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* AFPE Paul M. Scott Memorial Fellow. Present address: College of Pharmacy, University of Cincinnati, Cincinnati, OH 45221.

[x] To whom inquiries should be directed.

# Application of Gluconolactone in Direct Tablet Compression

**S. S. NASIR [x], L. O. WILKEN, Jr., and BEHROZE AKHTAR**

**Abstract** □ Gluconolactone was evaluated as an excipient for tablets prepared by direct compression using various drugs known to be difficult to compress. The physical properties of the tablets were evaluated after compression and after storage and were satisfactory. Comparative studies were conducted between gluconolactone and anhydrous lactose, a common direct compression diluent, for development of static charges during blending, flow, drug distribution, drug stratification, color distribution, compressibility, and preservation against mold growth. Gluconolactone possesses those properties necessary to produce high quality tablets by the direct compression process. Separate powdered mixtures of aspirin USP with gluconolactone, anhydrous lactose, spray-dried lactose, mannitol, and sorbitol were stored at various humidities and temperatures for specified periods and tested for the integrity of aspirin. Gluconolactone contributed least to the degradation of the drug as compared to other excipients studied. A preliminary *in vivo* study also was conducted on the bioavailability of aspirin from separate and similar mixtures with gluconolactone, anhydrous lactose, and starch. Gluconolactone did not show any inhibitory effect on aspirin absorption.

**Keyphrases** □ Gluconolactone—excipient in directly compressed tablets of various drugs, effect on physical characteristics □ Excipients—gluconolactone in directly compressed tablets of various drugs, effect on physical characteristics □ Tablets, direct compression—various drugs, gluconolactone as excipient, effect on physical characteristics □ Dosage forms—directly compressed tablets of various drugs, gluconolactone as excipient, effect on physical characteristics

In terms of economics and stability, the direct compression process offers distinct advantages over other methods used in the manufacture of compressed tablets. During the last decade, considerable interest has been shown in this process. Excipients such as spray-dried lactose (1), microcrystalline cellulose (2), fused mannitol (3), calcium phosphate (4), dextrose (5), amylose (6), anhydrous lactose (7), and directly compressible starch (8) have been studied for their ability to aid in the preparation of compressed tablets. The use of these materials had certain limitations including the difference in particle size and bulk density leading to stratification, the excipients to drug ratio necessary to effect compression, the requirement of an optimum amount of moisture, incompatibility with the drugs, the development of static charges during processing, and cost.

Table I—Properties of Gluconolactone (I) and Anhydrous Lactose

| Property | I | Anhydrous Lactose |
|---|---|---|
| Solubility in water at 25°, g/ml | 0.59 | 0.2 |
| Particle-size distribution[a] of commercial powders used, % retained | | |
| 20 mesh | 0.0010 | 0.00257 |
| 30 mesh | 0.0450 | 0.02318 |
| 40 mesh | 3.4000 | 0.21894 |
| 60 mesh | 3.8975 | 4.6623 |
| 80 mesh | 4.0525 | 11.9391 |
| 100 mesh | 4.250 | 14.90907 |
| Flow properties, angle of repose | | |
| Plain | 26° 23′ | 22° 43′ |
| With 1% magnesium stearate | 23° 50′ | 20° 12′ |

[a] A total of 84.354% of I and 64.246% of anhydrous lactose passed through the 100-mesh sieve.

Due to these factors, evaluation of new excipients is warranted. Preliminary experiments with gluconolactone (D-glucono-1,5-lactone, I) indicated considerable potential as an excipient in direct compression; therefore, a thorough study was undertaken.

Compound I was used previously in pharmaceuticals as a stabilizer for multivitamins (9) and tetracycline (10). It is prepared by the oxidation of glucose with bromine water (11) or by oxidation of glucose in *Acetobacter suboxydans* (12). Compound I has a sweet taste and is highly soluble in water (59 g/100 ml); it is slowly hydrolyzed by water to gluconic acid. The calcium and ferrous salts of this acid are

Table II—Physical Properties of Tablets Prepared with Gluconolactone (I) Formulations

| Tablet Formula | Hardness[a], kg ± *SD* | | Friability, % | | Thickness, mm ± *SD* | Weight, mg ± *SD* | Disintegration Time, min ± *SD* at 37° | |
|---|---|---|---|---|---|---|---|---|
| | Initial | 6 Months of Storage | Initial | 6 Months of Storage | | | Initial | 6 Months of Storage |
| Plain I tablets, Batch 1<br>I, 497.7 mg<br>Methylcellulose (1500 cps), 63 mg<br>Dried starch, 63 mg<br>Magnesium stearate, 6.3 mg<br>9.5-mm deep concave punches and dies | 6.670 ± 0.830 | 7.900 ± 0.464 | 0.45 | 0.43 | 5.63 ± 0.83 | 628.00 ± 9.520 | Water: 2.22 ± 0.23<br>SGF[b]: 2.13 ± 0.56<br>SIF[c]: 6.01 ± 0.42 | Water: 4.39 ± 0.489<br>SGF: 4.11 ± 0.48<br>SIF: 6.20 ± 0.11 |
| Plain I tablets, Batch 2<br>I, 560.7 mg<br>Methylcellulose (1500 cps), 63 mg<br>Magnesium stearate, 6.3 mg<br>11.1-mm standard concave punches and dies | 8.700 ± 0.100 | 8.840 ± 0.744 | 0.31 | 0.31 | 6.50 ± 0.057 | 630.00 ± 16.570 | Water: 3.55 ± 0.33<br>SGF: 6.57 ± 1.26<br>SIF: 6.91 ± 0.73 | Water: 5.39 ± 0.487<br>SGF: 7.30 ± 1.24<br>SIF: 7.1 ± 0.48 |
| Plain I tablets, Batch 3<br>I, 560.7 mg<br>Methylcellulose (1500 cps), 31.5 mg<br>Dried starch, 31.5 mg<br>Magnesium stearate, 6.3 mg<br>11.1-mm standard concave punches and dies | 6.040 ± 0.850 | 5.500 ± 0.964 | 0.43 | 0.48 | 5.60 ± 0.058 | 623.00 ± 6.570 | Water: 4.17 ± 0.43<br>SGF: 5.22 ± 0.31<br>SIF: 7.4 ± 0.8 | Water: 6.02 ± 0.42<br>SGF: 6.55 ± 0.38<br>SIF: 8.2 ± 1.7 |
| Ferrous sulfate tablets<br>Ferrous sulfate (anhydrous), 149 mg<br>I, 360 mg<br>Methylcellulose (1500 cps), 40 mg<br>Magnesium stearate, 11 mg<br>9.5-mm deep concave punches and dies | 5.150 ± 0.657 | 5.240 ± 0.363 | 0.65 | 0.64 | 5.50 ± 0.033 | 559.00 ± 9.23 | Water: 9.30 ± 0.810 | Water: 8.53 ± 0.508 |
| Phenobarbital tablets<br>Phenobarbital, 30 mg<br>I, 160 mg<br>Methylcellulose (1500 cps), 40 mg<br>Magnesium stearate, 1.25 mg<br>Stearic acid, 3.75 mg<br>7.9-mm standard concave punches and dies | 6.400 ± 0.917 | 5.400 ± 0.487 | 0.25 | 0.28 | 4.10 ± 0.00 | 243.00 ± 9.24 | Water: 6.03 ± 1.28 | Water: 7.77 ± 1.09 |
| Sodium chloride tablets<br>Sodium chloride, 600 mg<br>I, 540 mg<br>Methylcellulose (1500 cps), 60 mg<br>Magnesium stearate, 12 mg<br>12.7-mm flat-faced punches and dies | 5.20 ± 0.341 | 6.37 ± 1.31 | 0.050 | 0.045 | 6.26 ± 0.051 | 1211.00 ± 36.20 | Water: 6.28 ± 0.350 | Water: 9.36 ± 0.546 |
| Ephedrine hydrochloride tablets<br>Ephedrine hydrochloride, 30 mg<br>I, 135 mg<br>Methylcellulose, 15 mg<br>Stearic acid, 3 mg<br>Magnesium stearate, 2 mg<br>7.9-mm standard concave punches and dies | 4.60 ± 1.22 | 4.77 ± 0.535 | 0.30 | 0.35 | 3.62 ± 0.103 | 195.00 ± 20.0 | Water: 11.30 ± 0.18 | Water: 6.79 ± 0.909 |

