

Chemical and Physical Compatibility of Levalbuterol Inhalation Solution Concentrate Mixed With Budesonide, Ipratropium Bromide, Cromolyn Sodium, or Acetylcysteine Sodium

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BACKGROUND: Medications are frequently combined in the nebulizer cup, so it is important to determine their chemical and physical compatibility. **OBJECTIVE:** To determine the chemical and physical compatibility of levalbuterol with ipratropium bromide, cromolyn sodium, acetylcysteine sodium, and budesonide. **METHODS:** We mixed one dose of levalbuterol inhalation solution concentrate (1.25 mg/0.5 mL) with one dose of ipratropium bromide (0.5 mg/2.5 mL), cromolyn sodium (20 mg/2 mL), acetylcysteine sodium (1,000 mg/5 mL), or budesonide (0.5 mg/2 mL). Immediately after mixing the 2 drugs (time zero [T_0]), and again after 30 min at room temperature (T_{30}), we visually inspected the admixtures, measured their pH, and conducted high-pressure liquid chromatography (HPLC). **RESULTS:** There was no evidence of physical incompatibility with these drugs combinations. With all the admixtures, both drugs were chemically stable for at least 30-min. Admixture pH had not changed significantly at T_{30} . Drug recovery was 93.2–102.6% of the initial or control values. **CONCLUSIONS:** The 2-drug admixtures we studied were compatible for at least 30 min at room temperature. *Key words:* levalbuterol, budesonide, ipratropium bromide, cromolyn sodium, acetylcysteine sodium, compatibility, concentrate, admixture, asthma, bronchial asthma. [Respir Care 2008;53(12):1716–1722. © 2008 Daedalus Enterprises]

Introduction

Inhaled drug therapy is the most direct method of treating airway disease. This important administration route is used to deliver medications that control chronic disease and for quick relief of bronchospasm.¹ Although many asthma medications are administered via metered-dose in-

haler or powder inhaler, nebulization is preferable for some patients, such as the very young, the elderly, and patients with conditions that compromise the hand-breath coordination required with inhalers.¹ When concomitant treatment with 2 or more nebulizer medications is prescribed, simultaneous nebulization of all the drugs (ie, placing all the drugs in the nebulizer cup together) is practical and convenient and may encourage patient adherence to therapy, because simultaneous nebulization decreases administration time.² Studies of the efficacy and safety of mixing nebulizer medications³ have been limited, and few inhalation solutions are approved by the Food and Drug Administration (FDA) to be mixed with other agents. Several patient surveys have indicated that patients commonly mix nebulizer medications that are not compatible, which raises safety issues.^{4,5} Physico-chemical incompatibility may be a property of the drug or the excipients (eg, preservatives).⁴

Levalbuterol (R-albuterol) is approved for the treatment and prevention of bronchospasm in patients ≥ 6 years old.⁶ A low-volume concentrate of levalbuterol (1.25 mg/0.5 mL) is commercially available. Levalbuterol is not approved by the FDA to be mixed with any other compounds.

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Table 1. Preparation of Controls

Admixture Study	Control	Composition of Control
Levalbuterol/acetylcysteine	Levalbuterol Acetylcysteine	0.5 mL of levalbuterol (1.25 mg/0.5 mL) and 5.0 mL of saline* 4.0 mL of acetylcysteine (1,000 mg/5 mL) and 0.5 mL of saline
Levalbuterol/cromolyn	Levalbuterol Cromolyn	0.5 mL of levalbuterol (1.25 mg/0.5 mL) and 2.0 mL of saline 2.0 mL of cromolyn sodium (20 mg/2 mL) and 0.5 mL of saline
Levalbuterol/ipratropium	Levalbuterol Ipratropium	0.5 mL of levalbuterol (1.25 mg/0.5 mL) and 2.5 mL of saline 2.5 mL of ipratropium (0.5 mg/2.5 mL) and 0.5 mL of saline
Levalbuterol/budesonide	Levalbuterol Budesonide	0.5 mL of levalbuterol (1.25 mg/0.5 mL) and 2.0 mL of saline 2.0 mL of budesonide (0.5 mg/2 mL) and 0.5 mL of saline

