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Determination of Specific Rotation of Dextromethorphan HBr (Robitussin) as per USP <781S>

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ABSTRACT

Dextromethorphan hydrobromide (DXM or DM) is the active ingredient in many cough medicines, famously sold as Robitussin, working as a cough suppressant (antitussive) to calm the cough reflex, often combined with other drugs like guaifenesin (an expectorant) in formulations like Robitussin DM for multi-symptom relief of cough, congestion, and chest buildup, available in syrups (liquid), gels (cough gels), and lozenges (medi-soothers). While effective and generally safe when used as directed, misuse is possible, and it's important to follow label instructions and consult a doctor for conditions like asthma or liver disease.

The determination of the specific rotation of dextromethorphan HBr is done for several important reasons, mainly related to identity, purity, and quality control. Its levo isomer, however, is a narcotic.

Any contamination of the medication by the narcotic would have dangerous consequences and so its isomeric purity is extremely important. USP (United States Pharmacopeia) recommends that this purity be checked by measuring optical rotation, as it is the only convenient means.

Confirmation of optical activity and identity; Dextromethorphan HBr is a chiral compound. It rotates plane-polarized light in a specific direction and by a specific amount. Measuring its specific rotation helps confirm that the substance is dextro-rotatory dextromethorphan, not its levo isomer or a different compound.

In this experiment, dextromethorphan hydrobromide was measured using a P-2000 polarimeter with a halogen lamp and interference filter at 325 nm. Specific Rotation specification is within ±1% of USP Std., 250 nominal. Specific rotation, determined photoelectrically at 325 nm, does not differ from the similarly prepared solution of USP Dextromethorphan Hydrobromide RS by more than 1.0%, barely met the requirements.

Keywords

Specific Rotation, Dextromethorphan Hydrobromide, Rudolph Polarimeter.

Introduction

Dextromethorphan, sold under the brand name Robitussin among others, is a cough suppressant used in many cough and old medicines [1]. It is one of the active ingredients in many over-the-counter cold and cough medicines, including generic labels and store brands, Benylin DM, Mucinex DM, Robitussin, NyQuil, Vicks, Coricidin, Delsym, Theraflu, and others. In 2022, the US Food and Drug Administration (FDA) approved the combination dextromethorphan/bupropion to serve as a rapid-acting antidepressant in people with major depressive disorder [2].

Dextromethorphan is a prodrug of dextrorphan, which is the actual mediator of most of its dissociative effects through acting as a more potent NMDA receptor antagonist than dextromethorphan itself [3]. What role, if any, (+)-3-methoxymorphinan, dextromethorphan's other major metabolite, plays in its effects is

not entirely clear [4].

Dextromethorphan hydrobromide, almost white, crystalline powder, chemical name: ent-3-methoxy-17-methylmorfinan hydrobromide monohydrate. White, crystalline powder, freely soluble in alcohol, sparingly soluble in water. Molecular formula: $C_{18}H_{26}BrNO.H_2O$, Also known as DXM, it's sold under other brands like Delsym. Structural formula shown in Figure1.

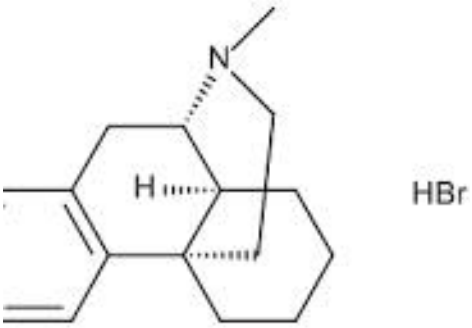

Figure 1: Structural formula of dextromethorphan hydrobromide.

Dextromethorphan is the dextrorotatory enantiomer of levmethorphan, which is the methyl ether of levorphanol, both opioid analgesics. It is named according to IUPAC rules as (+)-3-methoxy-17-methyl-9α,13α,14α-morphinan hydrobromide monohydrate; (+)-cis-1,3,4,9,10a-hexahydro-6-metoxy-11-methyl-2H-10, 4a-iminoethanophenanthrene hydrobromide monohydrate [5]. As its pure form, dextromethorphan occurs as an odorless, opalescent white powder. It is freely soluble in chloroform and insoluble in water; the hydrobromide salt is water-soluble up to 1.5 g/100 mL at 25°C [6].

The determination of the specific rotation of dextromethorphan HBr is done for several important reasons, mainly related to identity, purity, and quality control.

Synthesis

Several routes exist for the synthesis of dextromethorphan. Even though many of the syntheses have been known since the middle of the 20th century, researchers are still working to further develop the synthesis of dextromethorphan and, for example, to make it more environmentally friendly.

