

ORIGINAL ARTICLE

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Stability of commonly nebulized drugs in heated and humid conditionHaitham Saeed¹, Mohamed EA Abdelrahim^{1,2}, James B Fink³¹ Beni Suef University, Faculty of Pharmacy, Department of Clinical Pharmacy, Beni Suef, Egypt² Ahrum Canadian University, Faculty of Pharmacy, Department of Clinical Pharmacy, Giza, Egypt³ Georgia State University, Division Allied Health, Atlanta, GA, USAReceived 11 September 2017; Accepted 04 December 2017
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Abstract

Placement of nebulizer prior to heated humidifier has been reported to improve efficiency of aerosol delivery during ventilator support. Drugs nebulized in this position must travel through humidifier, rainout in reservoir and may be subjected to extended periods of heat up to 50°C. Toxic degradation may develop, posing potential risk to patient. The aim of this study was to evaluate chemical stability of commonly inhaled drugs administered to mechanically ventilated patients subjected to extended period of 50°C. Formulations of 8 commonly inhaled drugs were diluted to 50 mL total volume in water and exposed to 50°C for 7 days to simulate effect of heat in humidifier. High Performance Liquid Chromatography (HPLC) was performed before and after heating to determine drug stability and degradation. Drug integrity, color or pH changes were noted. Epinephrine, levalbuterol, tobramycin and colistin demonstrated >10% reduction in concentration but only acetylcysteine had additional peaks in HPLC chromatogram demonstrating potential degradation and possible production of by product. Changes in color were observed with epinephrine and acetylcysteine. All drugs retained their integrity after subjecting them to 50°C for 7 days except acetylcysteine. Acetylcysteine changed color and had new peak in HPLC chromatogram. Color change with epinephrine was not associated with any new peak in HPLC chromatogram. Further studies should determine whether acetylcysteine changes would result in any off gassing of vapor that might harm the patient.

Keywords: Ventilation, nebulizer, respirable Medication, heat, humidity, humidifier**Introduction**

Heated humidification is used to condition anhydrous gas mixtures and minimize adverse effects of by-passing upper airway in intubated patients [1]. Many drugs are administered as aerosol [2] using nebulizers for treatment of intubated mechanically ventilated patients [3].

It has been suggested that placement of nebulizers prior to humidifier can improve drug delivery distal to artificial airway in mechanically ventilated adult and pediatric patients in presence of bias flow, [4-6] patients receiving gas via high flow nasal cannula (HFNC), [7,8] as well as infants receiving nasal continuous positive airway pressure (nCPAP) and synchronized inspiratory positive airway pressure (Si PAP) [9]. While placement of aerosol generator at inlet of humidifier has been shown to improve aerosol delivery efficiency from range of nebulizers, it is not known whether aerosolized drug that rains out into the heated humidifier could result in undesirable drug changes that could have undesirable effect on patient.

Some drugs, such as epinephrine, are well known to change color over time, which has been associated with oxidation [10,11], and such color changes have been noted in humidifier reservoirs. This change in color is more obvious in clear humidifier reservoir than in blue corrugated inspiratory limb circuit where it may also occur. This observed change in color has raised question as to whether other commonly used drug administered via nebulizer may degrade and produce toxic byproducts over time under heated conditions. It is important to determine whether the by-products formed could be source of risk to ventilated patient.

The aim of present study was to evaluate effect of heat and dilution in water on chemical stability of eight commonly used drugs approved for inhalation used with mechanically ventilated and critically ill patients.

Material and Method**Materials**

The following commonly administered formulations via aerosol during ventilator support were studied: Colistin (Colomycin injection, powder for solution for injection, infusion or inhalation, Colistimethate Sodium, 2 million international units, Forest Laboratories, UK); Salbutamol respiratory solution (Farcolin

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respirator solution, 5000 µg/mL; Pharco Pharmaceuticals, Egypt); Levalbuterol with ipratropium bromide (Duolin respules 2.5 mL contain ipratropium bromide 500 µg and levalbuterol 1.25 mg, Cipla, India); Epinephrine (Epinephrine ampoule 0.25 mg in 1 mL, Misr Company for Pharmaceutical Industry, Egypt); Acetylcysteine (Rotacystiene 20% solution, each 1 mL contain N-acetyl-L-cysteine 200 mg, Biocapital, Egypt); Tobramycin (Tobirespules, 300 mg in 5 mL, Novartis, France); Budesonide (Pulmicort respules, 0.5 mg in 2 mL, AstraZeneca, Egypt); and Ipratropium bromide (Atrovent 0.5mg in 2mL solution for inhalation, Boehringer Ingelheim, Egypt). All formulations tested were within their current expiration date.

