# *In Vitro* Evaluation of an Anticholinergic Agent in a Timed-Release Solid Dosage Formulation

ROBERT H. GUMTOW ˣ, HEATHER BEECHER, DIANNE HARTNETT, and DIANE GLOGOWSKI

**Abstract** □ Determinations of intact drug content and *in vitro* dissolution tests were carried out on a commercially available brand of the anticholinergic drug propantheline in 15-mg single-dose and 30-mg sustained-release tablets. These tests were made following a report of unsatisfactory therapeutic response in human subjects after ingestion of the 30-mg sustained-release dosage form. A chemical assay, specific for intact drug, showed that all tablets contained essentially the labeled amount of active drug species (±4%). However, the slow dissolution of the first 15 mg of drug (a usual single dose) from the 30-mg dosage form, as observed in acidic solution (0.1 *N* HCl), was unexpected based on manufacturer claims. Older and fresher lots of the 30-mg formulation, both of which fell within a recently revised 2-year expiration period at the time of testing, released only 6.0 ± 1.4 mg of active ingredient during the 1st hr compared to 14.5 ± 0.7 mg from regular 15-mg tablets. Of the 30-mg tablets, the fresher lot released consistently more drug with time; the difference reached a statistically significant level of $p < 0.01$ at 2 hr. The dissolution rates of all tablets were enhanced in more alkaline media, and little difference ($p > 0.2$) was evident between the older and fresher sustained-release lots at any time during 4-hr dissolution trials when the medium had been adjusted to pH 6.38 or above at 1 hr. *In vitro* dissolution test results correlated well with *in vivo* findings and showed that rapid dissolution of the initial 15 mg of propantheline from solid dosage forms in acidic gastric juices is critical to its therapeutic effectiveness. It was concluded that reformulation of the 30-mg sustained-release dosage form to promote more rapid release of the first 15 mg of drug or full reliance on single-dose tablets is necessary to ensure therapeutic efficacy.

**Keyphrases** □ Propantheline—quantitative analysis and *in vitro* dissolution, regular and sustained-release tablets compared □ Tablets—propantheline, regular and sustained release, quantitative analysis and *in vitro* dissolution □ Dosage forms—regular and sustained-release tablets of propantheline, quantitative analysis and *in vitro* dissolution □ Dissolution, *in vitro*—propantheline regular and sustained-release tablets compared □ Anticholinergic agents—propantheline, quantitative analysis and *in vitro* dissolution, regular and sustained-release tablets compared

Propantheline is an anticholinergic drug extensively used in the treatment of peptic ulcers. Gibaldi and Grundhofer (1) followed salivary flow reduction as an index of drug activity. These data permitted comparison of the time of onset, intensity, and duration of effect derived from 15-mg regular and 30-mg sustained-release tablets and showed the 15-mg tablets to be superior in every respect. This discovery was unanticipated since the 30-mg tablets are reportedly designed to release a single 15-mg dose rapidly followed by relatively slow release of another 15 mg of active ingredient to sustain the desired therapeutic response. These investigators concluded that commercially available prolonged-acting tablets[1], containing 30 mg of propantheline bromide in timed-release (2) beads, apparently did not release 15 mg of intact drug during the 1st hr as claimed (3).

This investigation determined whether or not the failure of the 30-mg dosage form to produce a consistent anticholinergic effect might be attributed to a dissolution and/or chemical stability problem.

[1] Pro-Banthine P.A. tablets, Searle & Co., San Juan, PR 00936.

## EXPERIMENTAL

**Dissolution Apparatus**—The dissolution apparatus was similar to that of Levy and Hayes (4). However, a 400-ml jacketed Pyrex beaker was employed, through which heated water was circulated to maintain the beaker contents at 37 ± 0.1°.

**General Dissolution Procedure**—Dissolution medium, 300 ml, was placed in the beaker and allowed to equilibrate to 37°. The stirrer paddle was immersed to a depth of 27 mm in the medium and adjusted to rotate at 50 rpm[2]. Tablets were introduced at time zero by sliding them down the inside of the beaker and carefully releasing them just below the surface.

Cotton-filtered 5-ml samples of solution were removed at the times shown in Fig. 1. Aliquots of 5 ml of the appropriate replacement medium were added to the dissolution beaker immediately after the withdrawal of each sample.

