# Urea as a Tableting Agent for Benzalkonium Chloride

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**Abstract** □ Mixing benzalkonium chloride with urea provides an excellent means of obtaining a dry physical form of benzalkonium chloride suitable for tableting. Tablets containing benzalkonium chloride-urea admixtures, with and without antirust ingredients (sodium nitrite and sodium carbonate), were readily prepared using direct compression techniques. The tableting characteristics of the admixtures appear to be due to the formation of an adduct and not just the simple adsorption of benzalkonium chloride by urea. The tablets were evaluated under various stability conditions relative to changes in hardness, friability, dissolution rate, germicide content and activity, and anticorrosive action. Results indicated that the best tablets were those prepared using admixtures consisting of 1.5 to 2 parts urea to 1 part benzalkonium chloride.

**Keyphases** □ Benzalkonium Cl tablets—urea effect □ Urea-benzalkonium Cl tablets—direct compression □ Tablets, benzalkonium Cl-urea—physical properties □ Stability—benzalkonium Cl-urea tablets □ IR spectrophotometry—analysis

Since the introduction by Domagk (1935) of quaternary ammonium surfactants as general and medicinal disinfectants, benzalkonium chloride has received wide recognition as an effective germicide (1, 2). Besides its many other applications in surgical and medical practice, benzalkonium chloride is widely used for cold sterilization of surgical, medical, and dental instruments. To prevent the oxidation of metallic instruments it is recommended that antirust ingredients be included in cold sterilizing solutions containing quaternary ammonium germicides (3).

Benzalkonium chloride is a white or yellowish-white gelatinous compound (4). Being sticky in physical character, it is difficult to handle. To facilitate the preparation of commonly used dilutions (1:750–1:7500), a 17% aqueous concentrate of benzalkonium chloride is commercially available (5). A concentrate, however, has several inherent disadvantages: its bulkiness, cost of shipment, the necessity to measure, and, of course, the possibility of spillage. A solid dosage form such as a tablet would be more convenient to handle, store, and ship than a liquid.

It has been demonstrated that sticky, semisolid cationic surfactants can be converted to dry, easy-to-handle powders by complexing with urea (6). This suggested the possible use of urea as a tableting agent for benzalkonium chloride.

The objectives of this study are as follows: (*a*) the preparation of suitable tablets of benzalkonium chloride, with and without antirust ingredients, which can be readily dissolved in water to give clear solutions; (*b*) to study the stability of such tablets; (*c*) to determine the stability and effectiveness of benzalkonium chloride in solutions prepared from such tablets.

## EXPERIMENTAL

**Materials**—Benzalkonium chloride USP, 50% w/w concentrate,[1] urea NF,[2] sodium nitrite (crystal),[3] and sodium carbonate USP (monohydrate),[4] were employed.

**Preparation of Benzalkonium Chloride-Urea Admixtures**—Eighty grams of benzalkonium chloride 50% w/w aqueous concentrate was placed in a 1,000-ml. beaker. Eighty grams of urea was added and the mixture gently heated until a solution was formed. This solution was placed in a 75° oven and allowed to remain until practically all the solvent had evaporated. Then the large pieces of admixture material were broken up by trituration, and this granular powder dried at 75°. The material resulting from this treatment was a dry granular powder consisting of approximately 1 part benzalkonium chloride and 2 parts urea. The same procedure was used to prepare dry admixtures having various proportions of benzalkonium chloride and urea (see Table I).

**IR Analysis**—IR spectra were recorded on a spectrophotometer.[5] The urea-benzalkonium chloride admixtures were examined as mineral oil mulls. Spectra of the mixtures were compared to urea and to previously prepared urea-benzalkonium chloride adducts (6) to determine if any of the urea and benzalkonium chloride in the admixtures had undergone adduct formation.

**Preparation of Tablets**—Each of the benzalkonium chloride-urea admixtures was passed through a 20-mesh standard sieve before tableting. Benzalkonium chloride-urea tablets of appropriate weights as shown in Table I were made on a single-punch tablet machine[6] using 1.9-cm. (3/4-in.) flat punches at a rate of 45–50 tablets/min. To minimize the number of ingredients that might alter the bactericidal activity of the benzalkonium chloride and to ensure clarity of solutions prepared from tablets, no additives (*e.g.*, lubricant or disintegrating agents) were used in the preparation of these tablets.