Methodology

For each experiment 1 mL of each of eight drugs was diluted, with distilled water to total volume 50 mL to mimic dissolution of drug depositing in humidifier reservoir. This 50 mL was divided into two samples. Sample A consisted of 10 mL of diluted drug assayed using stability indicating high performance liquid chromatography (HPLC) method, described later for each formulation, and rest of sample A was stored at 40°C for physical characteristic comparison. Sample B consisted of 40 mL of diluted drug placed in container (50 mL PYREX® flat bottom boiling flask, Corning Life Sciences, USA) stored at 50°C for 7 days in oven (Stork tronik & De Lab, Treffurt, Germany). At end of storage period sample B was assayed using HPLC method and peaks of samples A and B were compared based on their shape, height and area. Any physical change between samples A and B post study period was recorded e.g. color change and pH change. Figure 1 represents a schematic diagram of methodology. This experiment was repeated 3 times for each drug (N=3).

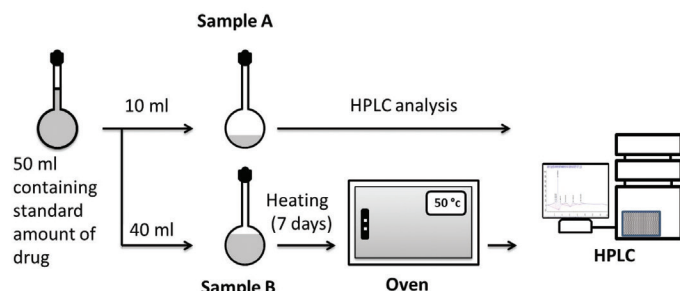


Figure 1. Schematic diagram of study

HPLC assay methods

Acetylcysteine

25 mm × 4.6 mm ZORBAX Eclipse Plus C18, ODS1 column (Agilent, USA) through which mobile phase consisted of mixture of 0.01 N potassium dihydrogen phosphate and methanol at ratio of 60:40 (v/v), respectively. Mobile phase was pumped at 1 mL/min using Agilent 1260 Infinity preparative pump (G1361A). Agilent 1260 Infinity Diode array detector VL (G131SD) was set at 210 nm with injection volume 20 µL [12].

Budesonide and Salbutamol

25 mm × 4.6 mm ZORBAX Eclipse Plus C18, ODS1 column (Agilent, USA) through which mobile phase consisted of mixture of 50 mmol sodium acetate buffer (A) and methanol (B) [pH 4.5 with glacial acetic acid]. Analytes were separated using following gradient: 20% B – 30% B from 0 to 2 min; 30% B – 70% B from

2 to 8.5 min; 70% B – 90% B at 8.5 min; hold 90% B from 8.5 to 12.5 min; 90% B – 20% B at 12.5 min; and hold 20% B from 12.5 to 14.0 min pumped at 2 mL/min using Agilent 1260 Infinity preparative pump (G1361A). Agilent 1260 Infinity Diode array detector VL (G131SD) was set at 240 nm with injection volume 20 µL [13].

Colistin

25 mm × 4.6 mm ZORBAX Eclipse Plus C18, ODS1 column (Agilent, USA) through which mobile phase consisted of mixture of sodium sulphate anhydrous, pH 6.3, and acetonitrile at ratio of 75:25 (v/v), respectively. Mobile phase was pumped at 1.5 mL/min using Agilent 1260 Infinity preparative pump (G1361A). Agilent 1260 Infinity Diode array detector VL (G131SD) was set at 215 nm with injection volume 20 µL, at 30°C temperature [14].

Epinephrine

25 mm × 4.6 mm ZORBAX Eclipse Plus C18, ODS1 column (Agilent, USA) through which mobile phase consisted of mixture of water, acetonitrile and 100 mmol/L solution of ammonium acetate, pH 5.0, at ratio of 88:2:10 (v/v/v), respectively. Mobile phase was pumped at 1.2 mL/min using Agilent 1260 Infinity preparative pump (G1361A). Agilent 1260 Infinity Diode array detector VL (G131SD) was set at 280 nm with injection volume 20 µL [15].

Ipratropium Bromide

25 mm × 4.6 mm ZORBAX Eclipse Plus C18, ODS1 column (Agilent, USA) through which mobile phase consisted of mixture of 0.01 M phosphate buffer, pH 3, and methanol at ratio of 50:50 (v/v). Mobile phase was pumped at 1 mL/min using Agilent 1260 Infinity preparative pump (G1361A). Agilent 1260 Infinity Diode array detector VL (G131SD) was set at 245 nm with injection volume 20 µL [16].

Levalbuterol

25 mm × 4.6 mm ZORBAX Eclipse Plus C18, ODS1 column (Agilent, USA) through which mobile phase consisted of mixture of monobasic ammonium phosphate buffer, pH 3.5, and acetonitrile at ratio of 87.5:12.5 (v/v). Mobile phase was pumped at 1.5 mL/min using Agilent 1260 Infinity preparative pump (G1361A). Agilent 1260 Infinity Diode array detector VL (G131SD) was set at 280 nm with injection volume 20 µL [17].