*Dissolution Media*—Acidic media included 0.1 (pH 1.09 ± 0.01) and 0.001 (pH 3.15 ± 0.01) *N* HCl. Measured portions of phosphate buffer (0.5 *M*) were used to raise the pH of the 0.1 *N* HCl medium to 6.38 or 7.38 ± 0.01.

*Conversion of Media*—Change of media was accomplished by adding 5 ml of 5 *N* NaOH to 300 ml of 0.1 *N* HCl, mixing well, removing 55 ml of the resulting solution, and finally incorporating 50 ml of the appropriate buffer to restore the original 300-ml volume.

The 30-mg prolonged-acting tablets were subjected to the change of medium procedure at 60 min *in situ* to simulate passage of the residual dosage form from the stomach into the upper small intestine.

**Assays**—Propantheline powder[3], standardized according to the USP (6), was utilized to prepare standard curves for Assays A and B. Assay B was developed for use with relatively basic media because Assay A was sensitive only to intact drug[4]. Propantheline hydrolyzes in solution above pH 5 to xanthinecarboxylic acid (7).

*Ion-Pair Extraction Assay (A)*—The calibration curve preparation for the propantheline assay *via* an organic dye salt partition technique, followed by spectrophotometric measurement of complex color intensity, was described previously (8).

*UV Spectrophotometric Assay (B)*—A series of drug solutions, prepared from propantheline powder in 0.1 *N* HCl, ranged from 0.0016 to 0.16 g/liter. Each solution was treated as described under *Conversion of Media*. Five-milliliter samples were then hydrolyzed with 5 ml of 1 *N* NaOH. After 10 min, 10 ml of 1 *N* HCl was added to acidify hydrolysates, which were diluted to 50 ml with 0.1 *N* HCl. Absorbances of the resulting solutions were read in a spectrophotometer[5] at 220 nm against a blank prepared without drug.

Corrections were made for all dilutions encountered during the change of medium, hydrolysis, and acidification steps. A reproducible Beer's curve, characterized by an absorptivity of 41.6 liters/g, was obtained. Identical absorptivity was found for standard curves prepared from drug in acidic media (0.001 and 0.1 *N* HCl). However, with the acidic media the conversion of media procedure was omitted and samples were processed by adding 1 ml of 1 *N* NaOH, waiting 10 min, acidifying with 1.5 ml of 1 *N* HCl, and finally diluting to 50 ml with 0.1 *N* HCl.

*Effect of Tablet Excipients on Assays A and B*—Three tablets of each lot[6] studied were crushed thoroughly and dissolved in both 0.1 *N* HCl

[2] Levy *et al.* (5) demonstrated reasonable *in vitro–in vivo* correlations between markedly different solid dosage forms at this degree of agitation in a similar apparatus.

[3] Lot 046A, Searle & Co., San Juan, PR 00936.

[4] When a solution of propantheline in 0.1 *N* HCl was hydrolyzed by the addition of sodium hydroxide and then reacidified and subjected to Assay A, zero absorbance was observed.

[5] Coleman model 101 Hitachi, Coleman Instruments Corp., Maywood, IL 60154.

[6] Lots 1074-461 (the "older" lot, which was manufactured in October 1974 and has an original expiration date of October 1979) and 875-503 (the "fresher" lot, manufactured in August 1975 with a revised 2-year expiration date of July 1977) of 30-mg Pro-Banthine P.A. tablets plus the same 15-mg Pro-Banthine tablets referred to in Ref. 1 (lot number unknown).

**Table I—Dissolution Experiments Conducted**

| Experiment | Number of Tablets Tested[a] | Tablet Strength, mg | Duration, min/pH | Assay |
|---|---|---|---|---|
| 1 | 5 | 15 | 60/1.09 | A[b] |
| 2 | 5 | 30[c] | 60/1.09, 180/6.38 | B[b] |
| 3 | 5 | 30[d] | 60/1.09, 180/6.38 | B[b] |
| 4 | 2 | 30[c] | 60/1.09, 180/7.38 | B |
| 5 | 5 | 30[c] | 240/1.09 | B[b] |
| 6 | 5 | 30[d] | 240/1.09 | B[b] |
| 7 | 2 | 15 | 5/7.12 | B |
| 8 | 2 | 30[d] | 60/7.12 | B |

[a] Each tablet represents a separate dissolution test. [b] Results depicted in Fig. 1. [c] Older lot of tablets. [d] Fresher lot of tablets.

and phosphate buffer (pH 6.38) with ample shaking. Cotton-filtered samples from each solution were assayed by Assay B, while only the acidic filtrates were analyzed by Assay A. No detectable influence on either assay by tablet excipients was observed since all lots yielded within ± 4% of the labeled amount of drug.