The antirust ingredients consisting of sodium carbonate (1.16 parts) and sodium nitrite (0.5 part) were mixed and passed through a 20-mesh standard sieve. The correct proportions of antirust mixture and benzalkonium chloride-urea admixture were mixed (see Table II) and passed through a 20-mesh standard sieve at least five times to ensure thorough mixing. Benzalkonium chloride-urea with antirust tablets were compressed in the same manner as described above.

## EVALUATION PROCEDURES

**Hardness**—Hardness of tablets was determined using a hand-operated hardness tester.[7]

[1] City Chemical Corp.
[2] Fisher.
[3] Fisher reagent grade.
[4] Mallinckrodt Chemical Works, St. Louis, Mo.
[5] Perkin-Elmer Infracord model 137.
[6] Stokes model F.
[7] Strong Cobb.

**Table I**—Benzalkonium Chloride-Urea Tablets

| Tablet No. | Ratio Benzalkonium Chloride: Urea | Amt. of Complex Equiv. to 1.26 g./quat.[a], g. | Wt. of Prepared Tablet ± *SD*, g.[b] | Dissolution Time, min. |
|---|---|---|---|---|
| 1 | 1:1 | Not obtained | — | — |
| 2 | 1:1.5 | 3.15 | Not compressible | — |
| 3 | 1:2 | 3.78 | 1.918 (0.01) | 3.5 |
| 4 | 1:2.5 | 4.41 | 2.246 (0.009) | 5.0 |
| 5 | 1:3 | 5.04 | 2.545 (0.012) | 5.5 |
| 6 | 1:3.5 | 5.67 | 1.469 (0.013)[c] | 3.25 |
| 7 | 1:4 | 6.30 | 1.627 (0.014)[c] | 3.5 |

[a] The amount of benzalkonium chloride (anhydrous) required to prepare 1 quart (945 ml.) of a 1:750 solution is 1.26 g. [b] Weight of each tablet represents the amount of admixture sufficient to prepare 1 pint of a 1:750 benzalkonium chloride solution. [c] Because of the large bulk it was necessary to divide the formulation so that two tablets added to a pint of water would give a 1:750 concentration of benzalkonium chloride.

***Dissolution Time***—A magnetic stirrer[8] along with a 3.5-cm. polytetrafluoroethylene-coated[9] stirring bar was used for determining the dissolution time of tablets at 25 ± 1°. A 400-ml. beaker containing 100 ml. of distilled water and the stirring bar, was placed on the magnetic stirrer. The speed control knob was set at the 7 position and a tablet dropped into the stirred water. The time for complete dissolution was recorded.

**Friability Value**—The Roche friabilator was used for determination of friability. Ten tablets were weighed and placed in the drum and the drum rotated for 4 min. (100 rotations). The intact tablets were cleaned with a camel's hair brush and loss of weight determined. The loss in weight expressed as percent was the friability value of the tablets.

**Effect of Aging**—To estimate the effect of aging at various temperatures on physical properties and germicide content, 15–20 tablets of each formula were placed in tightly capped amber bottles and stored at 5°, ambient room temperature, 40°, and 50°. At the end of each month for 3 to 4 months tablets were removed, visually inspected, and hardness, friability, dissolution times, benzalkonium chloride content, and bactericidal activity determined.

**Benzalkonium Chloride Assay**—The titrimetric method used to determine the amount of benzalkonium chloride in an admixture, in a tablet or solution was essentially that of Barr *et al.* (7) as modified by Auerbach (8) and is described in previous papers (6, 9).

**Stability of Aqueous Solutions Prepared from Tablets**—Aqueous solutions of benzalkonium chloride (1:750) were prepared by dissolving the prepared tablets in distilled water. The pH and benzalkonium chloride content of each solution were determined immediately after preparation. The solutions were then placed in 500-ml. beakers, covered with a watch glass, and allowed to stand at ambient room temperature. After 1 month and 4 months, each solution was analyzed and its pH determined. Solutions were adjusted to their original volume if any evaporation took place during the test period.