* Saline = 0.9% NaCl, pH 5.0

Several studies have investigated the compatibility of nebulizer solutions, including antibiotics and bronchodilators.⁷⁻¹⁵ One study investigated the in vitro chemical and physical compatibility of levalbuterol concentrate with budesonide, ipratropium bromide, cromolyn sodium, or acetylcysteine sodium,¹⁶ which are often placed together in the nebulizer cup. The approaches used in that study were similar to those in recent studies of compatibility of nebulizer solutions.^{7,8}

Methods

Preparation of Admixtures

Prior to admixing, we measured the pH (AR15 pH meter, Accumet Research, Fisher Scientific, Leicestershire, United Kingdom) of each individual drug solution from a composite solution made from 6 doses of the drug.

We prepared binary (2-drug) admixtures by mixing one dose of levalbuterol HCl inhalation solution concentrate (1.25 mg/0.5 mL, lot S4q006, Sepracor, Marlborough, Massachusetts) separately with one dose of each of: budesonide suspension (0.5 mg/2 mL, lot 405022, Astra Zeneca, London, United Kingdom), ipratropium bromide (0.5 mg/2.5 mL, lot M665, Dey, Napa, California), cromolyn sodium (20 mg/2 mL, lot A4A133, Alparma, Bridgewater, New Jersey), and acetylcysteine sodium (1,000 mg/5 mL, lot 3g70227, Bristol Meyers Squibb-Apothecon, New York, New York). All the binary admixtures were prepared in triplicate. Each solution was mixed (for 1–2 min) to homogeneity and analyzed immediately (time zero [T_0]) and after 30 min (T_{30}) at ambient ($23 \pm 2^\circ\text{C}$) temperature. The admixtures were gently mixed immediately prior to and throughout the T_0 and T_{30} time points. We chose 30 min because that is the approximate average time it takes for a patient to administer a nebulizer drug at home,¹⁷ and 30 min has been used in previous drug-compatibility studies.^{7,16}

To accurately account for the amount of each drug used in each admixture, we determined the volume of each drug used in each admixture as follows. We determined the density of the solution by measuring the weight of a known volume. We then weighed the amount of drug solution used in the admixture and calculated the volume of the drug in the admixture, based on the weight and density.

The budesonide formulation is a suspension. To ensure complete dissolution in the levalbuterol/budesonide study, we diluted the binary admixture and control 4-fold with the chromatography mobile phase solution (0.01 M sodium dihydrogen phosphate and 0.005 M sodium dodecyl sulfate, pH 5.0/acetonitrile, 65/35 v/v) prior to chromatography. The concentration of acetylcysteine and cromolyn in the admixture and controls were too high (approximately 200 mg/mL, and 1 mg/mL, respectively) for accurate high-pressure liquid chromatography, so, for the levalbuterol/acetylcysteine and levalbuterol/cromolyn studies we diluted the admixture and control solutions 1,000-fold and 20-fold, respectively, with distilled water prior to chromatography. All other binary admixtures and controls tested without additional dilution.

The control solutions (Table 1) were prepared by diluting the drug with saline solution (0.9% NaCl, pH 5.0) to equal the final dilution of the relevant admixture. Like the admixtures, the controls were prepared in triplicate and analyzed once at T_0 and T_{30} . The results presented are the means of 3 independent experiments.

Analysis of Admixtures

At T_0 and T_{30} the admixtures were subjected to visual inspection, pH measurement, and chromatography (with ultraviolet detection), with validated methods. We visually inspected the admixtures against a white background.