(continued)

Table II—(*Continued*)

| Tablet Formula | Hardness[a], kg ± *SD* | | Friability, % | | Thickness, mm ± *SD* | Weight, mg ± *SD* | Disintegration Time, min ± *SD* at 37° | |
|---|---|---|---|---|---|---|---|---|
| | Initial | 6 Months of Storage | Initial | 6 Months of Storage | | | Initial | 6 Months of Storage |
| Isoniazid tablets<br>Isoniazid, 50 mg<br>I, 260 mg<br>Methylcellulose (1500 cps), 40 mg<br>Magnesium stearate, 7 mg<br>7.9-mm standard concave, punches and dies | 5.25 ± 0.485 | 5.93 ± 0.574 | 0.41 | 0.39 | 5.45 ± 0.097 | 354.00 ± 7.24 | Water: 8.32 ± 0.50 | Water: 14.01 ± 0.350 |
| Methenamine tablets<br>Methenamine, 250 mg<br>I, 150 mg<br>Methylcellulose (1500 cps), 25 mg<br>Magnesium stearate, 4.4 mg<br>Stearic acid, 8.6 mg<br>11.1-mm standard concave punches and dies | 6.15 ± 0.885 | 6.11 ± 0.769 | 0.41 | 0.47 | 4.64 ± 0.097 | 445.00 ± 11.0 | Water: 6.25 ± 0.78 | Water: 6.22 ± 0.814 |
| Ascorbic acid tablets<br>Ascorbic acid, 300 mg<br>I, 240 mg<br>Methylcellulose (1500 cps), 80 mg<br>Magnesium stearate, 6 mg<br>Stearic acid, 12 mg<br>11.1-mm standard concave punches and dies | 6.55 ± 1.26 | 5.830 ± 0.799 | 0.81 | 0.75 | 6.640 ± 0.135 | 633.00 ± 14.80 | Water: 16.00 ± 0.00 | Water: 19.04 ± 1.29 |
| Sulfathiazole tablets<br>Sulfathiazole, 500 mg<br>I, 360 mg<br>Methylcellulose (1500 cps), 45 mg<br>Dried starch, 45 mg<br>Magnesium stearate, 4.8 mg<br>Stearic acid, 19.2 mg<br>12.7-mm flat-faced beveled-edge punches and dies | 6.80 ± 0.809 | 6.97 ± 1.139 | 0.40 | 0.45 | 5.900 ± 0.087 | 967.00 ± 22.17 | Water: 25.00 ± 4.73 | Water: 24.23 ± 3.57 |
| Ferrous gluconate tablets<br>Ferrous gluconate, 300 mg<br>I, 270 mg<br>Methylcellulose (1500 cps), 30 mg<br>Magnesium stearate, 6 mg<br>Stearic acid, 12 mg<br>11.1-mm standard concave punches and dies | 11.00 ± 1.80 | 8.860 ± 1.153 | 0.68 | 0.72 | 5.90 ± 0.10 | 627.00 ± 10.15 | Water: 9.77 ± 3.47 | Water: 12.13 ± 2.156 |
| Calcium lactate tablets<br>Calcium lactate, 300 mg<br>I, 240 mg<br>Methylcellulose (1500 cps) 60 mg<br>Magnesium stearate, 6 mg<br>Stearic acid, 12 mg<br>11.1-mm standard concave punches and dies | 13.30 ± 1.26 | 2.190 ± 0.378 | 0.71 | 0.10 | 6.50 ± 0.124 | 616.00 ± 20.28 | Water: 15.60 ± 3.22 | Water: 18.32 ± 3.11 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Aspirin tablets<br>Aspirin, 150 mg<br>I, 360 mg<br>Methylcellulose (1500 cps), 40 mg<br>Dried starch, 40 mg<br>Magnesium stearate, 6 mg<br>11.1-mm standard concave punches | 5.50 ± 0.687 | 5.73 ± 0.448 | 0.78 | 0.68 | 5.70 ± 0.141 | 607.00 ± 19.09 | Water: 3.88 ± 0.799 | Water: 5.92 ± 1.012 |
| Riboflavin tablets<br>Riboflavin, 5 mg<br>I, 90 mg<br>Methylcellulose (1500 cps), 10 mg<br>Magnesium stearate, 1 mg<br>6.3-mm deep concave punches and dies | 2.40 ± 0.394 | 2.73 ± 0.495 | 0.22 | 0.31 | 3.37 ± 0.105 | 108.00 ± 2.90 | Water: 5.38 ± 0.56 | Water: 7.93 ± 0.661 |
| Multivitamins and mineral tablets<br>Vitamin A, 5000 USP units<br>Vitamin D, 400 USP units<br>Thiamine, 2 mg<br>Riboflavin, 3 mg<br>Niacinamide, 20 mg<br>Ascorbic acid, 50 mg<br>Pyridoxine, 1 mg<br>Cyanocobalamin, 1 μg<br>Calcium pantothenate, 1 mg<br>Ferrous sulfate, 18 mg<br>Copper sulfate, 1 mg<br>Magnesium oxide, 5 mg<br>Magnesium citrate, 1 mg<br>Zinc chloride, 1.5 mg<br>I, 180 mg<br>Methylcellulose (1500 cps), 20 mg<br>Magnesium stearate, 3 mg<br>Stearic acid, 6 mg<br>9.5-mm deep concave punches and dies | 4.95 ± 1.01 | 4.00 ± 0.512 | 0.35 | 0.40 | 4.38 ± 0.103 | 312 ± 5.0 | Water: 5.78 ± 1.60 | Water: 7.30 ± 0.973 |
| Aminosalicylic acid tablets<br>Aminosalicylic acid, 250 mg<br>I, 320 mg<br>Methylcellulose (1500 cps), 80 mg<br>Magnesium stearate, 6 mg<br>Stearic acid, 14 mg<br>11.1-mm standard concave punches and dies | 6.55 ± 1.26 | — | 0.85 | — | 6.64 ± 0.135 | 700.00 ± 22.90 | Water: 16.0 ± 1.5 | — |
| Digitalis tablets<br>Digitalis, 50 mg<br>I, 400 mg<br>Methylcellulose (1500 cps), 80 mg<br>Magnesium stearate, 10.6 mg<br>9.5-mm deep concave punches and dies | 5.40 ± 0.817 | 6.26 ± 0.375 | 0.78 | 0.73 | 5.81 ± 0.316 | 526.00 ± 9.92 | Water: 11.33 ± 0.18 | Water: 15.41 ± 0.47 |

