TABLE II.—COMPARISON OF DIFFRACTION AND ULTRAVIOLET SPECTROPHOTOMETRIC ANALYSES OF INDIVIDUAL GLUTETHIMIDE TABLETS

| Tablet No. | Peak Ht., mm. | Deviation from Mean, mm. | Deviation from Mean, % | U.V. Analysis mg./Tablet | Deviation from Mean, mg. | Deviation from Mean, % |
|---|---|---|---|---|---|---|
| 1 | 128 | 1 | 0.5 | 498 | 3 | 0.6 |
| 2 | 130 | 1 | 0.5 | 491 | 4 | 0.6 |
| 3 | 131 | 2 | 1.8 | 489 | 6 | 1.1 |
| 4 | 133 | 4 | 2.7 | 511 | 16 | 3.3 |
| 5 | 132 | 3 | 1.9 | 497 | 2 | 0.6 |
| 6 | 136 | 7 | 4.8 | 496 | 1 | 0.2 |
| 7 | 120 | 9 | 6.6 | 484 | 11 | 2.1 |
| 8 | 133 | 4 | 2.8 | 493 | 2 | 0.2 |
| 9 | 119 | 10 | 7.1 | 491 | 4 | 0.7 |
| 10 | 129 | 0 | 0.3 | 495 | 0 | 0.1 |
| Av. | 129 | 4 | 2.9 | 495 | 5 | 1.0 |


## SUMMARY

This investigation has demonstrated that the percentage of drug weight in the total formulation weight must be large before one can consider the use of X-ray diffraction intact tablet analysis. From the data collected, it appears as if the drug must be at least 50% of the total formulation weight before analysis by this diffraction procedure could be contemplated. Of course, this judgement will depend on the crystalline character of the drug and the absorption effects of the tablet matrix.

It has also been shown that intact glutethimide tablets can be assayed by this X-ray diffraction technique with a reproducibility of ±3%.


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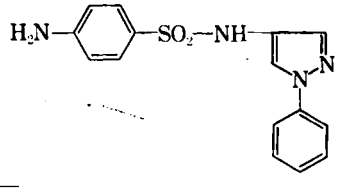
# *Drug Standards*

# Qualitative and Quantitative Tests for Sulfaphenazole

**Provisional, unofficial monographs are developed by the Drug Standards Laboratory, in cooperation with the manufacturers of the drug concerned, for publication in the *Journal of Pharmaceutical Sciences*. The ready availability of this information affords discriminating medical and pharmaceutical practitioners with an added basis for confidence in the quality of new drug products generally, and of those covered by the monographs particularly. Such monographs will appear on drugs representing new chemical entities for which suitable identity tests and assay procedures are not available in the published literature. The purity and assay limits reported for the drugs and their dosage forms are based on observations made on samples representative of commercial production and are considered to be reasonable within expected analytical and manufacturing variation.**

*N'* - (1 - PHENYLPYRAZOLYL - 5)SULFANILAMIDE; $C_{15}H_{14}N_4O_2S$; mol. wt. 314.37. The structural formula of sulfaphenazole may be represented

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Physicians Products Co., Inc., Petersburg, Va., has cooperated by furnishing samples and data to aid in the development and preparation of this monograph.


**Physical Properties.**—Sulfaphenazole occurs as a white to cream-colored, fine crystalline powder, m.p. 178–182°, U.S.P. XVI Class I. It is freely soluble in acetone, sparingly soluble in alcohol, and practically insoluble in water. Sulfaphenazole dissolves in dilute mineral acids and in solutions of alkali hydroxides.

**Identity Tests.**—To about 100 mg. of sulfaphenazole, add 5 ml. of diluted hydrochloric acid, and boil gently for about 5 minutes. Cool in an ice bath, add 4 ml. of a solution of sodium nitrite (1 in 100), dilute to 10 ml. with water, and place the mixture in an ice bath for 10 minutes. To 5 ml. of the cooled mixture, add a solution of 50 mg. of betanaphthol in 2 ml. of sodium hydroxide solution (1 in 10): an orange-red precipitate is formed.

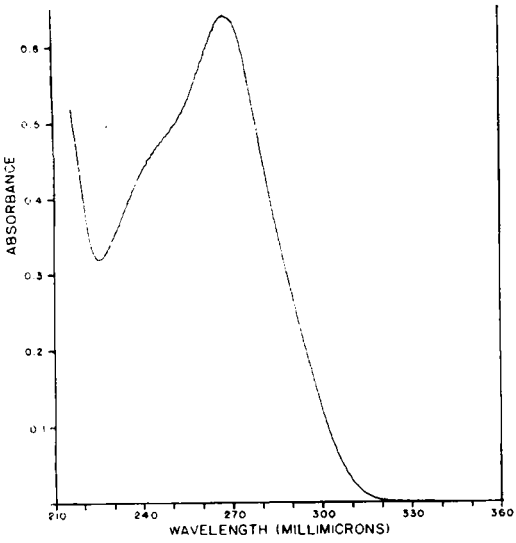


Fig. 1.—Ultraviolet absorption spectrum of sulfaphenazole in alcohol (10 mcg./ml.); Beckman model DK-2A spectrophotometer.

