Dissolution Testing of Nitroglycerin Tablets

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Abstract ◻ The available types of dissolution testing apparatus for tablets and capsules are inapplicable to sublingual tablets, since these tablets are formulated to release their drug content within minutes in a small volume of fluid. A simple dissolution test method was developed for nitroglycerin tablets based on the reduction of nitroglycerin at a rotating platinum electrode, which provides reproducible stirring. The system provides instantaneous and continuous measurement of dissolved nitroglycerin in a small constant volume of buffered isotonic sodium chloride solution over a period of seconds to several minutes, when reduction is complete as shown by the current–time curve. Since the height of the curve is directly proportional to the amount of nitroglycerin in solution, the method also can be used to determine the drug content of individual tablets.

Keyphrases ◻ Nitroglycerin—sublingual tablets, polarographic dissolution test ◻ Polarography—determination of dissolution of nitroglycerin sublingual tablets ◻ Dissolution—nitroglycerin sublingual tablets, polarographic determination ◻ Vasodilators, coronary—nitroglycerin, polarographic determination of dissolution of sublingual tablets

Absorption of drug from a buccal or sublingual tablet requires dissolution in a small volume of fluid in the mouth, affording prompt pharmacodynamic effect. Although the dissolution of drugs from such a dosage form is thus an important parameter, methods for studying it have been limited. Apparatus such as those described by USP (1), NF (2), and Goodhart *et al.* (3) use relatively large volumes of fluid and are not suitable for sublingual tablets.

Dorsch and Shangraw (4) recently described a discontinuous technique for nitroglycerin tablets. The tablet is placed on top of a microporous membrane filter[1] (0.45-μm pore size) in the upper chamber of a plastic syringe-type filter holder[2], and five 1-ml portions of water at 30° are flushed through the chamber at 0, 30, 60, 90, and 120 sec. The method is tedious and affords only discrete data points. Karlsen[3] suggested that a polarographic method could be worked out to provide a continuous record of the dissolution rate profile of a nitroglycerin tablet. This report describes an amperometric procedure for measurement of the dissolution rate of individual nitroglycerin tablets.

Nitroglycerin is electrochemically reducible. Flann (5) described the polarographic determination of nitroglycerin tablets, reporting a single, irreversible, diffusion-controlled wave consuming two electrons for each nitrate group, independent of pH in the range of 3–13. In the work reported here, amperometry at a polarized rotating platinum electrode in conjunction with a time-based recorder affords a graphical representation of nitroglycerin concentration against time. Constant stirring is provided by the rotating electrode, and the reduction current is unaffected by suspended solids.

EXPERIMENTAL

Electrolyte (Dissolution Medium)—Dissolve 8.5 g of sodium chloride, 245 mg of monobasic sodium phosphate, and 700 mg of anhydrous dibasic sodium phosphate in water and dilute to 1 liter. Adjust the pH, if necessary, to 7.1 ± 0.1 by adding more of either phosphate salt.

Apparatus—The rotating platinum electrode comprised a platinum electrode[4] and a 600-rpm motor[5]. The potentiostat[6] was fitted with a recorder[7]. Silver wire was used as the reference and counter electrode. The cell was a flat-bottom glass cylinder, about 5 cm long by 2.1 cm i.d., held in place under the rotating platinum electrode with a round-jaw buret clamp and charged with 5.0 ml of the electrolyte. The nitrogen gas used to flush the oxygen from the cell was bubbled through 100 ml of the electrolyte in a gas-washing bottle.

The cell was positioned below the rotating platinum electrode so that the rotating platinum electrode wire was 1 mm below the surface of the solution, the silver wire extended to the bottom of the cell, and the nitrogen inlet tube was inserted at one side of the cell, away from the rotating platinum electrode, with its tip extended under the solution surface. The cell bottom was flush with the bottom of the clamp, allowing easy repositioning of the cell after removal for cleaning between samples by using a flat surface to line up the bottoms of the clamp and the cell.

The following settings were used for the polarographic analyzer: drop timer, two electrodes; modulation amplitude, 50 mv; operating mode, pulse; initial voltage, −0.99 v; display direction, +; drop time, 2 sec; potential scan direction, −; range, 1.5 v; current range, 0.5 mamp full scale; and low pass filter, 3.

Standard Preparation—Standardize nitroglycerin spirit against potassium nitrate by the phenoldisulfonic acid method. Transfer 1.0 ml to a 100-ml volumetric flask, add 25 ml of alcohol USP, and dilute to volume with the electrolyte. Further dilute the solution with the electrolyte to obtain concentrations of about 40 and about 80 μg/ml.

Standardization Procedure—Transfer 5.0 ml of the less concentrated standard preparation to the cell. Place the electrodes so that the platinum wire of the rotating platinum electrode is about 1 mm below the surface of the solution and the silver reference electrode extends to the bottom of the cell and arrange the nitrogen inlet tube at one side of the cell under the solution surface so that it does not contact the rotating platinum electrode. Start the rotating platinum electrode motor and deaerate with nitrogen for about 5 min. After 5 min, lift the nitrogen inlet tube about 2 mm above the solution surface.

Start the chart and turn the selector switch to EXT CELL, marking "zero time" on the recorder chart at this point. Run the chart about 3 min at 5.1 cm (2 in.)/min. Reset the chart and perform a blank determination with the electrolyte in the cell. Measure the difference between the standard and the blank at 2 min to obtain the standard reading.

Repeat the procedure for the more concentrated standard preparation.

