 mg.; microcrystalline cellulose[7], 43.5 mg.; starch[8], 35.0 mg.; and stearic acid[5], 5.0 mg., to produce 350-mg. tablets. The tablets were compressed to three different hardnesses as determined by an electronic hardness tester[9]. The reported hardnesses are averages found after testing 50% of the tablets from each run.

The dissolution medium consisted of a buffer mixture (3) of potassium hydroxide[5] and dibasic potassium phosphate[5] at pH 8 with an adjusted sodium-ion concentration of 10^{-3} *M*.

Apparatus and Instrumentation—The apparatus (Fig. 1) was designed for use with either a sodium-ion electrode or UV spectrophotometer as the analytical module. The dissolution cell is a commercially available filter unit[10], using a standard 0.22-μ filter to prevent disintegrated tablet particles from leaving the cell. A peristaltic pump[11] was used to push the solvent at a constant flow rate from the reservoir through the dissolution cell and analytical system. The flow lines were made from Tygon tubing [formula B44-3, 0.15 cm. (0.06 in.) i.d.]. All flow rates were determined periodically by collecting samples of the liquid that had passed through the dissolution cell. All studies reported were carried out at ambient temperatures (25 ± 1°).

The analytical system used was either a spectrophotometer with an adapted time drive to record absorbance as a function of time or a sodium-ion electrode system with connected recorders (Fig. 1). While the use of a flow cell to hold a sodium-ion electrode was previously reported (4), Fig. 2 illustrates the unit designed to incorporate the sodium-ion electrode into the system. It consists of a cylindrical Teflon block with a horizontal channel to carry the dissolution medium past the sodium-ion and reference electrodes and on to the second analytical module or disposal vessel. Both the sodium-ion and reference electrodes are set into the block vertically such that the tip of each protrudes into the channel and no air space is left along the side or at the tip of the electrodes. A micro sodium-ion electrode was used and found to have a response equivalent to the full-size sodium-ion electrode previously reported (5). The analytical modules were connected singly or in series to the dissolution cell.

[1] Endo Laboratories.
[2] McNeil Laboratories.
[3] Lilly Laboratories.
[4] Model 216-RP Cherry-Burrell.
[5] Fisher Chemicals, Fairlawn, N. J.
[6] Foremost Dairy, San Francisco, Calif.
[7] Avicel, FMS Corp., Newark, Del.
[8] Ruger Chemical Co., Inc., Irving, N. J.
[9] Erweka Electronic.
[10] Swinnex-25, Millipore Corp.
[11] Harvard model 1201.

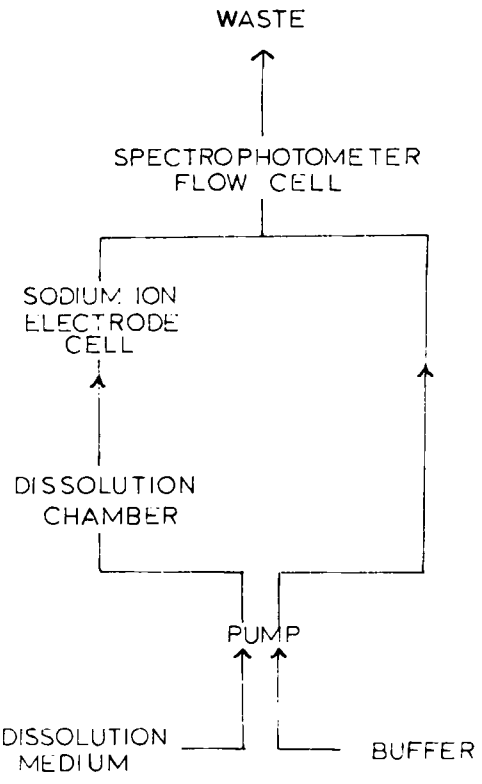

Figure 1—*Schematic representation of automated flow system.*

Samples were diluted to the analytical range of the spectrophotometer by mixing with a fixed ratio of solvent. The diluent was also used in the case of sodium butabarbital to adjust the pH to that level where the Beer–Lambert law was valid. Use of a buffered 0.001 *M* sodium-ion base solution, calibration of the sodium-ion electrode, and correlation of the sodium-ion electrode reading to spectrophotometric and atomic absorption readings were explained in a previous paper (5). Since all tablets exhibited significant differences in their dissolution profiles in the first 18 min. with a slow