**Dissolution Experiments**—Specifications for all dissolution tests performed in this study are summarized in Table I.

## RESULTS AND DISCUSSION

Dissolution curves generated from the 15-mg tablets and the two lots of 30-mg prolonged-acting propantheline tablets under different pH conditions are shown in Fig. 1. The markedly slower drug release from the prolonged-acting formulations in acidic media during the 1st hr parallels the comparatively poor *in vivo* response observed previously (1). Relatively slow release of drug from the prolonged-acting tablets during the initial stages of dissolution was surprising since the manufacturer claimed that: "on ingestion about half of the drug is released within an hour and the remainder continuously as earlier increments are metabolized" (3).

Both types of tablet could be expected to exhibit similar dissolution profiles early in the dissolution process provided that the sustained-release formulation was functioning as claimed. Suppression of salivary secretion following administration of 15-mg tablets to three human subjects was pronounced whereas that from the 30-mg preparations was either less than satisfactory or nil. When Subject 3 of Ref. 1 ingested two of the older 30-mg propantheline tablets, no detectable depression of salivary secretion occurred. The other subjects experienced only about 12% of the anticholinergic response produced by one 15-mg tablet when they took one of the older 30-mg tablets. When Subject 3 took two of the fresher 30-mg tablets, an area under the salivary flow *versus* time curve comparable to two 15-mg tablets was measured. That is, the subject experienced an effect equivalent to about half the dose contained in the fresher prolonged-acting preparation. However, the onset of action associated with the fresher 30-mg dosage form was delayed approximately 1.5 hr. Hence, although the fresher lot of 30-mg tablets exhibited better availability, improvement represented a less than satisfactory level of performance.

Accountability for the labeled amount of drug in all lots of 30-mg prolonged-acting tablets *via* Assay A precludes the possibility that inadequate therapeutic effect was due to chemical instability of drug in the solid dosage form.

No significant difference in dissolution patterns could be discerned between the older and fresher 30-mg tablets over 4 hr when they were subjected to the conversion of media procedure at 1 hr ($p > 0.2$). This result presumably is due to the natural leveling effect of enhanced dissolution on 30-mg tablets by basic media. (Results of Experiments 7 and 8 in Table I showed that drug dissolved about twice as rapidly from both dosage forms when the pH of the medium was raised from 1 to 7.) However, when dissolution in 0.1 *N* HCl was continued beyond the 1st hr[7], the difference in drug released from the older and fresher lots of 30-mg tablets steadily increased and became statistically significant between the 1st ($p > 0.3$) and 2nd ($p < 0.01$) hr and thereafter.

Apparently, the improvement in *in vivo* effectiveness derived from the fresher 30-mg product may be interpreted on the basis of dissolution dissimilarity in an acidic milieu. This experimental finding is consistent with literature reports indicating that the rate and extent of propantheline release from solid dosage forms, during residence in the gastric fluids, should be critical to its bioavailability and, hence, to the onset, intensity, and duration of the anticholinergic effect manifested. One report (7) indicated that almost no absorption of $^{14}C$-propantheline occurs from the stomach and that extensive decomposition takes place in the small intestine. Turnheim and Lauterbach (9) pointed out the main site of propantheline absorption is likely the upper small intestine where active uptake of other quaternary compounds has been postulated. Möller and Rosén (10) discovered that an oral dose of propantheline must be about 10 times as large as the usual parenteral dose to achieve similar pharmacological effect.

It follows that propantheline not in solution ready for absorption as it enters the upper small gut from the stomach cavity could be expected to exhibit low systemic availability and, consequently, reduced activity. The propantheline case is further complicated by the fact that anticholinergic drugs retard gastric emptying, making the dissolution rate process of drug from a solid dosage form in gastric fluids an extremely critical determinant of propantheline bioavailability.

Under these limitations, even careful optimization of the 30-mg prolonged-acting formulation may be insufficient to render it effective. Reformulation of the 30-mg sustained-release dosage form to promote more rapid release of the first 15 mg of drug or full reliance on regular tablets is necessary to ensure therapeutic efficacy.