[a] Stokes tester. [b] SGF = simulated gastric fluid. [c] SIF = simulated intestinal fluid.

Table III—Estimation of Sticking of Powders during Blending

| Drug | Weight per 500 ml of Powder, g | Amount Retained, g ± *SD* | Percent Retained |
|---|---|---|---|
| I | 336.8 | 3.8 ± 0.12 | 1.13 |
| Anhydrous lactose | 361.0 | 4.3 ± 0.10 | 1.19 |
| Spray-dried lactose | 318.0 | 0.8 ± 0.03 | 0.25 |

commonly administered orally in large doses for the effect of the cations.

## EXPERIMENTAL

**Particle-Size Analysis**—The particle-size distribution of I was determined with a testing sieve shaker[1] using stainless steel U.S. standard sieve series in 20-, 30-, 40-, 60-, 80-, and 100-mesh sizes. A 200-g sample was tested in the sieve shaker for 10 min.

**Moisture Content**—The moisture content of I was determined on a moisture determination balance[2]. The test was continued until three consecutive readings at 3-min intervals were constant.

**Flow Pattern of I**—The flow properties of I were estimated by determination of the angle of repose without and with 1% magnesium stearate by a described procedure (13). Flow properties of anhydrous lactose also were studied by the same method for comparison.

**Development of Static Charges during Blending**—A plastic V-shaped container with a volume of 848 ml and a smooth inner surface was used. The container was dried at 45° for 12 hr, cooled to room temperature in a desiccator, and filled with 500 ml of the specified powder of known weight. The V-shaped container with the material was then rotated[3] at 36 rpm for 15 min. Then the material was immediately poured out gently, without disturbing the powder sticking to the container, and weighed. The weight of the sticking material was then calculated. The environmental working conditions for the test were maintained at 29° and a relative humidity of 42%.

**Tablet Preparation**—Five thousand tablets of I and 5000 tablets each of I in combination with the following drugs were prepared: ferrous sulfate, phenobarbital, sodium chloride, ephedrine hydrochloride, isoniazid, methenamine, ascorbic acid, sulfathiazole, ferrous gluconate, calcium lactate, aspirin, riboflavin, multivitamins with minerals, aminosalicylic acid, and powdered digitalis.

Appropriate changes in the formulas were made to establish minimum quantities of I and other essential ingredients required to produce satisfactory tablets. All tablets were prepared on a four-station press[4] at 300 tablets/min using various types and sizes of punches and dies, with the exception of riboflavin and multivitamin tablets which were compressed on a single-punch press[5] at 60 tablets/min. The resulting tablets were

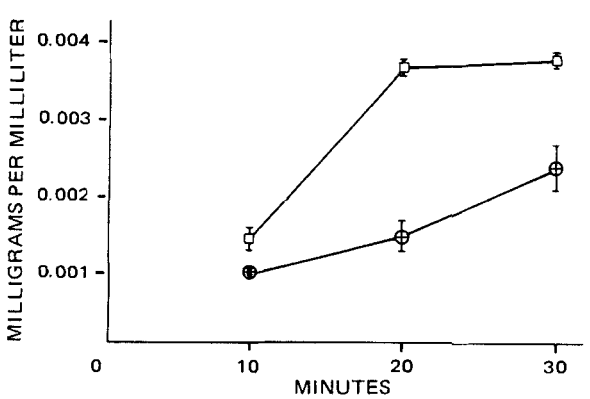


**Figure 1**—In vitro *dissolution rates of aspirin tablets. Key:* ⊕, *tablets with anhydrous lactose; and* □, *tablets with I.*

[1] Ro-Tap, W. S. Tyler Co.
[2] Model 6010, Ohaus Scale Corp., Union, N.J.
[3] Erweka motor drive model Ku-1, Chemical and Pharmaceutical Industry Co.
[4] Colton model 204, Cherry-Burrell Corp.
[5] Stokes model F-1.

Table IV—Color Distribution in Powder Mixture[a]

| Amaranth Concentration, mg/0.1 g ± *SD* | | |
|---|---|---|
| I | Anhydrous Lactose | Spray-Dried Lactose |
| 0.439 ± 0.001 | 0.475 ± 0.007 | 0.590 ± 0.005 |

[a] Powder formula was I, anhydrous lactose, or spray-dried lactose, 345.23 mg, and amaranth, 18.97 mg.

evaluated for the following properties:

1. Hardness[6].
2. Thickness—Thickness was measured by means of a vernier caliper graduated in millimeters.
3. Weight—Tablets were randomly collected during compression, and groups of 20 tablets from those collected were weighed individually. The weight variation was then calculated.
4. Friability—Friability was ascertained with a friabilator[7] using a 4-min cycle and at least 20 tablets or a minimum 6.0-g tablet sample.
5. Disintegration Time—Disintegration time of all tablets in water at 37° was determined by means of a USP XVIII apparatus using disks. Disintegration time of plain I tablets was also determined in simulated gastric fluid USP without pepsin and simulated intestinal fluid USP without pancreatin using the same apparatus and procedure.