Racemate separation

Since only one of the stereoisomers has the desired effect, the separation of a racemic mixture of hydroxy N- methyl morphinan using tartaric acid and subsequent methylation of the hydroxyl group is a suitable method. By using (D)-tartrate, the (+)-isomer remains as the product. This synthetic pathway was patented by Roche in 1950 [7].

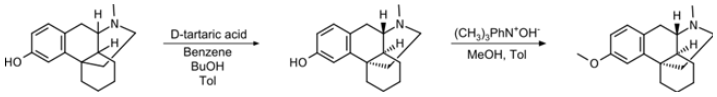

Figure 2: Synthesis reaction of dextromethorphan.

Section 1: Chemicals

- Dextromethorphan Hydrobromide Sample. Tris Pharma, Inc. New Jersey, USA. Do not store above 25 °C. Store in the original container. Keep the container tightly closed.
- Dextromethorphan Hydrobromide USP Reference Standard
- Carbon dioxide free D.I. Water, on the day of use. Water was purified using a Millipore
  Milly- Q system via a pure water device marked Purelab Option-Q7BP [8].

Section 2: Apparatus

- Polarimeter equipped with photoelectric detector capable of measurement at 325 nm sample cell for polarimeter, calibrated.
- Magnetic stirrer
- Analytical balance, Class B (± 0.1 mg resolution)
- 10 mL, and 25 mL volumetric flasks (one for reference standard, one for each sample to be tested)
- Sodium D-line light source (or equivalent)
- Visual Polarimeter-Rudolph Instruments, DigiPol Nova Polarimeter
- Sample cell for polarimeter: 100 mm length and 200 mm length available

Section 3: Solutions

Aqueous solutions of Dextromethorphan Hydrobromide standard and sample(s) are prepared as directed in "procedure", section 5.

Section 4: Calibration of Polarimeter with Quartz Standard

Polarimeter is zeroed with nothing in the light path. Optical rotation of Quartz standard is measured. Calculate the ratio of expected rotation / measured rotation. If ratio lies outside the range 0.999 - 1.001, sample and USP standard optical rotation readings must be corrected by multiplication with ratio mentioned above. Calibration of the Polarimeter depends upon the precise characteristics of all optics used, as also the health of all the mechanical components necessitating frequent checks [9].

Section 5: Procedure

This SOP describes the determination of specific rotation of Dextromethorphan Hydrobromide at 325 nm. The SOP is based on USP <781S>. The solutions were made with a nominal concentration of 1.8 % as per USP. Specific rotation is determined photo electrically at Rudolph Instruments by Dr. Kumar Utukuri. 400 Morris Avenue #120, Denville, NJ 07834 [10].

5.1 Test Solution is prepared at concentration of 18 mg/mL by weighing about 450 mg to nearest 0.1mg into 25 mL volumetric

flask. QF H_2O. Sonicate until fully dissolved (warm it, if necessary, to dissolve). Then mix thoroughly by repeated (at least 3 times) inversion of volumetric flask. Care must be taken to minimize moisture uptake during weighing.

5.2 USP Dextromethorphan Hydrobromide RS is prepared at a concentration of 18 mg/mL by weighing about 450 mg to nearest 0.1mg into 25 mL volumetric flask QF H_2O. Sonicate until fully dissolved. Then mix thoroughly by repeated (at least 3 times) inverstion of volumetric flask. Care must be taken to minimize moisture uptake during weighing.

5.3 Moisture of USP Dextromethorphan Hydrobromide RS must be determined at time of solution preparation if a previously opened vial is used. When a new, previously unopened vial was used, the % moisture previously determined for the same lot number may be used. For USP Dextromethorphan Hydrobromide RS Lot K0F118, the value is 4.6%

5.4 Moisture of sample must be determined at time of solution preparation. Exception to this rule is made upon client's request and if client provides moisture value for same sample lot and has provided sample in hermetically sealed vial.

5.5 In case moisture is to be determined Karl Fisher Titration Method.

5.6 Take the sample and USP reference solutions prepared in 5.2 and 5.3 to Rudolph Instruments and have performed the measurement.

5.7 Perform instrument standardization as described in section 4.

5.8 Fill sample cell with solvent (water), check that there are no bubbles, put in instrument, allow to thermally equilibrate, and zero the instrument. Record blank reading B.

5.9 Rinse sample cell with a small amount of sample solution, rinse, discard. Fill sample cell with sample solution, check that there are no bubbles, allow them to thermally equilibrate, and zero the instrument. Record sample reading R.

5.10 Rinse sample cell with a small amount of USP reference solution, rinse, discard. Fill sample cell with sample solution, check that there are no bubbles, put in instrument, allow them to thermally equilibrate, and zero the instrument. Record sample reading R.

5.11 Fill the data sheet with data for sample and USP reference. Calculate specific rotation as described in section 6: Calculations.