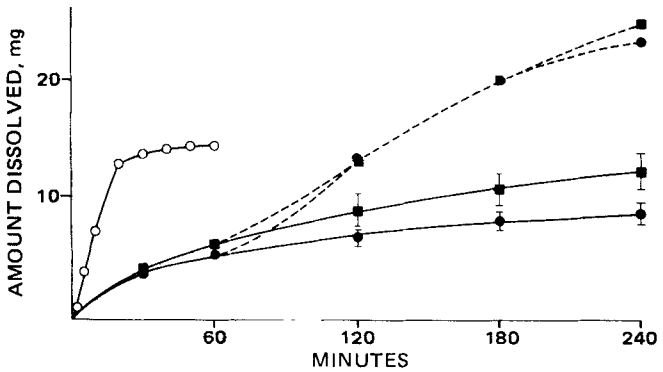


**Figure 1**—*Amount of propantheline dissolved as a function of time from 15-mg tablets (○) and older (●) and fresher (■) 30-mg prolonged-acting tablets in 0.1 N HCl (—) and pH 6.38 phosphate buffer (---) at 37°. Each data point represents the average of five separate trials. Vertical bars indicate ± 1 SD. The difference in amount of drug released from older and fresher 30-mg prolonged-acting tablets in 0.1 N HCl was statistically significant at 120 min and beyond ($p < 0.01$).*

## REFERENCES

(1) M. Gibaldi and B. Grundhofer, *Clin. Pharmacol. Ther.*, **18**, 457 (1975).

(2) "The National Formulary," 14th ed., Mack Publishing Co., Easton, Pa., 1975, pp. 985, 986.

(3) "Physicians Desk Reference," 30th ed., Medical Economics Co., Oradell, N.J., 1976, p. 1415.

(4) G. Levy and B. A. Hayes, *N. Engl. J. Med.*, **262**, 1053 (1960).

(5) G. Levy, J. R. Leonards, and J. A. Procknal, *J. Pharm. Sci.*, **54**, 1719 (1965).

(6) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 418.

(7) B. Beermann, K. Hellström, and A. Rosén, *Clin. Pharmacol. Ther.*, **13**, 212 (1971).

(8) L. G. Chatten and K. O. Okamura, *J. Pharm. Sci.*, **62**, 1328 (1973).

(9) K. Turnheim and F. Lauterbach, "Abstracts of Volunteer Papers, 5th International Congress on Pharmacology," San Francisco, Calif., 1972, p. 136; from D. M. Chaput de Saintonge and A. Herxheimer, *Eur. J. Clin. Pharmacol.*, **5**, 239 (1973).

(10) J. Möller and A. Rosén, *Acta Med. Scand.*, **184**, 201 (1968).

## ACKNOWLEDGMENTS AND ADDRESSES

Received November 2, 1976, from the *Department of Pharmaceutics,*

[7] Long-term dissolution runs in acidic media were considered realistic since the prolonged-acting tablets disintegrated slowly (hence, stand a greater chance of being retained in the stomach longer) and the anticholinergic effect of the drug could be expected to retard stomach emptying.

*School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14214.*

Accepted for publication March 2, 1977.

Supported in part by an award from the University Allocations Committee, State University of New York at Buffalo, Buffalo, NY 14214.

The authors thank Dr. Milo Gibaldi for his helpful review of the manuscript.

[x] To whom inquiries should be directed.

# Viscosity and Surface Tension of Dilute Salicylic Acid–Cetrimide Systems

LUCY S. C. WAN

**Abstract** □ The viscosity and surface tension of systems containing small amounts of salicylic acid in aqueous solutions of cetrimide were determined. An abrupt increase in viscosity was observed, and the molar ratio of salicylic acid to cetrimide at which this viscosity increase occurred was 1:2. The surface tension of these systems also increased sharply after an initial lowering. The salicylic acid concentration at which this behavior was demonstrated was almost the same as that at maximum solubility in the surfactant solution.

**Keyphrases** □ Salicylic acid–cetrimide—aqueous solutions, viscosity and surface tension □ Cetrimide–salicylic acid—aqueous solutions, viscosity and surface tension □ Viscosity—aqueous solutions of salicylic acid and cetrimide □ Surface tension—aqueous solutions of salicylic acid and cetrimide

Salicylic acid previously was found to interact with cetrimide in aqueous solutions, leading to a rise in viscosity (1). This interaction was attributed to the formation of macromolecules, and the interaction was shown to be highly specific. It is restricted to the *ortho*-hydroxy-substituted benzoic acid and does not apply to the amino, chloro, or nitro derivatives.