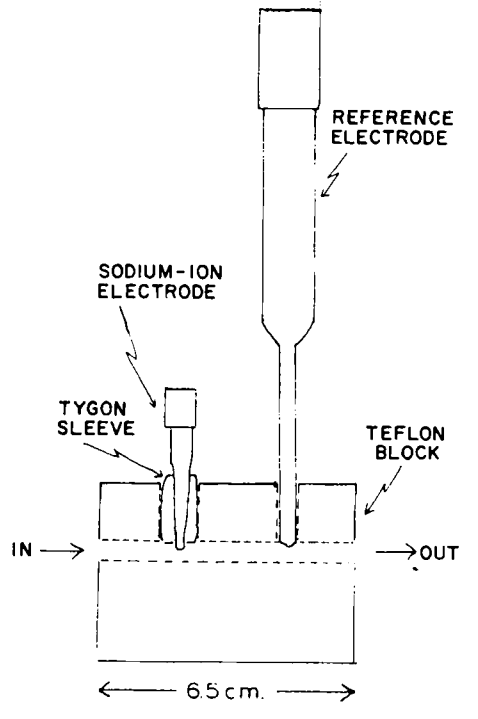

Figure 2—*Side view of sodium-ion electrode cell.*

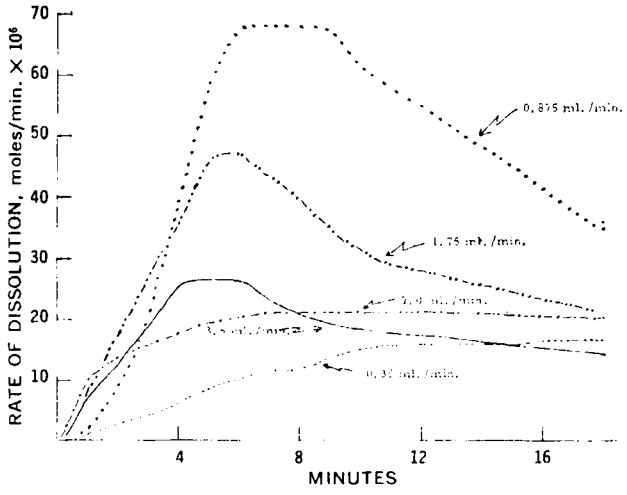

Figure 3—*Rate of dissolution of sodium butabarbital tablets at pH 8.0 as a function of flow rate.*

return to the blank concentration after that time, only the first 18 min. of each profile is presented.

Procedure—At the beginning of each tablet dissolution run, the analytical system was equilibrated to its baseline with the dissolution medium and the dissolution chamber was disassembled and dried. A weighed tablet was placed in the chamber, a new filter was set in, and the apparatus was closed. The pump was started and the changes in concentration were recorded as a function of time. The solution was discarded after being pumped through the analytical module. Variance in the rate of dissolution between tablets of the same batch was found to be comparable to the USP (6), Levy (7, 8) beaker, and magnetic basket (9, 10) methods of dissolution testing. All reported dissolution curves are the average of at least four separate determinations.

RESULTS AND DISCUSSION

Most dissolution data presented in this paper were collected using the sodium-ion electrode analytical module. However, dissolution profiles were obtained for sodium salicylate and sodium butabarbital using the spectrophotometer only and a combination of the spectrophotometer and sodium-ion electrode recorder module attached in series after the dissolution cell. The spectrophotometer produced results comparable to those seen by Tingstad and Riegelman (2). In fact, when the spectrophotometer and sodium-ion electrode recorder module were used in series to follow the dissolution of the same tablet, curves characteristic of that tablet were comparable.