**Drug Stratification**—Sufficient I to make 5000 tablets was mixed with the specified drug and other essential ingredients in a blender[8] for 5 min. Then a specified quantity of magnesium stearate was added and mixed for an additional 5 min.

Six samples were collected from different portions of mixed powder and analyzed for the drug content.

The mixed powder was collected in a hopper, a six-mesh stainless steel screen was fixed at the bottom of the hopper, and the hopper was then attached to a sieve shaker[9] and vibrated at a constant speed until all of the powder passed through the screen into a container. Six samples were withdrawn from different portions of the powder and analyzed for drug concentration.

The remaining powder, without further mixing, was compressed into tablets on a four-station press[4] at 300 tablets/min. Six 20-tablet samples were tested for drug distribution. Tablets of sulfathiazole, riboflavin, and aspirin were prepared and studied for drug distribution and stratification. Sulfathiazole and riboflavin were assayed by the USP XIV procedure and a described procedure (14), respectively.

Aspirin tablets were assayed by the following method. A sample of 20 tablets was powdered. A portion of this powder, equivalent to 300 mg of

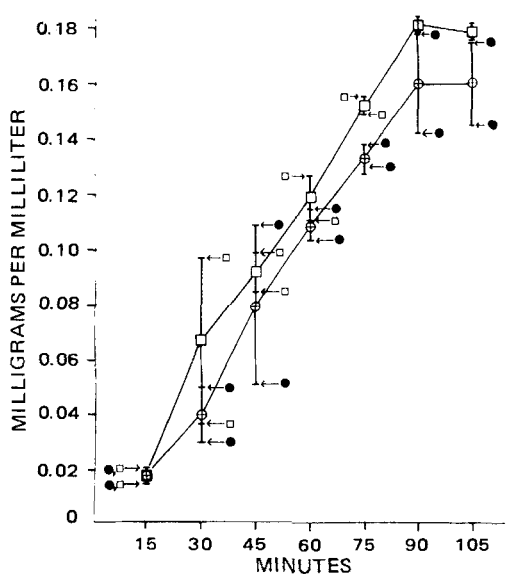


**Figure 2**—In vitro *dissolution rates of ferrous sulfate tablets. Key:* ⊕, *tablets with anhydrous lactose; and* □, *tablets with I.*

[6] Stokes hardness tester.
[7] Roche.
[8] Model LB4575, Patterson Kelley Co.
[9] Erweka type VT, Chemical and Pharmaceutical Industry Co.

**Table V—Color Distribution in Tablets**

| Tablet Formula | I | | | | Anhydrous Lactose | | | | Spray-Dried Lactose | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Weight, mg ± *SD* | Thickness, mm ± *SD* | Hardness[a], kg ± *SD* | Amaranth Concentration, mg/0.1 g ± *SD* | Weight, mg ± *SD* | Thickness, mm ± *SD* | Hardness[a], kg ± *SD* | Amaranth Concentration, mg/0.1 g ± *SD* | Weight, mg ± *SD* | Thickness, mm ± *SD* | Hardness[a], kg ± *SD* | Amaranth Concentration, mg/0.1 g ± *SD* |
| I, anhydrous lactose, or spray-dried lactose, 345.23 mg<br>Amaranth, 18.97 mg<br>Methylcellulose, 92.00 mg<br>Magnesium stearate, 4.60 mg | 456.700 ±4.120 | 6.120 ±0.040 | 5.750 ±0.490 | 0.428 ±0.001 | 461.200 ±0.694 | 7.040 ±0.120 | 7.350 ±1.330 | 0.363 ±0.002 | 463.000 ±6.113 | 6.390 ±0.060 | 5.800 ±0.590 | 0.422 ±0.005 |

[a] Stokes tester.

**Table VI—Drug Distribution in Powder Mixtures and Compressed Tablets**

| Tablet Formula | Milligrams of Drug per Tablet | Powder Mixtures | | | | Tablets | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | I | | Anhydrous Lactose | | I | | | | Anhydrous Lactose | | | |
| | | Blending Drug Concentration, mg ± *SD* | Sieving, Drug Concentration, mg ± *SD* | Blending, Drug Concentration, mg ± *SD* | Sieving, Drug Concentration, mg ± *SD* | Weight, mg ± *SD* | Thickness, mm ± *SD* | Hardness[a], kg ± *SD* | Drug Concentration per Tablet, mg ± *SD* | Weight, mg ± *SD* | Thickness, mm ± *SD* | Hardness[a], kg ± *SD* | Drug Concentration per Tablet, mg ± *SD* |
| Sulfathiazole tablets<br>I or anhydrous lactose, 360 mg<br>Methylcellulose, 45 mg<br>Starch, 45 mg<br>Magnesium stearate, 4.15 mg<br>Stearic acid, 19 mg<br>12.7-mm flat-faced beveled-edge punches and dies | 500.00 | 499.90 ±8.20 | 498.48 ±6.47 | 498.28 ±4.13 | 494.75 ±17.30 | 1086.90 ±29.04 | 6.58 ±0.14 | 5.14 ±0.47 | 503.19 ±5.67 | 1030.00 ±24.29 | 6.27 ±0.12 | 11.19 ±1.07 | 502.06 ±2.24 |
| Riboflavin tablets<br>I or anhydrous lactose, 265 mg<br>Methylcellulose, 60 mg<br>Magnesium stearate, 3 mg<br>8.7-mm standard concave punches and dies | 5.00 | 5.60 ±0.42 | 5.57 ±0.79 | 5.60 ±0.75 | 5.58 ±1.24 | 311.55 ±8.82 | 4.77 ±0.20 | 7.40 ±1.68 | 4.78 ±0.21 | 324.98 ±5.69 | 4.90 ±0.70 | 8.25 ±1.80 | 4.74 ±0.52 |
| Aspirin tablets<br>I or anhydrous lactose, 235 mg<br>Magnesium stearate, 5 mg<br>11.9-mm standard concave punches and dies | 300.00 | 297.46 ±3.56 | 297.25 ±3.47 | 297.00 ±3.49 | 307.33 ±10.20 | 663.00 ±14.41 | 6.14 ±1.50 | 2.45 ±0.83 | 298.23 ±2.37 | 617.00 ±11.47 | 6.28 ±0.15 | 1.55 ±0.19 | 299.27 ±2.75 |

[a] Stokes tester.

