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Nonaqueous Titration of Procainamide Hydrochloride

Keyphrases □ Procainamide hydrochloride—nonaqueous titration, interference of acetic anhydride □ Titration, nonaqueous—procainamide hydrochloride, interference of acetic anhydride

To the Editor:

The official assay for procainamide hydrochloride (1) involves visual nonaqueous titration, with perchloric acid as the titrant and glacial acetic acid as the titration solvent. Mercuric acetate is added to permit the titration of the tertiary amine hydrochloride portion of the molecule. Therefore, both the aromatic amine and the tertiary amine groups are titrated, and two inflections in the titration curve are obtained (Fig. 1). The first inflection is due to the aromatic amine group while the second is attributable to the tertiary amine hydrochloride group. When crystal violet indicator is used in conjunction with a potentiometric titration, the visual end-point corresponds to the second break in the curve.

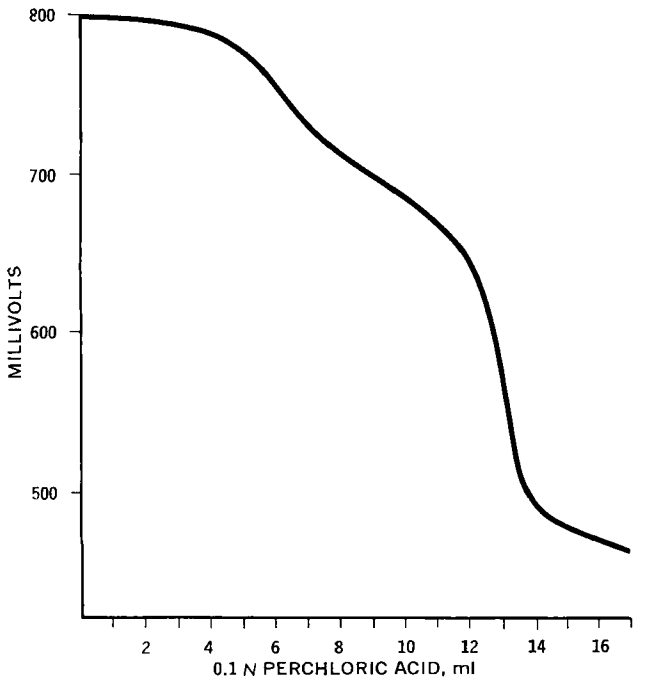

Figure 1—*Typical titration curve for procainamide hydrochloride, using glacial acetic acid as the titration solvent and perchloric acid as the titrant. Titration was performed in the presence of mercuric acetate.*

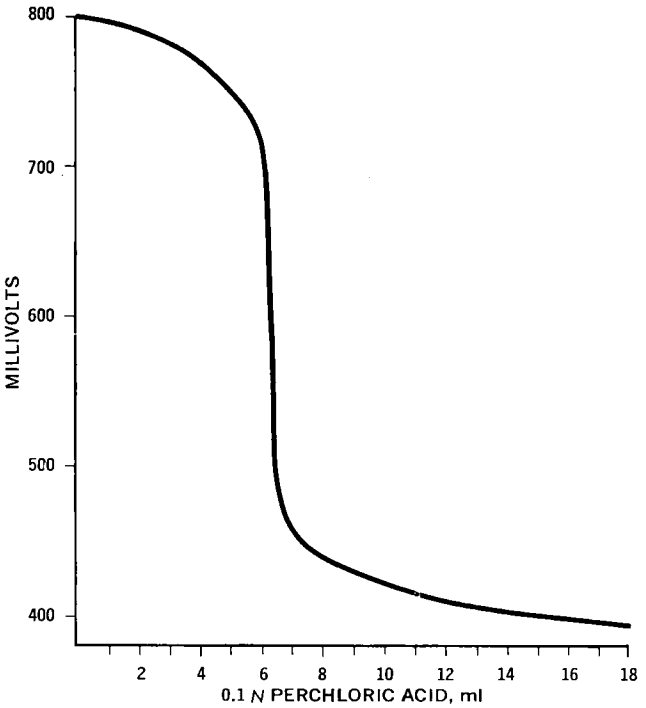

Figure 2—*Typical titration curve for procainamide hydrochloride using acetic anhydride–acetic acid (1:19) as the titration solvent mixture and perchloric acid as the titrant. Titration was performed in the presence of mercuric acetate.*

Acetic anhydride, a potential contaminant of glacial acetic acid, interferes with the first end-point in the titration by acetylating the aromatic amine group and rendering it nontitratable with perchloric acid. If 50 ppm acetic anhydride is present in the titration solvent, a decrease in the percent recovery of over 3% can theoretically be expected when the USP (1) assay directions are followed. However, in the presence of an excess of acetic anhydride (at least a sufficient amount to acetylate completely the aromatic amine group), an excellent titration curve is obtained; it demonstrates a single inflection due to the amine hydrochloride portion of the molecule (Fig. 2).

