Monitoring Tablet Dissolution with a Sodium Ion-Selective Glass Electrode

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Abstract □ The usefulness of the sodium ion-selective electrode (SIE) in measuring the disintegration and dissolution of tablets containing sodium salicylate was evaluated. This potentiometric measurement of sodium appearance in solution was found to agree with spectrophotometric assays for salicylate and sodium in solution. The SIE employed in this manner provides an accurate, inexpensive, and readily automated methodology for following tablet disintegration and dissolution.

Keyphrases □ Sodium ion-selective glass electrode—monitoring tablet dissolution □ Dissolution, monitoring tablets—use of sodium ion-selective electrode □ Potentiometric measurement of sodium—monitoring tablet dissolution

In recent years, a number of ion-selective electrodes were introduced and are now commercially available. These electrodes make it possible to measure the concentration of sodium, potassium, calcium, and other ions potentiometrically (1). These electrodes have many possible applications in pharmaceutics which have not been explored. One application is the monitoring of tablet dissolution when the tablet contains an ion to which the electrode will respond selectively. The advantages of a potentiometric measurement over the commonly employed spectrophotometric methods are twofold. First, the electrode may be placed in the dissolution media where it continuously measures ion concentration as a function of time. This eliminates the need for periodic sample collection or circulation of the sample for measurement outside the dissolution chamber. Second, the potentiometric method presents an alternative analytical technique when the spectrophotometric methods are limited by interferences or the drug does not absorb in the visible or UV spectrum. In this article, the utility of a sodium ion-selective electrode (SIE) in following the dissolution of tablets containing sodium salicylate is evaluated.

APPARATUS

The tablet dissolution apparatus employed was the same as described by Levy and Hayes (2). Measurement of sodium-ion activity was accomplished with a sodium-ion electrode[1], with a saturated calomel electrode[2] as reference. The electrode potential was measured with a pH meter[3] operated in the expanded millivolt position, with the signal relayed to a recorder[4]. All dissolution apparatus and calibrating solutions were maintained at 37 ± 1° by a water bath[5].

EXPERIMENTAL

The SIE was employed in its operable pH range of 7–10, and a 10^{-3} *M* sodium-ion concentration was included as a blank in all of the buffered solutions. In this manner, the pH was always at least four units higher than the pNa, as recommended by the manufacturer (3). The SIE was routinely calibrated before and after each tablet dissolution study; the potential drift was found to be insignificant. After the initial calibration, the electrode was stabilized in the dissolution media, a tablet was added, and the sodium concentration was followed as a function of time.

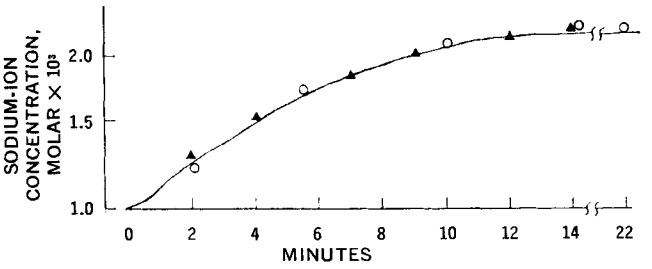

Figure 1—*Electrode response during tablet dissolution* (——). *Key:* ▲, *spectrophotometric salicylate assay; and* ○, *atomic absorption assay for* Na^+; *37 ± 1°, pH = 9.0.*

The reliability of the SIE in measuring the appearance of sodium ions in solution was checked three ways. Simulated tablet dissolutions were run by pumping concentrated sodium salicylate solutions (0.5–1.0 *M*) into the dissolution apparatus under conditions identical to the tablet dissolution studies, and the electrode response was recorded. These solutions were pumped at precisely determined rates (0.3–1 ml./min.) by a peristaltic pump[6] through 17-gauge Teflon tubing to the position in the apparatus where a tablet would have been placed. Two independent analytical techniques were used to evaluate the response of the SIE during actual tablet dissolution studies. For each technique, 1-ml. samples were drawn from the dissolution media in the proximity of the SIE by pipeting through a pledget of glass wool. Suitable dilutions of these samples were assayed for total sodium concentration using an atomic absorption spectrophotometer[7]. The salicylate concentration of the samples was determined at pH 9 using a spectrophotometer[8] at 296 nm.

All sodium salicylate tablets employed in this study were prepared in these laboratories from the same batch numbers of raw materials and under identical tableting conditions. Each tablet contained approximately 50 mg. sodium salicylate, 100 mg. lactose, 345 mg. cornstarch, and 5 mg. stearic acid.

RESULTS AND DISCUSSION

In all work using the SIE, it is necessary to calibrate the electrode in the range of sodium-ion concentration expected from the tablet dissolution. Since the manufacturer recommends a pH range of 7–10 and a pH at least four units greater then the highest pNa (2), a base concentration of sodium was established at 1×10^{-3} *M*. All work was done in this pH range and at a sodium concentration between 1×10^{-3} and 3×10^{-3} *M*. The electrode was found to respond linearly with concentration in this range, with no drift from the established calibration during the maximum time necessary for a tablet dissolution. It was also found that when changing the pH of the system, minimum electrode response time and maximum stability could be ensured if the electrode was immersed overnight in the medium to be used.