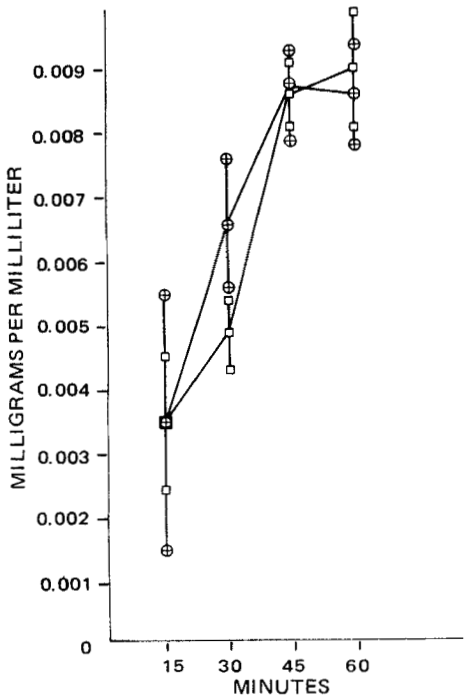


**Figure 3**—In vitro *dissolution rates of phenobarbital tablets. Key:* ⊕, *tablets with anhydrous lactose; and* □, *tablets with I.*

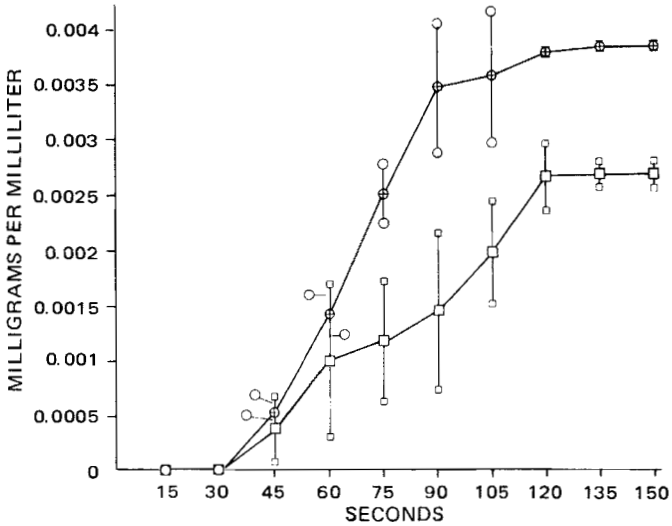


**Figure 4**—In vitro *dissolution rates of benzoic acid tablets. Key:* ⊕, *tablets with anhydrous lactose; and* □, *tablets with I.*

aspirin, was weighed accurately, mixed with 60 ml of ether, stirred for 5 min, and then filtered to remove the excipients. Then 45 ml of water and 5 ml of 95% alcohol were added to the filtrate, and the filtrate was heated to remove the ether. The resulting solution was assayed according to a described procedure (15). For comparison, anhydrous lactose was evaluated for drug stratification by the same procedure using the same drugs.

**Color Distribution**—To study the color uniformity in I tablets, 0.5% amaranth USP was used as a source of color. A specified quantity of amaranth was mixed with a portion of I, added to the remainder of the lactone in a blender[8], and mixed for 15 min. The intensifier was turned on at 5-min intervals for 15 sec. Six random samples were withdrawn from the mixture and assayed for amaranth spectrophotometrically at 385 nm.

Specified quantities of methylcellulose, 1500 cps, and magnesium

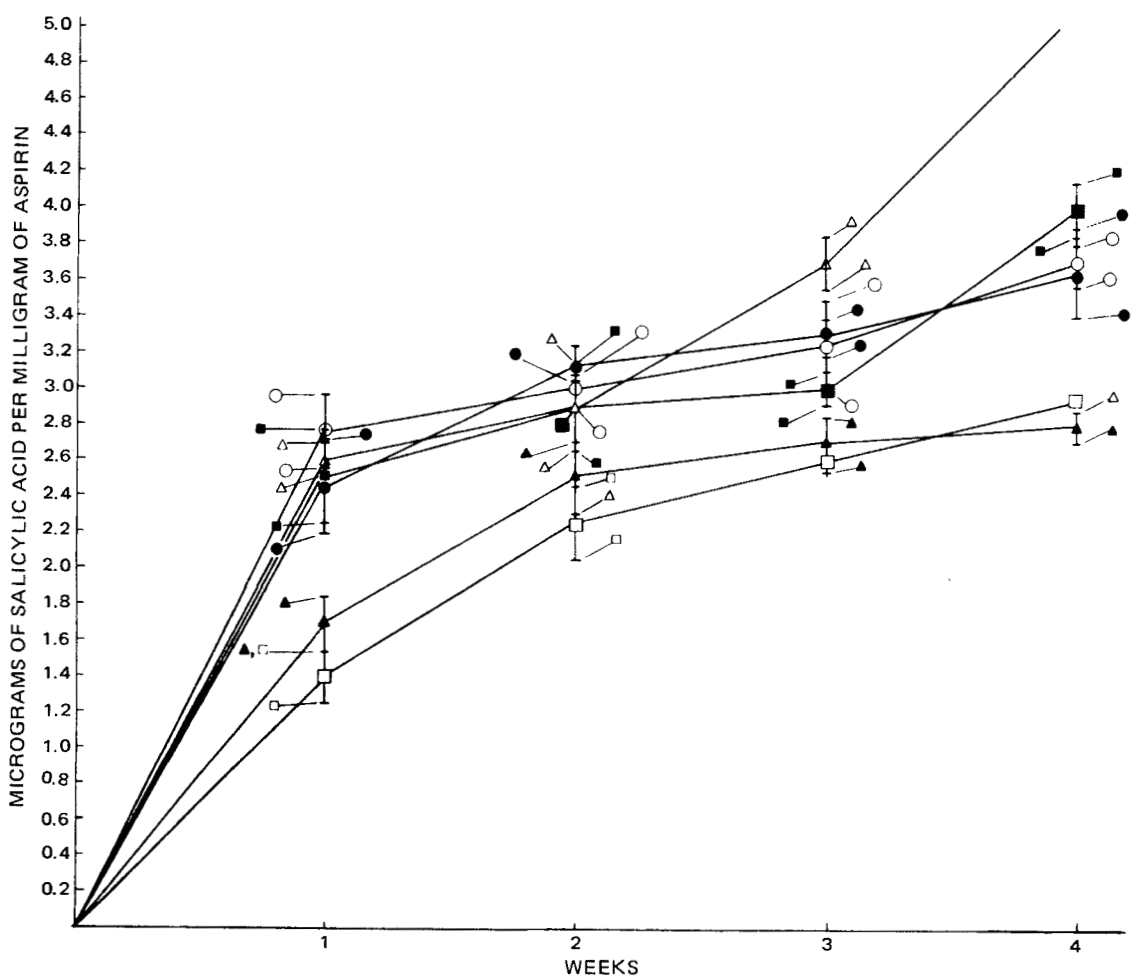


**Figure 5**—*Stability of aspirin with various diluents at 52% relative humidity. Key:* ○, *anhydrous lactose;* □, *I;* △, *sorbitol;* ■, *mannitol;* ●, *spray-dried lactose; and* ▲, *aspirin.*