The concentration of each drug in the admixture (C_{ad} , in mg/mL) was determined via high-pressure liquid chro-

Table 2. Chromatography Parameters

	Levalbuterol/Acetylcysteine	Levalbuterol/Cromolyn	Levalbuterol/Ipratropium	Levalbuterol/Budesonide
Column	Phenomenex Gemini C-18 250 × 4.6 mm, 5 μm	Waters μBondapak C-18 3.9 × 150 mm, 5 μm	Waters Spherisorb S5 C-8 150 × 4.6, 5 μm	Agilent Zorbax 4.6 × 250 nm SB-CN, 5 μm
Temperature	Ambient	Ambient	Ambient	Ambient
Mobile Phase	0.05 M ammonium phosphate buffer, pH 4.8/methyl alcohol, 81.7/18.3 v/v	0.05 M ammonium phosphate buffer, pH 4.8/methyl alcohol, 76/24 v/v	0.012 M heptanesulfonic acid, pH 3.2/acetonitrile, 62.3/37.8 v/v	0.01 M sodium dihydrogen phosphate and 0.005 M sodium dodecyl sulfate, pH 5.0/acetonitrile, 65/35 v/v
Flow (mL/min)	1.0	2.5	2.7	1.25
Wavelength (nm)	Levalbuterol: 278 Acetylcysteine: 214	254	210	Levalbuterol: 278 Budesonide: 240
Injection volume (μL)	20	20	20	20

matography (1100 series chromatograph, Agilent, Santa Clara, California, with a Multichrom data-acquisition system, VG Instruments, Danvers, Massachusetts), with an external standard that contained the drug at the nominal concentration.

The validation studies examined the specificity, accuracy, and linearity in the range of 80–120% of nominal sample concentration. The methods were designed to assay the parent compounds in the admixtures, not to measure impurities.

We did not conduct forced degradation, because degradation of the parent compound under the typical forced-degradation study conditions (eg, stronger acidic or basic conditions) was not expected within the 30-min test interval, under our relatively mild mixing conditions.

Table 2 summarizes the chromatography parameters. With the levalbuterol/acetylcysteine admixture the detection wavelength was initially set at 214 nm to quantify acetylcysteine, which eluted at around 3.5 min. After 5 min we changed the wavelength to 278 nm, to quantify levalbuterol, which eluted at about 6.8 min. Similarly, with the levalbuterol/budesonide admixture the detection wavelength was initially set at 278 nm to quantify levalbuterol, which eluted at around 4.4 min, and after 10 min we changed the wavelength to 240 nm to quantify budesonide, which eluted as 2 components (the 2 isomers of budesonide): one at approximately 18 min and the other at approximately 20 min. The recovery of the drug in the admixture (R_{ad} , in mg/dose), defined as the amount of the drug per theoretical dose, was calculated as:

$$R_{ad} = C_{ad} \frac{V_{ad-total}}{V_{ad}} V_{theoretical} \quad (1)$$

where V_{ad} is the volume of drug added to the admixture, $V_{ad-total}$ is the total volume of the admixture (the sum of

the volume of the 2 drugs used to make the admixture), and $V_{theoretical}$ is the theoretical fill volume of each drug.

With levalbuterol, cromolyn, ipratropium, and budesonide, V_{ad} was determined from the weight of the drug used in the admixture and the density of the drug solution. With acetylcysteine we used a fixed volume of 4.0 mL as one dose. $V_{theoretical}$ was 0.5 mL for levalbuterol, 2.0 mL for budesonide and cromolyn, 4.0 mL for acetylcysteine, and 2.5 mL for ipratropium.

Similarly, the concentration of each drug in the control (C_{con} , in mg/mL) was determined via chromatography, and the recovery of the drug in the control (R_{con} , in mg/dose) was calculated as:

$$R_{con} = C_{con} \frac{V_{con-total}}{V_{con}} V_{theoretical} \quad (2)$$

where V_{con} is the volume of the drug used in making the control, and $V_{con-total}$ is the total volume of the control.

Drug compatibility was evaluated by comparing the recovery in the admixture to the recovery in the control solution. The comparison is calculated as percentage of control (%Control):

$$\%Control = \frac{R_{ad-avg}}{R_{con-avg}} \times 100 \quad (3)$$

where R_{ad-avg} is the average recovery (ie, mean of the 3 chromatography runs) of each active in the admixture, and $R_{con-avg}$ is the average recovery (ie, mean of the 3 chromatography runs) of the drug in the corresponding control solution. The %Control was determined at T_0 and T_{30} .