5.12 Specific rotation for sample must not differ from that of the USP Dextromethorphan Hydrobromide RS by more than 1.0%. If this criterion is met, test is complete.

Section 6: Calculations

The solutions were made with a nominal concentration of 1.8 % as per USP. Specific rotation is determined photo electrically at Rudolph Instruments by Dr. Kumar Utukuri, 400 Morris Avenue #120, Denville, NJ 07834. All samples were warmed slightly to aid dissolution as suggested in USP and cooled to room temperature subsequently. Measurements of specific Rotation is performed using polarimeter. Table 1 and 2. The general equation used in polarimetry is:

$$Specific\ Rotation = \frac{(R-B)}{(\frac{m}{V}\frac{L}{100})} \text{ x } \frac{100}{S}$$

Where;

R=observedrotationofsolutionofsampleorUSPreferencestandard.
B = observed rotation of blank
m = mass (g) of sample or USP reference standard in volume V
V = volume (mL) of solution (i.e. volumetric flask size)
L = length (mm) of sample cell.
S = per cent solids (= 100 - % moisture)

For liquid samples, the same equation is used, but now

m/V = sample's liquid density (g/mL)
S = percent "solid" (= 100 - % moisture).

Results and Discussion

The determination of the specific rotation of dextromethorphan HBr is done for several important reasons, mainly related to identity, purity, and quality control:

1. Confirmation of optical activity and identity

Dextromethorphan HBr is a chiral compound. It rotates plane-polarized light in a specific direction and by a specific amount. Measuring its specific rotation helps confirm that the substance is dextro-rotatory dextromethorphan, not its levo isomer or a different compound.

2. Verification of correct isomer

Only the dextro isomer has the desired antitussive (cough suppressant) effect. The levo isomer (levomethorphan) has different pharmacological properties. Specific rotation ensures the correct stereochemistry is present.

3. Assessment of purity

Deviations from the official or literature value of specific rotation can indicate:

- Presence of impurities
- Partial racemization
- Incorrect concentration or solvent issues

4. Control in pharmaceuticals

Pharmacopoeias (USP, BP, IP) include specific rotation as an official test. It ensures batch-to-batch consistency and compliance with regulatory standards.

5. Detection of adulteration or degradation

Changes in optical rotation can signal chemical degradation or substitution with an incorrect or mixed isomer.

The extremely important since the specified tolerance of 1% between the USP standard and sample cannot be accurately judged at longer wavelengths, these values are shown in Table 1.

Conclusion

The determination of specific rotation of dextromethorphan HBr is performed to confirm identity, ensure the correct active isomer, assess purity, and maintain pharmaceutical quality and safety. The numbers in table X demonstrate the reason for choosing 325 nm: instrumental errors constitute a large fraction of the tolerance window at all longer wavelengths making the test practically useless. The DigiPol Nova Polarimeter which can measure at 325 nm and can use 200 mm cells comfortably handles this task with instrumental error at just 5% of the window. Other Polarimeters which can only handle 100 mm cells and do not have the 325 nm capability can barely meet the requirements.

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Table 1: Variation of Specific Rotation of Dextromethorphan HBr with wavelength 325 nm.

Wavelength, nm	Specific Rotation	Optical rotation 1.8%USP conc. In a cell of		Max allowed diff between USP Std. & Sample % of measured value		DigiPol Nova Polarimeter accuracy
		100 nm	200 nm	100 nm	200 nm	
325	265°	4.77°	9.54°	0.0477°	0.095°	0.005°
334	225°	4.05°	8.10°	0.0405°	0.081°	-
365	145°	2.61°	5.22°	0.0261°	0.052°	0.005°
589	28°	0.504°	0.0050°	0.0050°	0.010°	0.003°

Table 2: Specific Rotation of Dextromethorphan HBr with wavelength 325 nm as per USP <781>. Equipment used: DigiPol-Nova-M6U, Serial No: 800.

Sample Description	Standard	Sample	Sample – Dup
Sample weight, W (gram)	0.4501	0.9086	0.9086
Error percentage	0.015%	0.015%	0.015%
Moisture percentage, m %	5.65	4.99	4.96
Solution volume, V (mL)	25	50	50
Error (Grade A), mL	0.03	0.05	0.05
Error%	0.12%	0.10%	0.10%
Path Length, L	200.00	200.00	200.00
Blank Rotation, B°	0.000	0.000	0.000
Observed Rotation, R°	9.080	9.202	9.168
Error (DigiPol), °	0.005	0.005	0.005
Error %	0.06%	0.05%	0.05%
Specific Rotation, α	267.3	266.5	265.4
Total error in specific rotation, %	0.13%	0.11%	0.11%
Total error in specific rotation, °	0.36	0.31	0.31
%Deviation from Standard		0.29%	0.69%
%Deviation <1% Pass / >1% Fail		PASS	PASS

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