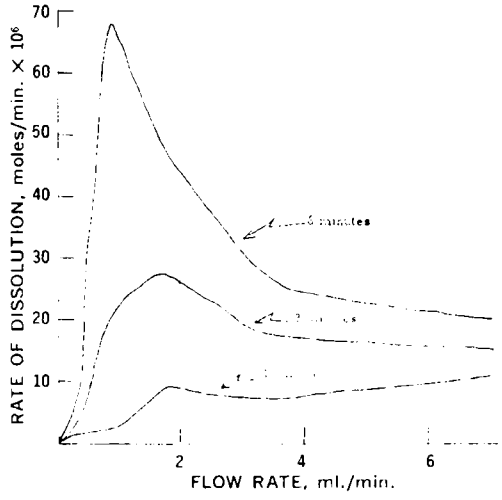

Figure 4—*Effect of flow rate on the rate of dissolution at increasing time intervals.*

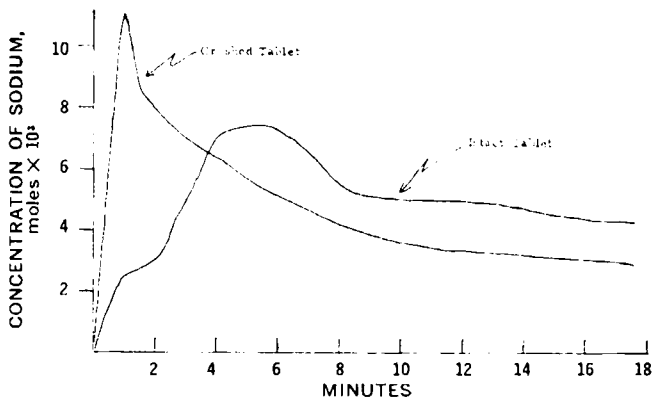

Figure 5—*Comparison of crushed and intact sodium butabarbital tablets at pH 8.0 and a flow rate of 3.5 ml./min.*

When using the continuous-flow dissolution apparatus in Fig. 1, one obtains a continuous readout of logarithm concentration of the drug in the dissolution medium *versus* time. The data can be presented in a number of ways that permit evaluation of the tablet dissolution. The obvious presentation, as previously reported (1, 2), consists of multiplying the concentration by the volume flow rate of the solution through the apparatus to obtain the instantaneous dissolution rate as a function of time. Figure 3 shows the effect of the volume flow rate on the instantaneous dissolution rate–time plot for sodium butabarbital tablets from the same batch. The importance of the proper flow rate selection can be seen. The flow rate should be coordinated with the characteristics of the tablet being studied to produce the most meaningful results. Figure 3 shows that as the volume flow rate was increased from 0.35 to 0.875 ml./min., the instantaneous dissolution rate during the first 18 min. increased. This is analogous to increasing the stirring rate when using the beaker method. Further increase in the volume flow rate above 0.875 ml./min. resulted in a decrease in the instantaneous dissolution rate.

In Fig. 4, the changing effect of flow rate on the instantaneous rate of dissolution at several different times can be seen. At 1 min. elapsed time, the faster flow rates have produced the fastest rates of dissolution. However, as the time of dissolution increased through 3 min., 6 min., and greater, the instantaneous dissolution rate increased for the slower flow rates until it peaked at 0.875 ml./min. This produces what seems to be a contradiction in that the greater the rate of flow the higher should be the rate of dissolution. However, further examination of the data reveals several possible explanations. Visual observation of the tablets at increasing elapsed times of dissolution indicates that this flowing stream method produces a "peeling" away of the outer layers of the tablets examined and a much slower disintegration than that seen in other dissolution methods using larger volumes of medium. Thus, the change in surface area would be small and the rate of dissolution of the drug would be maximized to a constant such that the dissolution taking place at the faster flow rates would be limited.

In addition, although the effects of the higher flow rates were not

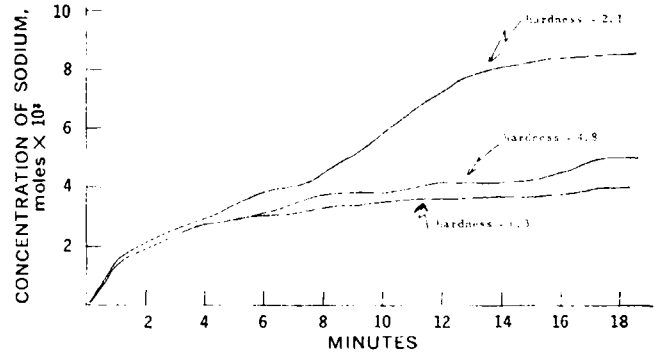

Figure 6—*Effect of hardness on the dissolution of sodium salicylate tablets at pH 8.0 and a flow rate of 0.75 ml./min.*

studied in detail, it would seem that the decrease in the dissolution rate could occur due to excessive turbulence of the dissolution medium inside the confined space of the chamber and/or the compression of the tablet against the upper filter. So ultimately the concentration of drug appearing in solution at the slower flow rates exceeds the correction made for rate of flow in calculation of the instantaneous dissolution rate. This behavior is substantiated by the fact that if the dissolution of a tablet is allowed to run to completion, the tablet being dissolved at a slower flow rate returns to the baseline before that being dissolved at the higher rate.