***Corrosion Test***—Enough tablets were dissolved in distilled water to give a 1:750 concentration of germicide. Sixty milliliters of each solution was placed in 120-ml. glass prescription bottles. Two highly polished wire nails (20 penny) previously cleaned with carbon tetrachloride and dried were placed upright in each bottle. Preliminary experiments indicated that common nails were much more susceptible to rusting than stainless steel instruments, and therefore would be a more sensitive test material for detecting corrosive properties of test solutions. Control solutions of distilled water and benzalkonium chloride aqueous solution (1:750) were also included in this study. The nails were observed for rusting after 15 days and 4 months.

**Bacteriological Test**—The use dilution method using *Staph. aureus* (10) was employed to test the bactericidal activity of benzalkonium chloride in aqueous solutions prepared from tablets. The test procedure was carried out at 20° and the activities expressed as phenol coefficients.

[8] Mag Mix, Precision Scientific Co.
[9] Teflon, E. I. du Pont de Nemours & Co., Wilmington, Del.

**Table II**—Benzalkonium Chloride-Urea with Antirust Tablets

| Tablet No. | Ratio Benzalkonium Chloride: Urea | Total Wt. of Ingredients Required to Prepare 1 qt. of Sterilizing Solution, g.[a] | Wt. of Prepared Tablet ± *SD*, g.[b] | Dissolution Time, min. |
|---|---|---|---|---|
| 1AR | 1:1 | Not obtained | — | — |
| 2AR | 1:1.5 | 9.79 | 2.465 (0.02) | 6.25 |
| 3AR | 1:2 | 10.42 | 2.647 (0.023) | 6.25 |
| 4AR | 1:2.5 | 11.05 | 2.792 (0.013) | 6.5 |
| 5AR | 1:3 | 11.68 | 2.951 (0.013) | 6.75 |
| 6AR | 1:3.5 | 12.31 | 3.113 (0.015) | 7.0 |
| 7AR | 1:4 | 12.94 | 3.28 (0.016) | 7.0 |

[a] The weight of benzalkonium chloride-urea admixture plus 6.64 g. of antirust ingredients (1.16 part sodium carbonate and 0.5 part sodium nitrite) recommended for 1 qt. of sterilizing solution (3). [b] Four tablets of each sample represent the amount of ingredients needed to prepare 1 qt. of aqueous sterilizing solution (1:750 benzalkonium chloride).

## RESULTS AND DISCUSSION

It appears that mixing benzalkonium chloride with urea can provide an excellent means of obtaining a dry physical form of benzalkonium chloride suitable for tableting. Mixtures containing 2 to 4 parts urea to 1 part benzalkonium chloride were satisfactorily tableted using direct compression techniques (Table I). The dissolution times of these tablets were between 3.5 and 5 min. The admixture containing 1.5 parts of urea could not be tableted because of its tendency to stick to the punches. To prepare a suitable tablet, compression pressures had to be used that produced tablets having hardnesses from 15 to 28 Strong Cobb units (S.C. units) depending on the tablet composition (see initial hardnesses in Table III). Lower compression pressures caused sticking or jamming of the tablet machine due to adhesion of material to punches and die. In the case of Tablet No. 3 compression pressures producing softer or harder tablets than the suitable tablet (15 S.C. units) resulted in adhesion of material to the punches.

Tablets containing urea-benzalkonium chloride and antirust ingredients were readily prepared using admixtures consisting of 1.5 to 4 parts urea (Table II). The dissolution rates of these tablets were between 6 and 7 min. Although the mixture containing 1.5 parts urea could not be compressed as such, combining this admixture with antirust ingredients allowed the preparation of a suitable tablet. It appeared that the additional bulk of the anti rust ingredients affected the sticking tendency of the urea-benzalkonium admixture. As the urea proportion in sample tablets increased, with concomitant increases in tablet weights, more pressure had to be used to prepare a satisfactory tablet (see initial hardnesses in Table IV). Use of lower compression pressures resulted in sticking of the material to punches and die.