When the assay directions specified (1) for procainamide hydrochloride were followed, only one inflection was obtained in the titration curve, which resembled Fig. 2, when the titration solvent contained in excess of 0.5% acetic anhydride. In the presence of 0–0.5% acetic anhydride, the volume of perchloric acid required to reach the first potentiometric end-point decreased with an increase in the acetic anhydride content of the titration solvent. The best visual end-points were obtained when the solvent contained 2–25% acetic anhydride. For example, the percent recovery for a series of 10 analyses was 100.6 ± 0.30 when the titration solvent contained 5% acetic anhydride.

To preclude an error in the assay of procainamide hydrochloride due to the presence of acetic anhydride as a contaminant in glacial acetic acid, it is suggested that the titration solvent contain sufficient acetic anhydride to assure complete acetylation of the aromatic amine group. This precaution is taken (perhaps fortuitously) in the official assay for chloro-

procaine hydrochloride (2) but not in the official assay for proparacaine hydrochloride (3).

(1) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 542.
(2) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, p. 157.
(3) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 555.

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Albumin Microspheres as Vehicles for Achieving Specificity in Drug Delivery

Keyphrases □ Albumin microspheres—vehicles for specific drug delivery systems □ Microspheres, albumin—vehicles for specific drug delivery systems □ Drug delivery systems—albumin microspheres, vehicle for mercaptopurine delivery

To the Editor:

There is a growing need in modern day drug therapy to develop methods of drug delivery that are highly cell or tissue specific. Cancer chemotherapy, for example, demands that drugs with pronounced systemic toxicities be delivered to target tissues in precise dosages and with minimal interaction with normal tissues. Past approaches to achieving specificity have centered around structural modification of the drug, alterations in route of administration or dose regimen, and efforts to physically position a drug delivery device, such as a polymeric implant, in the closest possible proximity to the target tissue.

The phagocytic cells of the reticuloendothelial system provide a physiological means of achieving cell and tissue specificity in drug delivery that has enormous potential. Radiologists utilize the phagocytic activity of these cells to achieve specificity in the delivery of radiolabeled albumin and sulfur colloids (1). Gregoriadis (2) entrapped anticancer agents within phospholipid vesicles, reported the phagocytic uptake of the vesicles by the liver in rats, and mentioned the possibility of directing drug-containing vesicles to other cell types by manipulation of the vesicle surface. Trouet *et al.* (3) reported reduced toxicity and increased effectiveness in the treatment of leukemia when DNA complexes of the anticancer agent daunomycin are pinocytized from solution. In an attempt to find a phagocytizable carrier capable of accommodating a wide variety of drugs, the anticancer agent mercaptopurine was entrapped within human albumin microspheres.

Table I—Incorporation of Mercaptopurine-8-^{14}C Hydrate in Human Albumin Microspheres

Total Drug Available, μg/mg Albumin	Drug Associated with Microspheres[a], μg/ml Albumin	Entrapment, %
4.00[b]	3.46	86.5
4.00	3.59	87.3
8.00[c]	1.57	—
10.5	1.32	—

[a] Average of two determinations. [b] Drug present in emulsion prior to denaturation (1 mg/ml in internal phase). [c] Drug added to previously prepared albumin microspheres (1 mg/ml).

Albumin microspheres provide a potentially useful means of delivering drugs to endocytic cells because they are physically and chemically stable, rapidly removed from the vascular system by phagocytosis, amenable to preparation in large batches, nonantigenic, metabolizable, and capable of accommodating a wide variety of drug molecules in a relatively nonspecific fashion. Human serum albumin microspheres containing the anticancer agent mercaptopurine were prepared by a modification of the method of Scheffel *et al.* (4). One milliliter of a 27% dimethylformamide–water solution containing 1 mg of mercaptopurine-8-^{14}C hydrate[1] and 250 mg of human serum albumin[2] was emulsified with 100 ml of cottonseed oil USP by repeated passage through a hand-operated homogenizer[3]. The emulsion was added with constant stirring to an additional 100 ml of oil that had been heated to 175°, held at that temperature for 10 min, and cooled. No degradation of mercaptopurine could be detected in dimethylformamide–water solutions kept at 175° in sealed ampuls for similar periods.

Two hundred milliliters of ether was then added and the suspension was filtered through a 0.5-μm filter[4]. The spheres were washed repeatedly with ether to remove residual oil and dried. The quantity of drug entrapped was determined by digesting the spheres in 0.5 *N* NaOH and counting on a liquid scintillation counter[5], using appropriate internal standards. Over 85% of the mercaptopurine present in the original emulsion was associated with the microspheres (Table I).

Since albumin would be expected to adsorb drug from solution, an experiment was performed to determine how much mercaptopurine could be adsorbed onto previously prepared drug-free microspheres. The microspheres were suspended in a 27% dimethylformamide–normal saline solution containing 1 mg mercaptopurine-8-^{14}C hydrate/ml (the same concentration present in the internal phase of the emulsion used to prepare drug-containing spheres), stirred well, centrifuged, and washed five times with a large excess of distilled water. About 40% as much drug was associated with the spheres as when drug was incorporated in the original emulsion (Table I).

[1] New England Nuclear.
[2] Sigma Chemical Co.
[3] C. W. Logeman Co.
[4] Solvent resistant, Millipore Corp.
[5] Packard Tri-Carb model 2009.