To about 20 mg. of sulfaphenazole suspended in 5 ml. of water add, dropwise, sodium hydroxide T.S. until dissolved, then add 2 or 3 drops of cupric sulfate T.S.: a characteristic light bluish-green precipitate forms which remains unchanged on standing.

A 1:100,000 solution of sulfaphenazole in alcohol exhibits an ultraviolet absorbance maximum at about 268 mμ [absorptivity (1%, 1 cm.) about 640] and a minimum at about 225 mμ. The spectrum is shown in Fig. 1.

The infrared spectrum of a 0.5% dispersion of sulfaphenazole in potassium bromide, in a disk of about 0.82 mm. thickness, is shown in Fig. 2.

**Purity Tests.**—Dry about 1 Gm. of sulfaphenazole, accurately weighed, at 105° for 4 hours: it loses not more than 0.5% of its weight.

Char about 1 Gm. of sulfaphenazole, accurately weighed, cool the residue, add 1 ml. of sulfuric acid, heat cautiously until evolution of sulfur trioxide ceases, ignite, cool, and weigh: the residue does not exceed 0.2%. Retain the residue for the heavy metals test.

Dissolve the sulfated ash obtained from 1 Gm. of sulfaphenazole in a small volume of hot nitric acid and evaporate to dryness on a steam bath. Dissolve the residue in 2 ml. of diluted acetic acid, dilute to 25 ml. with water, and determine the heavy metals content of this solution by the U. S. P. XVI heavy metals test, method I: the heavy metals limit for sulfaphenazole is 20 p.p.m.

Digest 2 Gm. of sulfaphenazole with 100 ml. of carbon dioxide-free water at about 70° for 5 minutes, cool at once to about 20°, and filter. To 25 ml. of the filtrate, add 2 drops of phenolphthalein T.S. and determine the acidity by titration with 0.1 *N* sodium hydroxide: not more than 0.25 ml. is required for neutralization. Retain the remainder of the filtrate for the chloride and sulfate limit tests.

Determine the chloride content of sulfaphenazole by the U.S.P. XVI chloride limit test, using a 25-ml. portion of the filtrate prepared in the test for acidity: the sample shows no more chloride than corresponds to 0.1 ml. of 0.02 *N* hydrochloric acid (140 p.p.m.).

Determine the sulfate content of sulfaphenazole by the U.S.P. XVI sulfate limit test, using a 25-ml. portion of the filtrate prepared in the test for acidity: the sample shows no more sulfate than corresponds to 0.2 ml. of 0.02 *N* sulfuric acid (400 p.p.m.).

**Assay.**—Weigh accurately about 500 mg. of sulfaphenazole, previously dried at 105° for 4 hours, and transfer to a 250-ml. beaker. Add 20 ml. of hydrochloric acid and 50 ml. of water, stir until dissolved, cool to room temperature, add about 25 Gm. of crushed ice, and slowly titrate with 0.1 *M* sodium nitrite, stirring vigorously, until a glass rod dipped into the titrated solution produces an immediate blue ring when touched to starch iodide paper. When the titration is complete, the end point is reproducible after the mixture has been allowed to stand for 1 minute. Each milliliter of 0.1 *M* sodium nitrite is equivalent to 31.44 mg. of $C_{15}H_{14}N_4O_2S$. The amount of sulfaphenazole found is not less than 99.0% and not more than 101.0% of the weight of the sample taken.

## DOSAGE FORMS OF SULFAPHENAZOLE

### Sulfaphenazole Tablets

**Identity Test.**—Finely powder a number of sulfaphenazole tablets. To a portion of the powder equivalent to about 100 mg. of sulfaphenazole, add 5 ml. of diluted hydrochloric acid, boil gently for about 5 minutes, and filter. Cool the filtrate in an ice bath, add 4 ml. of a solution of sodium nitrite (1 in 100), dilute to 10 ml. with water, and place the mixture in an ice bath for 10 minutes. To 5 ml. of the cooled mixture, add a solution of 50 mg. of betanaphthol in 2 ml. of sodium hydroxide solution (1 in 10): an orange-red precipitate is formed.

**Assay.**—Weigh and finely powder not less than 20 sulfaphenazole tablets. Weigh accurately a portion of the powder, equivalent to about 500 mg. of sulfaphenazole, and transfer to a 250-ml. beaker. Proceed as directed in the *Assay* in the monograph for sulfaphenazole beginning with "Add 20 ml. of hydrochloric acid. . . ." Each milliliter of 0.1 *M* sodium nitrite is equivalent to 31.44 mg. of $C_{15}H_{14}N_4O_2S$. The amount of sulfaphenazole found is not less than 95.0% and not more than 105.0% of the labeled amount.