Dissolution Procedure—Pipet 5.0 ml of the electrolyte into the cell, arranged as already described; then start the rotating platinum electrode motor and deaerate with nitrogen. After 5 min, lift the nitrogen inlet tube about 2 mm above the solution surface. Turn the electrode selector switch to EXT CELL, zero the chart, and start the recorder. Within 30 sec of the time the nitrogen inlet tube is lifted, drop in the tablet to be tested and mark the recorder chart "zero time." Allow the system to operate until no further increase in reduction current is observed.

[1] Millipore.
[2] Millipore Swinnex 25.
[3] J. Karlsen, University of Oslo, Oslo, Norway, personal communication *via* R. F. Shangraw, School of Pharmacy, University of Maryland, Baltimore, MD 21201, 1974.

[4] Sargent-Welch S30421.
[5] Sargent-Welch S76485.
[6] Princeton Applied Research polarographic analyzer, model 174.
[7] Heath-Schlumberger model EU-205-11 recorder with model EU-200-01 potentiometric amplifier.

Table I—Nitroglycerin Dissolution from Three 0.4-mg Sublingual Tablet Lots

Lot	Average Percent Dissolved at 0.25 min	0.5 min	0.75 min	1.0 min	t_{90} Average	t_{100} Average	Average Micrograms per Tablet
1	31 (16–37)[a]	78 (66–84)	93 (88–95)	97 (95–98)	0.70	1.6 (1.2–2.4)[b]	433 (418–452)[b]
2	24 (19–30)	72 (69–76)	89 (86–94)	96 (94–98)	0.78	1.5 (1.2–1.8)	443 (424–459)
3	33 (28–39)	82 (71–90)	94 (92–97)	98 (95–100)	0.57	1.2 (1.0–1.5)	394 (360–415)

[a] Range for 10-tablet sample. [b] Range.

Perform a blank determination with the electrolyte to compensate for the small amount of oxygen that diffuses into the cell and take the difference in recorder chart reading between the sample and the blank at each time interval as the sample reading. With no change in experimental conditions, the blank remains constant during the day and only one blank determination need be obtained each day.

Calculate the quantity of nitroglycerin, in milligrams per tablet, from the formula $5C(U/S)$, where C is the concentration, in milligrams per milliliter, of the standard preparation used, whichever is closer to the sample reading; and U and S are the chart readings for the tablet and the standard preparation, respectively.

Note as t_{100} the time required for 100% of the drug to dissolve; this value is determined from the chart as that point where no further rise in reduction current occurs. Calculate the percent of drug released at any time, t, in seconds from the formula (milligrams measured at time t/total milligrams released) × 100.

RESULTS AND DISCUSSION

The proposed dissolution test was performed using 10-tablet samples of each of three lots of a commercial 0.4-mg sublingual tablet formulation[8]. Table I shows the average percentage of drug dissolved from the tablets at 15-sec intervals during the 1st min and the average time required for 90 and 100% of the drug content of the tablets to dissolve. Use of percentage affords direct comparison among individual tablets of differing drug content, thus normalizing the data. Since prompt onset of action is an important criterion for a sublingual nitroglycerin tablet, these data may have clinical significance.

Another advantage of the method is that it provides a measure of the nitroglycerin in each tablet. The data shown in Table I (last column) are consistent with those obtained for these tablets by Dorsch and Shangraw (4), who used an automated assay method. Their method is less time consuming than the dissolution procedure and probably would be preferable if content uniformity information is the only consideration.

[8] NITROPRN Tablets, Warner-Chilcott Laboratories, Morris Plains, NJ. Lot 1 was control number 490254B, Lot 2 was control number 4917124B, and Lot 3 was control number 5964124A.

REFERENCES

(1) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 651.

(2) "The National Formulary," 14th ed., Mack Publishing Co., Easton, Pa., 1975, p. 893.

(3) F. W. Goodhart, R. H. McCoy, and F. C. Ninger, *J. Pharm. Sci.*, **62**, 304(1973).

(4) B. Dorsch and R. Shangraw, *Am. J. Hosp. Pharm.*, **32**, 795(1975).

(5) B. C. Flann, *J. Pharm. Sci.*, **58**, 122(1969).

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Synthesis and Preliminary Antimicrobial Screening of Two Thiosulfonates

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Abstract □ Tetramethylene bis(methanethiosulfonate), the S-ester analog of busulfan, was prepared by reacting 1,4-dibromobutane with potassium methanethiosulfonate. 2,4-Dichlorophenyl methanethiosulfonate was prepared by reacting sodium methanesulfinate with 2,4-dichlorobenzenesulfenyl chloride. Neither compound showed antifungal activity against *Microsporum audouini* or *Trichophyton mentagrophytes*. Although tetramethylene bis(methanethiosulfonate) was more active against *Staphylococcus aureus* than was 2,4-dichlorophenyl methanethiosulfonate, neither compound was as active as the streptomycin control.

Keyphrases □ Thiosulfonates—synthesis of tetramethylene bis(methanethiosulfonate) and 2,4-dichlorophenyl methanethiosulfonate, antimicrobial screening □ Sulfur analog of busulfan—synthesized, antimicrobial screening □ Structure–activity relationships—thiosulfonates synthesized, antimicrobial screening □ Antimicrobial activity—thiosulfonates synthesized and screened

Although thiosulfonates have been known for more than 100 years, the demonstration of antimicrobial activity of some members of this chemical class has been relatively recent (1–3). Two different types of thiosulfonates were made for antimicrobial screening. Busulfan, a bis(sulfonate) ester, is used for treatment of chronic myelocytic leukemia (4). The bis(S-ester) analog of this compound was prepared for testing of its antibacterial and antifungal activities and for future screening for antileukemic activity. In addition, the S-ester analog of 2,4-dichlorophenyl methanesulfonate, a long acting soil nematocide (5), was prepared. These new thiosulfonates were tested for antibacterial activity against *Staphylococcus aureus* and for antifungal ac-