Urea appears to be a unique tableting agent for benzalkonium

**Table III**—Effect of Storage at Various Temperatures on Hardness of Benzalkonium Chloride-Urea Tablets[a]

| Time Elapsed, months | Temp., °C. | Hardness (S.C. Units)[b] — Tablet No. 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Initial | | 15 | 25 | >28 | 25 | 20 |
| *1* | 40 | 15 | 25 | >28 | 25 | 21 |
| | 50 | 18 | >28 | >28 | >28 | >28 |
| *2* | 40 | 15 | 25 | >28 | 26 | 20 |
| | 50 | 19 | >28 | >28 | >28 | >28 |
| *3* | Room temperature | 18 | >28 | >28 | >28 | >28 |
| | 40 | 18 | >28 | >28 | >28 | >28 |
| | 50 | >28 | >28 | >28 | >28 | >28 |
| *4* | 5 | 15 | >28 | >28 | >28 | >28 |
| | Room temperature | 18 | >28 | >28 | >28 | >28 |
| | 40 | 19 | >28 | >28 | >28 | >28 |
| | 50 | 28 | >28 | >28 | >28 | >28 |

[a] Each result represents an average of four determinations. [b] Strong Cobb units.

Table IV—Effect of Storage at Various Temperatures on Hardness of Benzalkonium Chloride-Urea with Antirust Tablets[a]

| Time Elapsed, months | Temp., °C. | Hardness (S.C. Units)[b] Tablet No. 2AR | 3AR | 4AR | 5AR | 6AR | 7AR |
|---|---|---|---|---|---|---|---|
| Initial | | 10 | 14 | 15 | 20 | 25 | >28 |
| *1* | Room temperature | 10 | 15 | 15 | 20 | 25 | >28 |
| | 40 | 11 | 20 | 20 | >28 | >28 | >28 |
| | 50 | 15 | 8 | 9 | 25 | 15 | >28 |
| *2* | 40 | 12 | 20 | 20 | >28 | >28 | >28 |
| | 50 | 9[c] | 4 | 5 | 20 | 10 | 15 |
| *3* | 40 | 12 | 21 | 21 | >28 | >28 | >28 |
| | 50 | 15[c] | 12 | 9 | >28 | 15 | 15 |
| *4* | 5 | 14 | >28 | 25 | >28 | >28 | >28 |
| | Room temperature | 15 | >28 | 26 | >26 | >28 | >28 |
| | 40 | 10 | 22 | 21 | >28 | >28 | >28 |
| | 50 | 5[c] | 5 | 8 | >28 | 8 | 9 |

[a] Each result represents an average of four determinations. [b] Strong Cobb units. [c] A light yellow discoloration was noticed after one month at 50°. This color did not become darker on further storage.

chloride. Preliminary experiments were carried out in this study to determine if soluble inorganic salts (*e.g.*, potassium and sodium chloride, ammonium chloride, sodium nitrite, potassium and sodium carbonate) could be used to adsorb benzalkonium chloride using as high as 10 parts salt to 1 part benzalkonium chloride. In all cases the granulations were greasy to the touch, and when tableting was attempted, picking or sticking and/or jamming of the machine occurred.

As reported in an earlier study (6) urea forms canal complexes with benzalkonium chloride and the pure adduct has a urea to benzalkonium chloride molecular ratio of 16.7 to 1 (approximately 2.82 parts urea to 1 part benzalkonium chloride on a weight basis). In this study IR spectra (Fig. 1) indicate that urea-benzalkonium chloride adducts were present in all the admixtures prepared. The shift in the band near 12.5 $\mu$, as a result of a change in the urea crystal lattice, is characteristic of adduct formation (11). Therefore, the tableting characteristics of the admixtures are probably due to formation of adduct and not just the simple adsorption or dilution of benzalkonium chloride by urea. Very satisfactory tablets were prepared from urea-benzalkonium chloride admixtures containing only 2.0 to 2.5 parts urea to 1 part benzalkonium chloride. These amounts of urea are not sufficient to bring about complete adduction of all the quaternary compound present. Possibly all of the benzalkonium chloride had been partially adducted or some of the benzalkonium had been completely adducted and the remainder adsorbed by the solid material. There is also the possibility that under the conditions of preparation adduction of the urea was incomplete and the admixture consisted of urea-benzalkonium adduct (hexagonal urea), tetragonal urea, and benzalkonium chloride. Whatever the exact composition of the mixtures might be, those admixtures containing less than the theoretical amount of urea for complete adduction (2.8:1) required less pressure to produce a satisfactory tablet (Tables III and IV)