### Sulfaphenazole Suspension

**Identity Tests.**—To a volume of sulfaphenazole suspension equivalent to about 100 mg. of sulfaphenazole, add 5 ml. of diluted hydrochloric acid and proceed as directed in the *Identity Test* in the monograph for sulfaphenazole tablets beginning with ". . . boil gently for about five minutes. . . ."

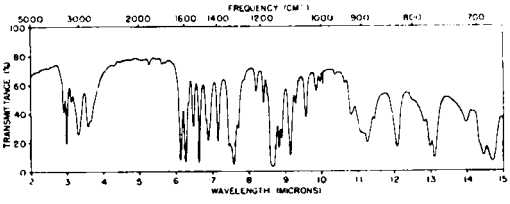


Fig. 2.—Infrared spectrum of sulfaphenazole in potassium bromide disk (0.5%); Perkin-Elmer model 21 spectrophotometer, sodium chloride prism.

Transfer a volume of sulfaphenazole suspension equivalent to about 500 mg. of sulfaphenazole to a glass-stoppered centrifuge tube, add 15 ml. of water, and shake vigorously. Centrifuge, decant and discard the supernatant liquid, and wash the residue with two additional 15-ml. portions of water, centrifuging and decanting each time. Transfer the residue of sulfaphenazole to a piece of filter paper or porous plate and allow to air dry. Prepare a 0.5% dispersion of the dry residue in potassium bromide and compress. The infrared spectrum in the range of 2 to 15 $\mu$ exhibits absorbance maxima at the same wavelengths as a similar preparation of sulfaphenazole reference standard.

**Assay.**—Determine the specific gravity of sulfaphenazole suspension. Weigh accurately an amount of suspension equivalent to about 500 mg. of sulfaphenazole and transfer to a 250-ml. beaker. Proceed as directed in the *Assay* in the monograph for sulfaphenazole beginning with "Add 20 ml. of hydrochloric acid. . . ." Each milliliter of 0.1 *M* sodium nitrite is equivalent to 31.44 mg. of $C_{15}H_{14}N_4O_2S$. By means of the specific gravity, calculate the amount of sulfaphenazole present in the volume of the suspension taken. The amount of sulfaphenazole found is not less than 93.0% and not more than 107.0% of the labeled amount.

## DISCUSSION

U.S.P. and N.F. terminologies for solubility, melting range, reagents, etc., have been used wherever feasible.

Sulfaphenazole,[1] synthesized by Schmidt and Druey (1), is a rapidly absorbed, long-acting sulfa drug. The tests and standards provided in these monographs are closely patterned after those present in U.S.P. XVI and N.F. XI for similar sulfonamides and their dosage forms.

**Identity Tests.**—The chemical tests provided give results which are characteristic of many and do not serve to distinguish sulfaphenazole from other sulfa drugs. Such distinction can be made by comparing the ultraviolet and infrared spectra with those which have been published for a number of the official sulfonamides (2). A short review of publications dealing with identification methods for sulfonamides was prepared by Woods and Schneller (3).

**Quantitative Methods.**—The functional groups common to most sulfonamides are the primary aromatic amine and the acidic hydrogen of the sulfonamide group. Upon these are based most of the analytical methods which have been used for the determination of these compounds. Because of the presence of the amine group, sulfonamides have been determined volumetrically by diazotization, bromination, iodination, and by nonaqueous titration with acetous perchloric acid. The acidic hydrogen has been titrated argentimetrically and acidimetrically with alkali metal alkoxides in nonaqueous media. Among the many colorimetric methods which have been used for the sulfonamides, most prominent is the diazotiazation and coupling method of Bratton and Marshall. These and other methods were extensively discussed by Woods and Schneller (4).

The diazotization reaction made use of in the nitrite titration assay procedure which is common to many of the official sulfonamide monographs is irreversible and complex, the kinetics being influenced by such factors as the basicity of the amine group, the acidity of the medium, and the presence of a catalyst such as bromide ion. The methods of end point detection include the use of (*a*) external indicators such as starch iodide paste or paper, acriflavine, and 3,7-thiaxanthenediamine-5,5-dioxide (Eastman 8776), (*b*) internal indicators such as orange IV, metanil yellow, and diphenylbenzidine disulfonic acid, (*c*) photometric titration, and (*d*) various electrometric methods. The latter include amperometric, conventional potentiometric (at zero current), potentiometric at constant current, and dead-stop titration methods. The various methods may have advantages in increased accuracy, precision, sensitivity, speed,[2] or applicability to unusual situations, but the classical starch iodide method usually suffices for most pharmaceutical control purposes. Analysis of bulk sulfaphenazole gave an average value of 100.2 ± 0.1%, while analysis of commercial tablets (500 mg.) and suspension (100 mg. per milliliter) gave respective average values of 100.1 ± 0.1% and 103.7 ± 0.1% of the labeled amounts.

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(4) *Ibid.*, pp. 137–179.

[1] Marketed as Sulfabid by Physicians Products Co., Inc., Petersburg, Va.

[2] Especially true of potentiometry at constant current with automatic recording equipment.