In addition to comparing the admixture to the control, we also compared the admixtures at T_0 and T_{30} as:

CHEMICAL AND PHYSICAL COMPATIBILITY OF 5 NEBULIZER MEDICATIONS

Table 3. pH of Drugs and Drug Admixtures

Admixture Study	pH of Drug Solution Prior to Admixing		pH of Admixture		Change in pH (T ₀ vs T ₃₀)	Change in pH (T ₀ vs T ₃₀) %
	Levalbuterol	Other Drug	T ₀	T ₃₀		
Levalbuterol/acetylcysteine	4.05	6.91	6.95 ± 0.09	6.84 ± 0.09	-0.11 ± 0.03	-1.58
Levalbuterol/cromolyn	4.17	5.44	5.24 ± 0.08	5.48 ± 0.19	0.24 ± 0.13	4.58
Levalbuterol/ipratropium	4.57	3.54	3.61 ± 0.03	3.66 ± 0.03	0.05 ± 0.03	1.39
Levalbuterol/budesonide	4.05	4.50	4.30 ± 0.11	4.39 ± 0.12	0.09 ± 0.12	2.09

T₀ = immediately after mixing drugs
T₃₀ = 30 min after mixing drugs

$$\%T_{30}/T_0 = \frac{R_{ad-avg} \text{ at } T_{30}}{R_{ad-avg} \text{ at } T_0} \times 100 \quad (4)$$

These acceptance criteria are consistent with previous studies.^{7,16}

where %T₃₀/T₀ is the ratio of percent recovery at T₃₀ versus T₃₀.

Acceptance Criteria

Admixtures were considered compatible and stable if the following 4 acceptance criteria were met:

- No visible signs of change (eg, precipitation, discoloration)
- pH difference between T₀ and T₃₀ is ≤ 10%
- Percent recovery (%Control) is within 90.0–110.0%
- %T₃₀/T₀ is within 90.0–110.0%

Results

We saw no visual evidence of precipitation or physical incompatibility in any admixture at T₀ or T₃₀. We saw a slight cloudiness in the levalbuterol/budesonide admixtures, which we attributed solely to the budesonide, which is in suspension, and the cloudiness did not change after mixing or over time.

Table 3 summarizes the pH data. The pH of the admixtures was closer to the pH of the non-levalbuterol solution, probably due to the small levalbuterol volume (approximately 0.5 mL), compared to the other solution volumes (2–5 mL) and the levalbuterol’s lack of buffering capacity. The admixtures’ pH had changed little at T₃₀; the range of change was -0.11 to 0.24 pH units, which was within the

Table 4. Drug Admixture Stability

Admixture Study	Component Assayed	Recovery of Control (mean ± SD mg/dose)*	T ₀		T ₃₀		T ₃₀ /T ₀ (mean %) [§]
			Recovery (mean ± SD mg/dose) [†]	% of Control (mean) [‡]	Recovery (mean ± SD mg/dose) [†]	% of Control (mean) [‡]	
Levalbuterol/acetylcysteine	Levalbuterol	1.19 ± 0.06	1.18 ± 0.05	100.0	1.19 ± 0.04	100.6	100.6
	Acetylcysteine	1,043 ± 4	1,052 ± 8	100.9	1,054 ± 6	101.1	100.2
Levalbuterol/cromolyn	Levalbuterol	1.25 ± 0.03	1.26 ± 0.06	101.1	1.26 ± 0.06	101.5	100.4
	Cromolyn	22.17 ± 0.29	22.74 ± 0.52	102.6	22.55 ± 0.50	101.7	99.1
Levalbuterol/ipratropium	Levalbuterol	1.29 ± 0.07	1.21 ± 0.04	93.2	1.21 ± 0.04	93.1	99.9
	Ipratropium	0.55 ± 0.00	0.55 ± 0.01	100.9	0.55 ± 0.01	100.7	99.8
Levalbuterol/budesonide	Levalbuterol	1.19 ± 0.09	1.22 ± 0.05	102.4	1.22 ± 0.05	102.4	100.0
	Budesonide	0.43 ± 0.02	0.42 ± 0.06	97.4	0.42 ± 0.06	97.5	100.1