Table V—Effect of Storage at Various Temperatures on Friability Values of Benzalkonium Chloride-Urea Tablets[a]

| Time Elapsed, months | Temp., °C. | Friability, % Tablet No. 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Initial | | 0.65 | 1.40 | 1.45 | 1.02 | 0.92 |
| *1* | 40 | 0.60 | 1.45 | 1.48 | 1.00 | 0.98 |
| | 50 | 1.31 | 1.71 | 1.78 | 1.70 | 1.58 |
| *2* | 40 | 0.68 | 1.40 | 1.51 | 1.10 | 0.85 |
| | 50 | 1.40 | 1.70 | 1.75 | 1.75 | 1.51 |
| *3* | 5 | 0.62 | 1.45 | 1.51 | 1.20 | 0.84 |
| | Room temperature | 0.80 | 1.52 | 1.55 | 1.18 | 1.40 |
| | 40 | 0.89 | 1.60 | 1.50 | 1.25 | 1.38 |
| | 50 | 1.58 | 1.90 | 2.02 | 2.13 | 1.61 |

[a] Each result represents an average of three determinations.

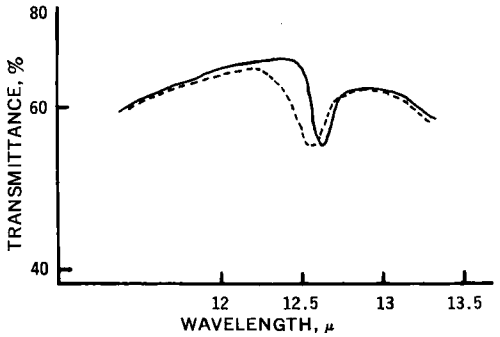


**Figure 1**—*IR spectra of urea-benzalkonium chloride admixtures. Key: —, urea; ---, urea-benzalkonium chloride pure adduct (6), and various urea-benzalkonium chloride admixtures.*

Table VI—Effect of Storage at Various Temperatures on Friability Values of Benzalkonium Chloride-Urea with Antirust Tablets[a]

| Time Elapsed, months | Temp., °C. | Friability, % Tablet No. 2AR | 3AR | 4AR | 5AR | 6AR | 7AR |
|---|---|---|---|---|---|---|---|
| Initial | | 0.78 | 0.80 | 1.05 | 0.97 | 0.75 | 0.80 |
| *1* | Room temperature | 0.78 | 0.75 | 1.00 | 1.06 | 0.70 | 0.81 |
| | 40 | 1.42 | 1.95 | 2.01 | 1.92 | 1.36 | 1.08 |
| | 50 | 1.50 | 2.90 | 3.10 | 2.10 | 1.60[b] | 1.15 |
| *2* | 40 | 1.49 | 1.98 | 1.00 | 1.96 | 1.52 | 1.00 |
| | 50 | 1.10 | 3.32 | 3.56 | 1.50 | 1.51[b] | 1.75[b] |
| *3* | 5 | 0.75 | 2.00 | 1.95 | 1.76 | 1.50 | 0.98 |
| | Room temperature | 0.98 | 2.05 | 1.90 | 1.80 | 1.55 | 1.01 |
| | 40 | 1.05 | 1.90 | 1.90 | 1.90 | 1.62 | 1.41 |
| | 50 | 1.58 | 2.85 | 2.65 | 2.25 | 1.80[b] | 1.80[b] |

[a] Each result represents an average of three determinations. [b] Because of excessive sticking of powder to tablets, figures do not represent true friability values. Tablets appeared to be moist.