[1] Beckman No. 39278.
[2] Coleman No. 3-152.
[3] Corning model 12.
[4] Varian G 1000.
[5] Blue M model MW 1120.
[6] Harvard model 1201.
[7] Perkin-Elmer 290 B.
[8] Beckman DU.

Table I—Time–Dissolution Comparison for Sodium Salicylate Tablets by Three Methods[a]

Minutes	Concentration, m*M*		
	SIE	Atomic Absorption	UV Spectrophotometer
2	0.300	0.300	0.350
4	0.580	0.600	0.625
7	0.850	0.860	0.830
10	0.95	1.00	1.15
14	1.25	1.30	1.34
22	1.20	1.40	1.37

[a] All assays carried out with phosphate buffer at pH 9 and at 37°.

The equilibration time of electrode response to changes in sodium-ion concentration was determined by pumping a concentrated sodium salicylate solution into the beaker under conditions of tablet dissolution. It was found that the electrode-recording system follows the change in sodium concentration even at rates more than twice those observed during actual tablet dissolution.

To control extraneous sodium content, the initial tablet dissolutions were carried out using compressed tablets manufactured in these laboratories. Identical tablet dissolutions were recorded in systems buffered at pH 7.5 and 9.0, and no significant change in drug release was noted.

Figure 1 shows the change in electrode potential for the dissolution of a sodium salicylate tablet. Since the tableting procedure introduces some inherent variation in the individual characteristics of each tablet, it was necessary to ascertain that the recorded variation was indeed due to the tablet and not to the analytical method. This was accomplished by correlation with results from atomic absorption spectrophotometry and UV spectrophotometric analysis. Table I shows the values obtained by each of the three assay methods. Note the agreement of molar concentrations determined by the SIE system and the atomic absorption method. Both of these methods assay for sodium ions. The UV spectrophotometric method assays for salicylate content and, within experimental variation, confirms the sodium-ion data.

In summary, the SIE with attached recording devices provides a means of measuring tablet dissolution that is accurate and relatively inexpensive. It also provides a continuous direct readout of drug appearance without the disadvantages incurred by repeated sampling and was shown to be as reproducible and accurate as either of the spectrophotometric methods used.

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Synthesis and Pharmacological Evaluation of 1,4-Dihydro-2*H*-3,1-benzoxazin-2-one Derivatives

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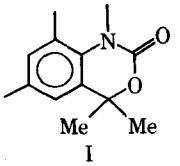
Abstract □ Some 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives were synthesized and tested for pharmacological activity. 4-Phenyl-6-chloro-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (Compound 4) exhibited anticonvulsant activity against chemically and electrically induced seizures and low acute toxicity in mice. Structure–activity relationships are discussed.

Keyphrases □ 1,4-Dihydro-2*H*-3,1-benzoxazin-2-one derivatives—synthesis as possible anticonvulsants, screened for pharmacological activity, structure–activity relationships □ Anticonvulsants, potential—synthesis and pharmacological screening of 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives, structure–activity relationships □ 3,1-Benzoxazin-2-one derivatives—synthesis and pharmacological screening as possible anticonvulsants, structure–activity relationships

3,1-Benzoxazin-2-ones are relatively new potential therapeutic agents. A number of derivatives of Structure I were recently reported by Bernardi *et al.* (1) to have anticonvulsant activity. A series of structurally related 1,3-benzoxazin-2-ones was described by the same authors (2), among which 2,3-dihydro-4*H*-1,3-benzoxazin-2-one-3-acetamide (II) showed antireserpine activity (3–5). Some 4-phenyl-substituted-3,1-benzoxazin-2-ones were also synthesized (6, 7), but apparently no pharmacological data were reported. The present paper deals with the synthesis and pharmacological evaluation of the 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives listed in Table I.

CHEMISTRY

N-Alkylation of the known 1,4-dihydro-2*H*-3,1-benzoxazin-2-one with 2-bromoacetamide in the presence of sodium hydride gave Compound 1. Benzoxazinones 2, 4, and 8 were more conveniently obtained by sodium borohydride reductive cyclization of the corresponding 2-trichloroacetamidobenzophenones (8) than through basic cyclization of 2-trichloroacetamidobenzhydrols (8, 9) or by reaction of 2-aminobenzhydrols with phosgene (6, 7). *N*-Methylation of Compounds 2, 4, and 8 with methyl iodide in the presence of sodium hydride gave benzoxazinones 3, 5, and 9, respectively. Similarly, Compounds 6 and 7 were obtained from Compound 4 by alkylation with 2-bromoacetamide or ethyl bromoacetate.



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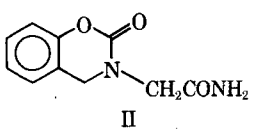

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