* By equation 2, average of three values (from triplicate sample preparations)

† By equation 1

‡ By equation 3

§ By equation 4

T₀ = immediately after mixing drugs

T₃₀ = 30 min after mixing drugs

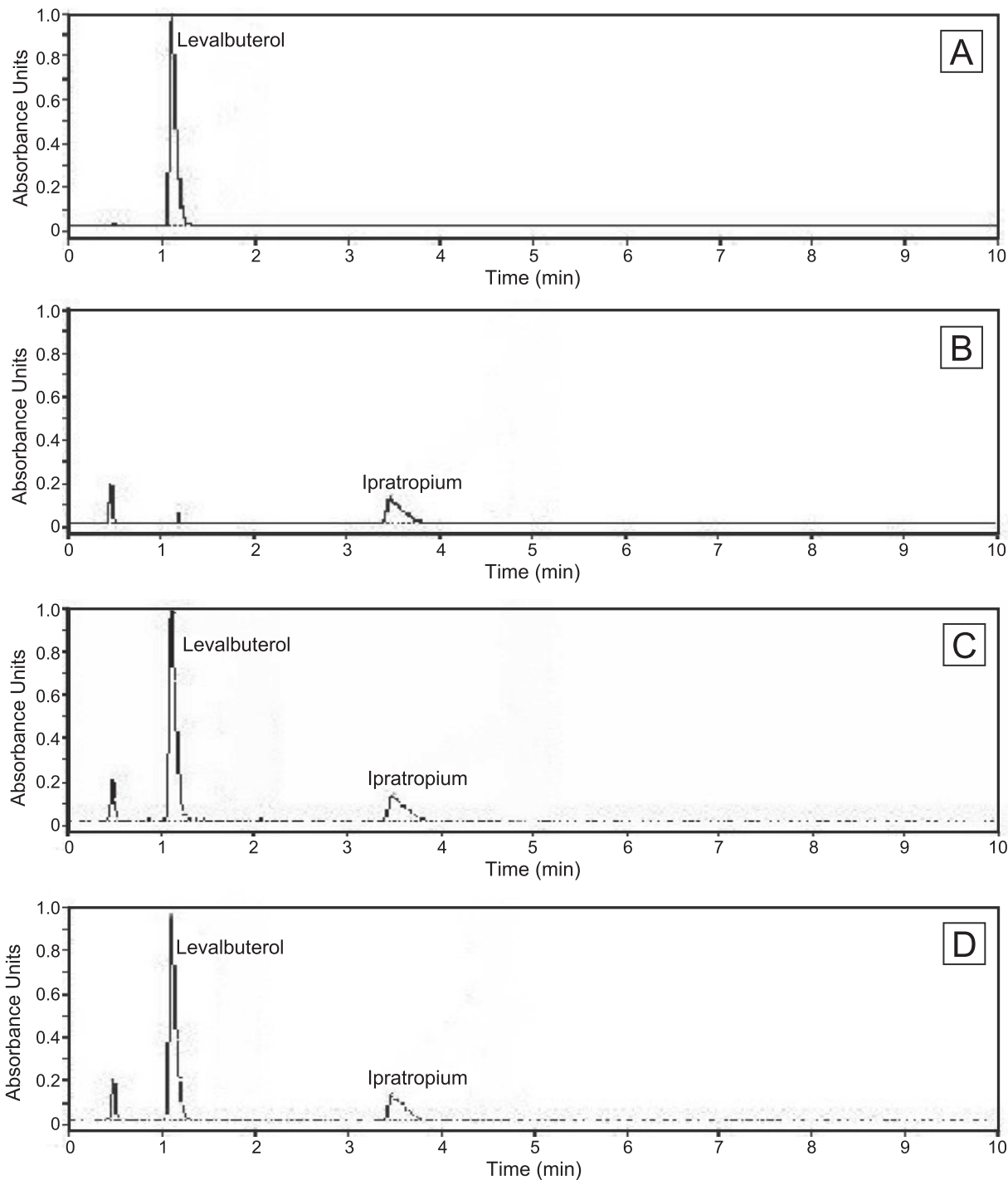


Fig. 1. HPLC chromatogram from the levalbuterol/ipratropium bromide experiment. A: Levalbuterol control. B: Ipratropium bromide control. C: Levalbuterol/ipratropium bromide admixture at time zero. D: Levalbuterol/ipratropium bromide admixture at 30 min.

typical precision of the pH measurement. The range of relative pH change from T_0 to T_{30} ranged from -1.58% to 4.58% , which was $< 10\%$, which indicates that the pH of the admixture was stable 30 min after admixing.

The range of values for percent recovery ($\%Control$) for all drugs was $93.2\text{--}102.6\%$ at T_0 and $93.1\text{--}102.4\%$ at T_{30} (Table 4). The percent recovered was similar at T_0 and T_{30} ; the range of $\%T_{30}/T_0$ was $99.1\text{--}100.6\%$, which meets

the acceptance criterion of 90.0–110.0% and indicates that the admixing of the 2 drugs was essentially the same as the admixing of one drug with the control solvent, and that the admixtures were stable over the 30-min test period. In all the tests of the admixtures, there were no chromatogram peaks other than the active drug peaks (Fig. 1).

Discussion

Drug admixture studies such as this are commonly used to evaluate the physical and chemical compatibility of nebulizer medications.^{2,3,7-16} To our knowledge, only one other study has investigated the compatibility of levalbuterol with ipratropium bromide, cromolyn sodium, acetylcysteine sodium, or budesonide. That study¹⁶ was on an admixture of levalbuterol (0.63 mg/3 mL or 1.25 mg/3 mL) and budesonide (0.25 mg/2 mL or 0.5 mg/2 mL). The authors found the admixture chemically and physically stable after 30 min, with no change in pH, appearance, or admixture composition. Our lower