It was also observed that the dependence of the dissolution rate on volume flow rate varied with hardness, strength, and formulation of the tablet. With each different type of tablet, the flow rate had to be empirically determined to provide the most revealing dissolution rate. In addition to the nature of the tablet, the limitations of the analytical module must be considered in selecting the volume flow rate. The concentration of the dissolving drug must be maintained within the linear calibration range of the sodium-ion electrode or spectrophotometer.

The ability of the dissolution apparatus to monitor common variables is shown in Figs. 5 and 6. In Fig. 5, the dissolution profile for a sodium butabarbital tablet is compared to the dissolution profile for a tablet from the same batch that had been crushed to a powder before placement in the dissolution apparatus. As expected, the initial dissolution rate was greatly increased when the disintegration phase was eliminated. This observation is in agreement with the data by Tingstad and Riegelman (2). Figure 6 illustrates the ability of the apparatus to differentiate between tablets of exactly the same formulation but of different hardnesses. The sodium salicylate tablets used were prepared in these laboratories and, as expected, a rate of dissolution increasing in rank order of decreasing tablet hardness was seen.

The versatility of this apparatus is further illustrated with the dissolution of sodium warfarin tablets. A flow rate of 0.75 ml./min. allows the instrument to differentiate among 5-, 10-, and 25-mg. tablets. The dissolution of sodium bicarbonate tablets was also followed by adjustment of the flow rate to 3.5 ml./min.

The use of a flowing stream dissolution apparatus in conjunction with either the sodium-ion electrode or spectrophotometric module provides an automated means of following tablet dissolution quickly and accurately. The apparatus differentiates between the common tablet parameters of hardness and drug potency and provides a variability adjustment through flow rate. In conclusion, this apparatus provides a quick and accurate means of analyzing *in vitro* tablet dissolution.

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ACKNOWLEDGMENTS AND ADDRESSES

Received February 20, 1973, from the *Department of Pharmacy, School of Pharmacy, University of Georgia, Athens, GA 30601*

Accepted for publication June 25, 1973.

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Effect of Adverse Storage Conditions on Vacuum-Holding Ability of Large-Volume Parenteral Containers

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Abstract □ The ability of large-volume vacuum-packed parenteral containers to maintain vacuum under adverse conditions of temperature and agitation was examined. It was the intent of the study to examine the possible effects of accelerated aging during travel and storage. Containers were stressed by being subjected to alternating high and low temperatures for 30 days (24-hr. intervals) and by shaking for 30 days at temperatures up to 50°. Preliminary tests were carried out to establish a statistically significant number of experiments. It was found, in all cases, that the vacuum seal was maintained under these conditions. It is concluded that such factors as decomposition of ingredients and faulty glassware should be suspected if vacuum loss is found with these types of containers.

Keyphrases □ Parenteral containers, large volume—effects of temperature and agitation on vacuum-holding ability □ Large-volume parenteral containers—effects of temperature and agitation on vacuum-holding ability □ Vacuum retention—effects of temperature and agitation on large-volume parenteral containers □ Containers, large-volume parenteral—effects of temperature and agitation on vacuum-holding ability

In the last decade, there has been a surge of interest regarding the safety of parenteral preparations. Recent reports have been concerned with particulate matter (1–4), sterility control (5, 6), and contamination during opening, preparation, and use (7–9).

That serious problems can still occur with this type of preparation is indicated by recent references to septicemias caused by microbial contamination (10–12). Some of these infections have been attributed to improper use or handling of the parenteral product itself (10). Other problems have been caused by introduction of contaminants during administration (11, 12).

One possible source of contamination is the failure of the closure during storage. A means of testing for