Table VII—Physical Properties of Tablets Used for Dissolution Studies

| Tablet | Hardness[a], kg ± *SD* | | Thickness, mm ± *SD* | | Weight, mg ± *SD* | |
|---|---|---|---|---|---|---|
| | Anhydrous Lactose | I | Anhydrous Lactose | I | Anhydrous Lactose | I |
| Aspirin | 1.55 ± 0.19 | 1.45 ± 0.83 | 6.28 ± 0.15 | 6.14 ± 0.15 | 616.60 ± 11.47 | 663.00 ± 14.41 |
| Benzoic acid | 5.08 ± 0.52 | 5.90 ± 0.46 | 6.49 ± 0.07 | 6.13 ± 0.05 | 423.70 ± 7.20 | 413.70 ± 9.77 |
| Ferrous sulfate | 11.25 ± 0.78 | 11.03 ± 0.87 | 6.65 ± 0.07 | 6.04 ± 0.13 | 572.30 ± 14.21 | 552.25 ± 24.86 |
| Phenobarbital | 3.90 ± 0.93 | 4.70 ± 0.43 | 3.73 ± 0.04 | 3.74 ± 0.05 | 111.30 ± 1.13 | 116.45 ± 2.62 |

[a] Stokes tester.

stearate were added to the amaranth–I mixture and compressed on a four-station rotary press; 5000 such tablets were prepared. Six 20-tablet random samples were collected and assayed for amaranth by this procedure. Anhydrous and spray-dried lactose also were studied for color distribution by the same procedure as described for I. Finished tablets were stored at room temperature for 6 months and observed for color changes.

**Dissolution Studies**—To investigate the effect of I on tablet dissolution, phenobarbital, benzoic acid, aspirin, and ferrous sulfate were selected as representative drugs. Tablets of these drugs were prepared with I and anhydrous lactose as excipients. Attempts were made to maintain equal weight and hardness for similar tablets.

Dissolution rates of these tablets were determined in water at 37° with the USP XVIII dissolution apparatus. Samples were withdrawn at specified intervals and assayed for drug concentration. Phenobarbital was assayed according to a described procedure (16). Similarly, benzoic acid (17) and aspirin (18) were analyzed by reported procedures. Ferrous sulfate was assayed by the following procedure.

To each 1-ml sample were added 1 ml of hydrogen peroxide and 5 ml of a reagent consisting of 5.835 mg of sodium salicylate, 200 mg of mercuric chloride, and 0.6 ml of 1 *N* hydrochloric acid dissolved in water. The resulting solution was assayed spectrophotometrically at 540 nm.

**Mold Growth**—Tablets of phenobarbital, ferrous sulfate, and aspirin prepared with I and anhydrous lactose for dissolution studies and plain tablets of I from Batch 1 were stored at 95% relative humidity at room temperature for 2 months and observed for mold growth.

**Effect of I on Stability of Moisture-Sensitive Drugs**—Aspirin was selected as a representative drug, and anhydrous lactose, spray-dried lactose, mannitol, and sorbitol were selected as excipients for comparison with I.

Aspirin, 6 g, and 59 g of each excipient were mixed separately. Six samples of each type were prepared and stored at 52 and 81% relative humidity and 50 and 60°. These samples were assayed at 1-week intervals for 4 weeks for free salicylic acid content by a reported procedure (19). These mixtures also were stored at room temperature for 3 months and then assayed for free salicylic acid by the same procedure.

**Preliminary Bioavailability Assessment**—To obtain some rudimentary information about the influence of I on drug absorption, a comparative *in vivo* study was conducted on aspirin absorption from separate combinations with I, anhydrous lactose, and starch. Each dose consisted of 50 mg of aspirin mixed with 50 mg of I or anhydrous lactose and with 12.5 mg of starch.

Each combination was studied on a group of six male rabbits, approximately 3 kg. Each dose, in a No. 2 gelatin capsule, was administered