recovery of levalbuterol from the levalbuterol/ipratropium admixture probably reflects experimental variability, and is within the acceptance criteria for compatibility (%Control 90–110%). The experimental variability in the evaluation of the concentrated levalbuterol inhalation solution (1.25 mg/0.5 mL) is apparent in the 12 controls, which ranged from 1.09 mg/dose to 1.33 mg/dose (see Table 4).

Physical and chemical compatibility is one consideration when determining the appropriateness of mixing medications for nebulization. Other issues to consider include changes in aerodynamic behavior of the aerosol, the effects of increased volume in the nebulizer cup, admixture temperature change during nebulization, and the risk of adding or worsening adverse effects.^{4,18,19} Several studies have found that the aerosol characteristics (eg, respirable fraction, respirable mass, and aerodynamic diameter) of admixtures differ from those of the admixtures' component drugs.²⁰⁻²² Moreover, the choice of nebulizer/compressor system may affect the above mentioned variables²³ and, consequently, compatibility and safety issues. Additional studies would be needed on differences in aerosol characteristics of admixtures versus the individual medications. The FDA has not approved admixture/co-nebulization of budesonide, cromolyn sodium, acetylcysteine sodium, or levalbuterol. Ipratropium bromide is only approved to be mixed with racemic albuterol.²⁴

Conclusions

Under our experimental conditions, levalbuterol was physically and chemically compatible with ipratropium bromide, cromolyn sodium, acetylcysteine sodium, and budes-

onide for at least 30 min at room temperature. However, we did not evaluate the clinical efficacy or safety of these admixtures.

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CHEMICAL AND PHYSICAL COMPATIBILITY OF 5 NEBULIZER MEDICATIONS

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