**Table VII**—Stability of Tablets and Aqueous Solutions Prepared from Tablets[a]

| Sample No. | pH of Solutions After | | | % of Theoretical Concn. (1:750) Benzalkonium Chloride in Solutions After | | | Phenol Coeff. of Benzalkonium Chloride in Solutions After | |
|---|---|---|---|---|---|---|---|---|
| | Initial[b] | 1 month | 4 months | Initial[b] | 1 month | 4 months | Initial[b, d] | 4 months[d] |
| 3 | 6.00 | 6.02 | 7.72 | 102.6 | 103.4 | 99.7 | 248 | 239 |
| 4 | 6.02 | 6.05 | 7.75 | 97.9 | 99.9 | 98.9 | — | — |
| 5 | 6.10 | 6.10 | 7.90 | 100.2 | 102.8 | 100.7 | 251 | 241 |
| 6 | 6.15 | 6.12 | 7.92 | 99.6 | 98.9 | 98.6 | — | — |
| 7 | 6.22 | 6.20 | 8.0 | 102.6 | 101.8 | 103.9 | 237 | 246 |
| 2AR | 10.90 | 10.95 | 10.90 | 103.9 | 101.1 | 100.2 | — | — |
| 3AR | 10.95 | 10.90 | 10.95 | 97.2 | 98.8 | 102.6 | 242 | 239 |
| 4AR | 10.95 | 10.92 | 10.90 | 104.4 | 99.8 | 105.9 | — | — |
| 5AR | 10.92 | 10.92 | 10.95 | 101.1 | 97.7 | 97.8 | 252 | 249 |
| 6AR | 10.90 | 10.90 | 10.92 | 102.4 | 98.8 | 101.3 | — | — |
| 7AR | 11.0 | 11.20 | 11.25 | 97.7 | 99.9 | 100.2 | 243 | 240 |

[a] Each result represents an average of two experiments. [b] Similar pH values, assay results, and phenol coefficients were obtained for solutions prepared from tablets that had been stored 4 months at room temperature, 40°, and 50°. [c] Dilutions and calculations were based on an initial theoretical concentration of 1:750. [d] The phenol coefficients for a control solution of benzalkonium chloride were 246 initially and 241 after 4 months.

**Table VIII**—Effect on Wire Nails of Aqueous Benzalkonium Chloride Solutions (1:750) Prepared from Tablets[a]

| Time Elapsed | Water (Control) | 1:750 Benzalkonium Chloride Solution | Solutions Prepared from Tablets Sample No. | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 3 | 4 | 5 | 6 | 7 | 2AR-7AR |
| 15 days | + | + | ++ | ++ | +++ | +++ | ++++ | 0 |
| 4 months | ++++ | ++++ | ++++ | ++++ | ++++ | ++++ | ++++ | 0 |

[a] 0, no corrosion; +, slightly spotted nails; ++, spotted nails with slight brown deposit in container; +++, completely rusty nails with brown ppt. in container; ++++, thick cluster of rust on nails with large amount of brown ppt. in container.

than admixtures with higher ratios of urea. These tablets also were less friable (Tables V and VI). It appeared that the presence of some free benzalkonium chloride in the admixtures provided tablet granulations with good binding properties.

Inclusion of urea in the tablet formulation did not affect the chemical stability or bactericidal activity of benzalkonium chloride in the prepared tablets and in solutions prepared from tablets (Table VII). After 4 months, slight increases in pH (approx. 1.8 pH units) were noticed in solutions prepared from benzalkonium chloride-urea tablets. These increases were probably due to the breakdown of some of the urea to ammonia.

Solutions containing urea and benzalkonium chloride were more corrosive than control solutions after 15 days, however, urea did not adversely affect the protective action of antirust ingredients (Table VIII).

Tablets of benzalkonium chloride-urea showed very little change in their physical characteristics when stored at room temperature and 40° for 3 and 4 months. After storage at 50°, however, there were increases in hardnesses and friability values (Tables III and V). The changes might be attributed to the effect of this relatively high temperature on the adduct lattice structure. There was essentially no change in the dissolution times after the tablets had been stored for 4 months at room temperature, 40°, and 50°.

Tablet No. 3 exhibited the best initial values for hardness, dissolution time, and friability and least changes in these values during storage at various temperatures.

Tablets of benzalkonium chloride with antirust ingredients displayed changes in physical characteristics during their storage at various temperatures (Tables IV and VI). Except for Tablet 5AR, there were considerable decreases in hardnesses of the sample tablets at 50°. After 4 months at room temperature and 40° the hardness of Tablet 2AR was least affected. Essentially no changes were observed in the dissolution times of all tablets at all test temperatures. Except for Tablet 2AR, all antirust tablets displayed large increases in their friability values at all test temperatures.

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## ACKNOWLEDGMENTS AND ADDRESSES


Received May 6, 1968, from the *School of Pharmacy, University of Georgia, Athens, GA 30601*

Accepted for publication November 7, 1968.

Abstracted from a thesis submitted by Qamar-Ul-Islam to the Graduate School, University of Georgia, Athens, Ga., in partial fulfillment of Master of Science degree requirements.

This investigation was supported in part by the Office of General Research, University of Georgia, Athens.