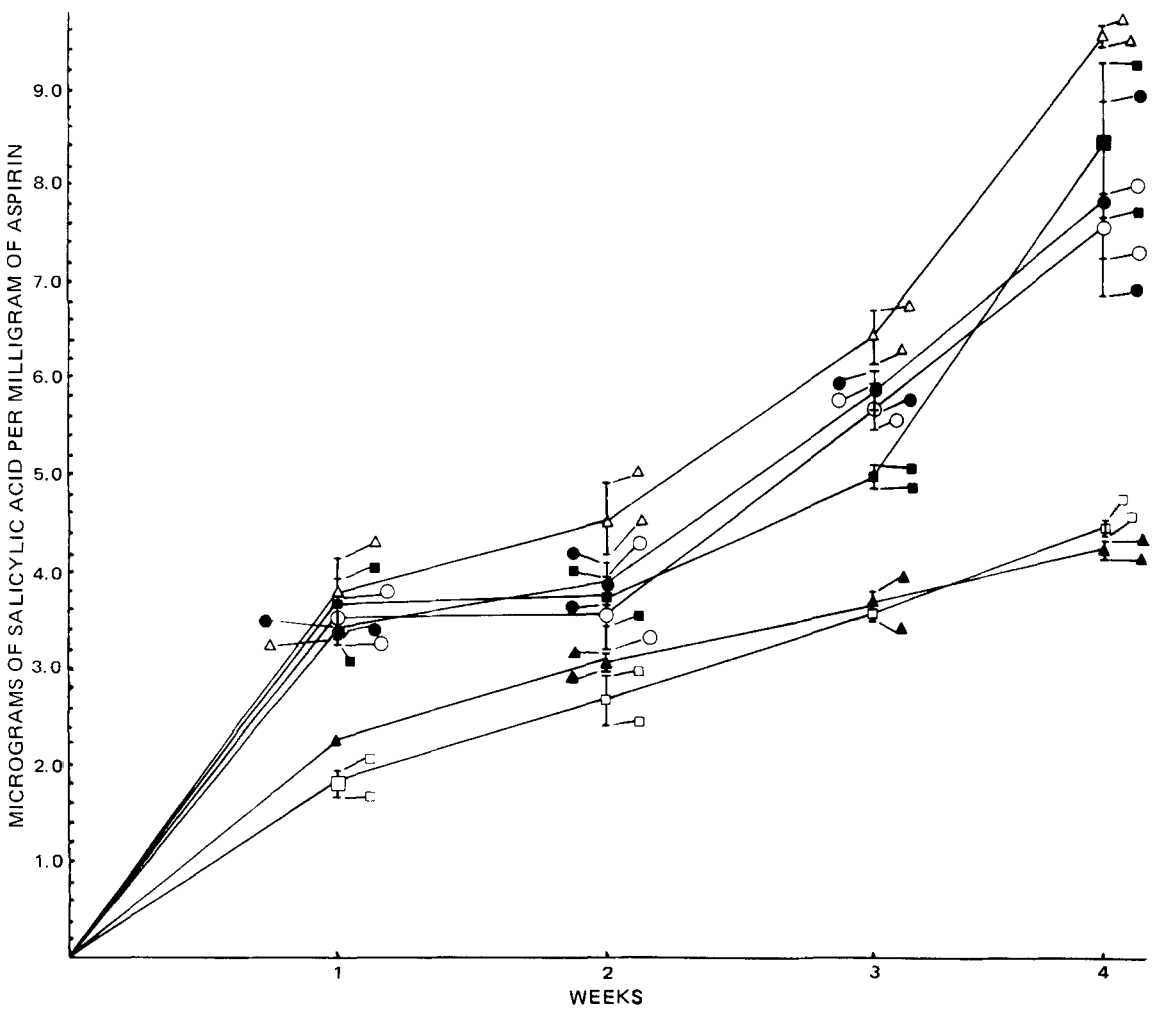


**Figure 6**—*Stability of aspirin with various diluents at 81% relative humidity. Key, ○, anhydrous lactose; □, I; △, sorbitol; ■, mannitol; ●, spray-dried lactose; and ▲, pure aspirin.*

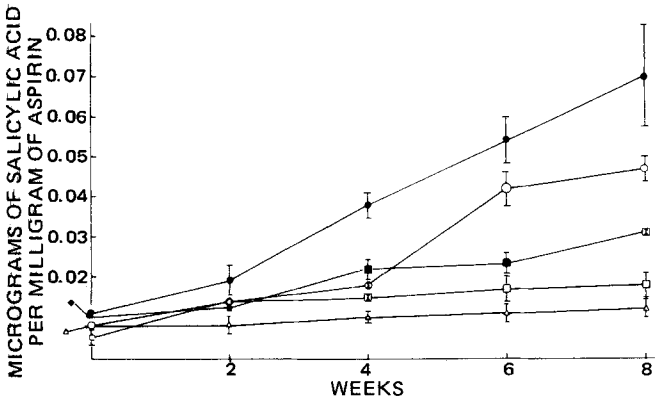


**Figure 7**—*Stability of aspirin with various diluents at 50°. Key: ○, anhydrous lactose; □, I; △, pure aspirin; ■, mannitol; and ●, spray-dried lactose.*

orally to a rabbit. Blood samples were taken at 0, 30, 60, 90, 120, 150, 210, 270, and 330 min from the ear marginal vein and assayed for salicylic acid by a reported procedure (20).

## RESULTS AND DISCUSSION

Most particles of I are finer than 100 mesh. This particle-size distribution is advantageous for tableting (Table I) because most drugs formulated as tablets fall in a fine particle-size range. Due to the similarity in particle size, the drugs can be blended with the excipient more easily, and stratification and separation can be avoided at the compression stage.

Compound I has only 0.5% moisture, which can be an advantage in the preparation of compressed tablets of drugs that decompose by hydrolysis and of drugs whose deterioration or interaction with other drugs is accelerated by moisture.

Compound I has a higher angle of repose than anhydrous lactose (Table I). This property does not seem disadvantageous, because the flow of I in the tablet press did not differ from that of anhydrous lactose. Pharmaceutically acceptable tablets of various drugs with different properties and amounts per tablet were prepared with I (Table II). After 6 months of storage at room temperature, the tablets did not show any undesirable changes in hardness, friability, and disintegration time, with the exception of calcium lactate tablets, the hardness of which decreased considerably.

The disintegration time and hardness of sodium chloride and ferrous sulfate tablets did not increase considerably. Undesirable increases are expected in conventionally prepared tablets of these salts.

Since the aminosalicylic acid tablets were not coated, no attempt was made to evaluate their physical properties on storage. Properties of ascorbic acid, sulfathiazole, aspirin, and aminosalicylic acid tablets prepared with I indicate that this excipient can be used successfully with

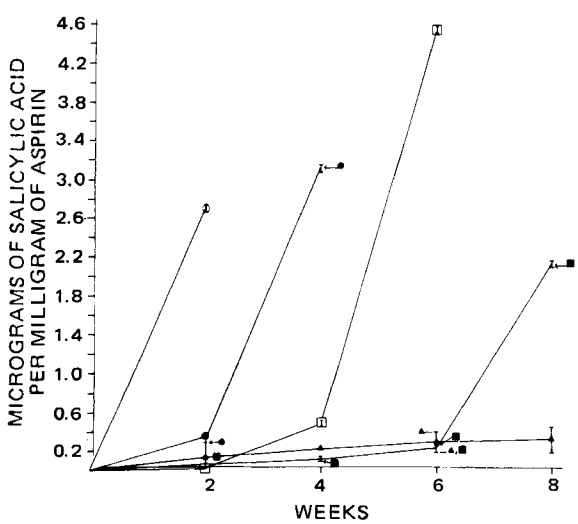


**Figure 8**—*Stability of aspirin with various diluents at 60°. Key: ○, anhydrous lactose; □, I; ■, mannitol; ●, spray-dried lactose; and ▲, pure aspirin.*

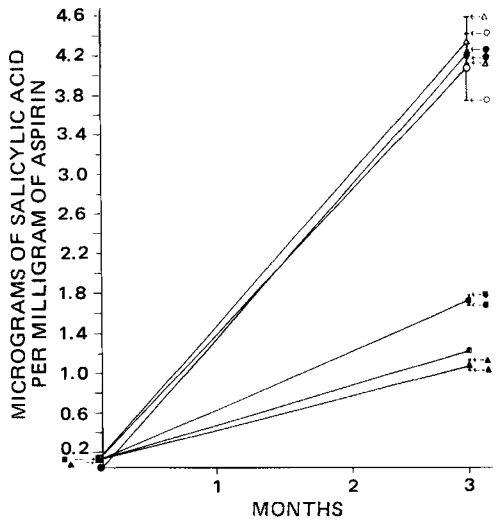


**Figure 9**—*Stability of aspirin with various diluents after 3 months of storage at room temperature. Key: ●, spray-dried lactose; ○, anhydrous lactose; ■, mannitol; □, I; ▲, aspirin; and △, sorbitol.*

these materials. The amount of I required depends on the amount and inherent compression properties of the drug.

In the test for estimation of sticking of a material to a surface due to static charges (Table III), the amounts of anhydrous lactose lost were approximately 0.05% less and 0.91% more than those lost with I and spray-dried lactose, respectively. Less sticking of spray-dried lactose was probably due to its larger particle size. In addition to production of static charges, the loss of material in this test can be attributed to the shape and size of particles and the number of fines in the powder.