Determination of viscosity in previous studies involved the use of a viscometer that limited the lower range of viscosity measurements that could be made. Dilute concentrations of salicylic acid in cetrimide solutions produce much less viscous systems, and their viscosity can be determined using a U-tube viscometer. The purpose of this investigation was to determine whether the viscosity behavior observed in the salicylic acid–cetrimide systems studied earlier (1) also occurs in similar, but much more dilute, systems. Since the surface activity of these systems is likely to be affected by the interaction between salicylic acid and cetrimide, surface tension measurements made at the same temperature also are included.

## EXPERIMENTAL

The recrystallized salicylic acid, mp 158–159°, and cetrimide[1] BP used were the same as described previously (2). The viscosity was measured using a U-tube viscometer, equilibrated in a thermostatically controlled water bath at 25 ± 0.5°. The drop-weight method, employing a micrometer syringe[2], was used to determine the surface tension at the same temperature.

## RESULTS AND DISCUSSION

An abrupt increase in viscosity occurred in surfactant solutions of varying concentrations when the salicylic acid content was increased (Fig. 1). The sudden viscosity increase indicated that interaction took place and that macromolecules were formed. At concentrations less than 0.0149 *M* cetrimide in the presence of different amounts of salicylic acid, no such rise in viscosity was produced. This result may have been due to the fact that the quantities of the acid and surfactant used were small and not adequate to demonstrate this pattern of behavior. The degree of interaction produced under such conditions may be inappreciable.

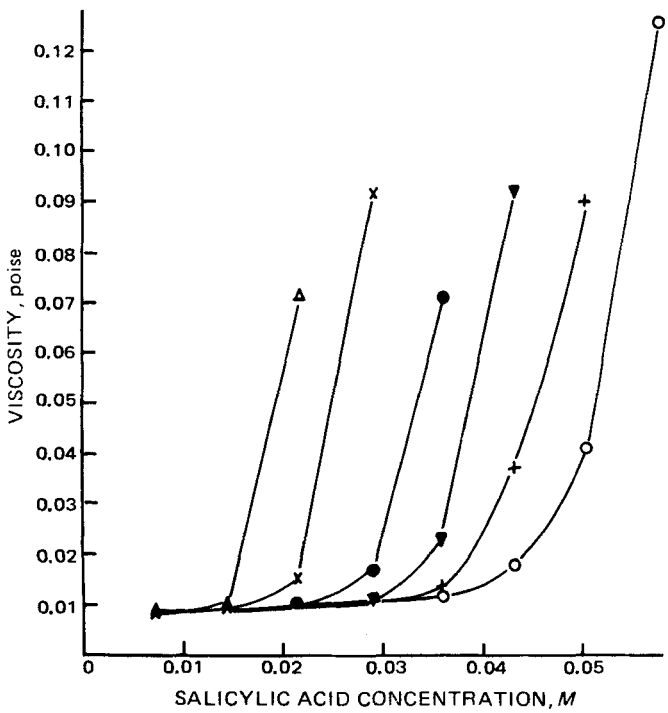


**Figure 1**—*Viscosity change in cetrimide solutions containing salicylic acid at 25°. Key [cetrimide concentration (M)]: △, 0.0149; ×, 0.0298; ●, 0.0446; ▼, 0.0595; +, 0.0744; and ○, 0.0893.*

Aqueous solutions of cetrimide gave rise to this viscosity change only when certain quantities of salicylic acid were present. The acid needed for this purpose increased proportionately with cetrimide concentration (Fig. 2). The molar ratio of salicylic acid to cetrimide needed for this viscosity change to occur was 1:2, as calculated from the slope of the graph in Fig. 2. In addition, as the cetrimide concentration approached zero, the corresponding concentration of salicylic acid required to cause the viscosity increase approached that of its solubility in water, *i.e.*, 0.0156 *M*, as determined by taking the mean between a clear aqueous solution and one in which excess salicylic acid was present.

This water solubility value was in good agreement with literature values (3–8), suggesting that the minimum amount of salicylic acid necessary to bring about an increase in viscosity must exceed that required to saturate the aqueous phase. The minimum amount of cetrimide required for the same purpose has to be greater than 0.0149 *M*. This surfactant

[1] Glovers Chemicals Ltd., Leeds 12, England.

[2] Agla, Burroughs Wellcome and Co., London, England.