In the color distribution studies with amaranth, the dye was more uniformly distributed in I than anhydrous lactose and spray-dried lactose; the deviations between samples assayed for amaranth concentration were less with I compared to the other two materials (Tables IV and V).

Similar results were obtained from tablets compressed from these powders. Color distribution was most uniform in tablets with I, followed closely by anhydrous lactose tablets. Mottling was predominant in spray-dried lactose tablets. None of these tablets showed any signs of fading after 6 months of storage.

Sulfathiazole, riboflavin, and aspirin were selected for drug stratification studies. The quantity of each drug was such that it represented a certain drug to excipient ratio.

In all cases, the drug distribution at blending, sieving, and compression stages was well within acceptable limits, both with I and anhydrous lactose, but anhydrous lactose had considerably higher deviation at the sieving stage as compared to I. The uniform distribution of a small quantity of riboflavin in a large quantity of I shows that this material also can be used for making tablets with small quantities of drugs by the direct compression process (Table VI).

A comparative dissolution rate study was conducted between tablets prepared with I and anhydrous lactose. Aspirin, ferrous sulfate, phenobarbital, and benzoic acid were studied. Similar tablets of these drugs were prepared with each excipient and tested for dissolution. Properties of these tablets are shown in Table VII. Aspirin and ferrous sulfate tablets

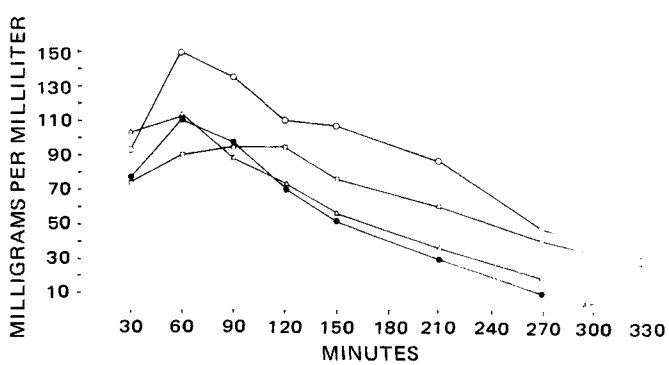


**Figure 10**—*In vivo bioavailability of aspirin from tablets with various diluents. Key: ○, lactose; □, I; △, starch; and ●, pure aspirin.*

prepared with I had faster dissolution than the tablets with anhydrous lactose. The dissolution rate of phenobarbital tablets with anhydrous lactose was higher than that of tablets with I. This result may be due to the greater hardness of tablets with I. This hardness was needed to produce satisfactory tablets. The dissolution rate of benzoic acid tablets with I was considerably less than that of tablets made with anhydrous lactose. This finding can be attributed to a further decrease in dissolution medium pH due to the hydrolysis of I to gluconic acid. The results of the dissolution studies are shown in Figs. 1–4.

Aspirin, ferrous sulfate, and phenobarbital tablets prepared with I, anhydrous lactose, and spray-dried lactose and plain tablets of I were stored at 95% relative humidity for 2 months. Mold growth was observed on aspirin tablets and phenobarbital tablets prepared with anhydrous lactose and spray-dried lactose, respectively. None of the tablets prepared with I showed any signs of mold growth.

A comparative study was conducted at various humidity and temperature conditions on the stability of aspirin in a mixture with I and other excipients such as anhydrous lactose, spray-dried lactose, mannitol, and sorbitol. Aspirin hydrolyzed less when mixed with I as compared to other excipients (Figs. 5–9). Mannitol, which is an excellent excipient for moisture-sensitive drugs due to its water-repellent properties (21), contributed more to the hydrolysis of aspirin as compared to I.

No attempt was made to study aspirin–sorbitol mixtures at higher temperatures because a preliminary investigation showed excessive hydrolysis of aspirin in such mixtures.

These results on the stability of aspirin indicate that I probably takes up the environmental moisture for its own hydrolysis into gluconic acid, thereby preventing the hydrolysis of aspirin. A similar mechanism is expected for the stability of other drugs that deteriorate in moisture. A detailed study on this aspect is being conducted.

A preliminary *in vivo* bioavailability study was conducted to obtain information on the effect of I on drug absorption. The results shown in Fig. 10 do not indicate any inhibitory effect of I on aspirin absorption. Detailed bioavailability studies are being conducted on various drugs in combination with I using different test animals. Compound I and anhydrous lactose seem to prolong blood aspirin levels for a greater period as compared to pure aspirin and aspirin–starch mixtures.

Compound I merits serious consideration for use as a direct compression excipient. It can effect compression of problem drugs at relatively low concentrations and yields tablets possessing desired characteristics for pharmaceutical use. The enhancement of stability of moisture-sensitive drugs with I is an additional advantage.

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[x] To whom inquiries should be directed. Present address: Aspro-Nicholas (Pakistan) Limited, C/36, Estate Avenue, S.I.T.E., Karachi, Pakistan.


# Electrochemical Analysis of the Cephalosporin Cefamandole Nafate


**EUGENE C. RICKARD [x] and GARY G. COOKE**



**Abstract** □ The polarographic assays for cefamandole sodium and its formyl ester, cefamandole nafate, are described. Controlled potential coulometry is used as an absolute method for the assignment of purity of these compounds without the need for a reference material. The precision, accuracy, and selectivity of these assays were better than for the microbiological autoturbidimetric and automated iodometric assays. NMR, TLC, GC, and polarography are used to detect and quantitate likely impurities and degradation products.



**Keyphrases** □ Cefamandole nafate—polarographic analysis, prepared samples □ Polarography—analysis, cefamandole nafate, prepared samples □ Antibacterials—cefamandole nafate, polarographic analysis, prepared samples


Cefamandole (I) has *in vitro* activity against various Gram-positive and Gram-negative bacteria (1–3). A formyl ester, cefamandole nafate (II), was prepared for use in the clinical formulation because it can be purified in a crystalline form having good long-term stability. The ester is hydrolyzed rapidly to cefamandole *in vivo* (4) or in basic aqueous solution (5). Title 21 of the Code of Federal Regulations, Part 442, Cepha Antibiotics, generally provides for both microbiological and chemical assay procedures for cephalosporin antibiotics. However, the microbiological assay results are considered conclusive even though this assay is not specific for any one compound. This paper focuses on the additional tests necessary to characterize completely antibiotic materials such as cefamandole and cefamandole nafate.

Electrochemical techniques are uniquely suited for the assay of compounds containing reducible or oxidizable functions. These include the cephalosporin antibiotics