Tobramycin

25 mm × 4.6 mm ZORBAX Eclipse Plus C18, ODS1 column (Agilent, USA) through which mobile phase consisted of mixture of 0.2 mol/L monobasic potassium phosphate buffer, pH 6.5, and acetonitrile at ratio of 70:30 (v/v), respectively. Mobile phase was pumped at 1 mL/min using Agilent 1260 Infinity preparative pump (G1361A). Agilent 1260 Infinity Diode array detector VL (G131SD) was set at 210 nm with injection volume 20 µL [18].

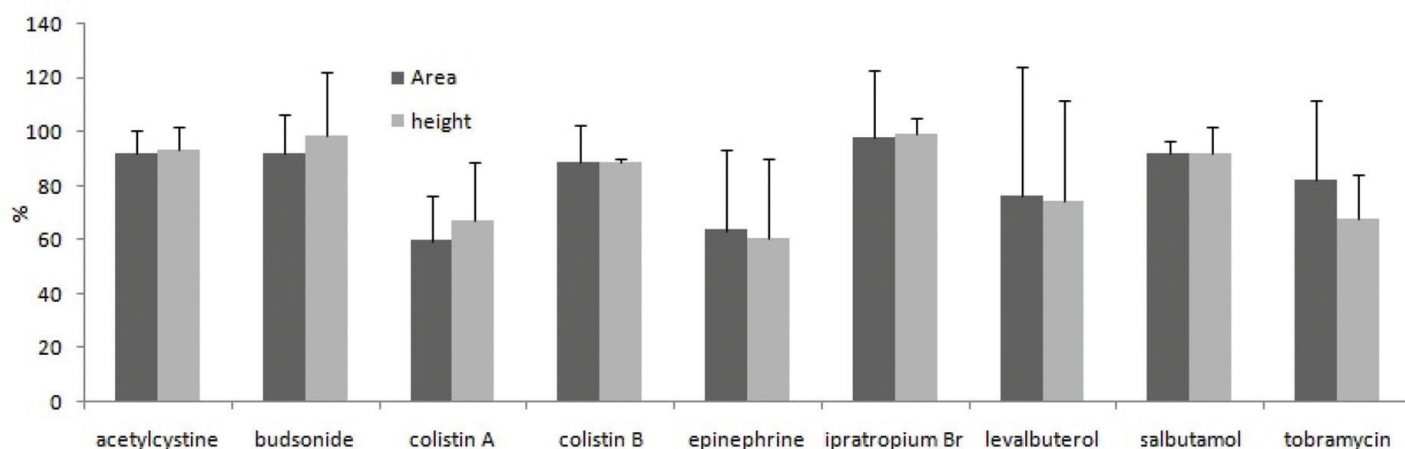
Results

Mean (SD) area and height of samples A and B (before and after storage at 50°C for 7 days, respectively) of each formulation are shown in Table 1. Mean (SD) area and height of sample B as percentage of sample A to demonstrate formulation degradation are shown in Table 1 and Figure 2. Chromatograms of samples A and B of 8 drugs studied are shown in Figures 3 a-h.

Table 1 shows that all drugs decreased in concentration post storage at 50°C for 7 days but rate of degradation varied across formulations.

Table 1. Mean (SD) of area and height and sample integrity of samples A and B for each drug (N=3)

Drug	Sample-A		Sample-B		Sample IntegritySample-B as percentage of Sample-A (%)	
	Area	Height	Area	Height	Area	Height
Acetylcysteine	2298.45 (107.10)	150.35 (10.36)	2109.85 (124.80)	139.66 (4.43)	92.02 (8.55)	93.26 (8.30)
Budesonide	798.30 (29.79)	108.01(18.36)	734.14 (113.85)	103.93 (7.08)	92.01 (14.51)	98.78 (23.14)
Colistin	A 236.89 (128.35)	16.95 (2.35)	131.17 (69.60)	11.74 (4.91)	59.58 (16.99)	67.33 (21.10)
	B 405.64 (28.93)	16.21 (2.24)	358.80 (51.12)	14.40 (1.83)	88.78 (13.93)	88.97 (1.24)
Epinephrine	324.79 (116.33)	37.27 (12.86)	184.41 (59.13)	20.08 (5.56)	63.45 (29.96)	60.65 (29.73)
Ipratropium	30.54 (6.76)	1.98 (0.25)	28.89 (2.72)	1.96 (0.14)	98.01 (24.83)	99.50 (5.82)
Levalbuterol	856.51 (247.66)	69.68 (24.30)	715.50 (501.30)	57.83 (38.81)	76.48 (47.57)	74.37 (37.22)
Salbutamol	1919.60 (358.76)	112.29 (8.91)	1770.03 (397.00)	103.12(6.53)	91.73 (5.01)	92.22 (9.50)
Tobramycin	336.11 (118.70)	7.76 (2.58)	254.52 (34.39)	5.015 (1.20)	82.47 (29.26)	67.58 (16.55)

**Figure 2.** Mean (SD) area and height of sample-B as percentage of sample-A of all studied drugs

Budesonide, ipratropium bromide and salbutamol retained > 90 % drug-integrity and therefore were not considered to be significantly affected by extended-period of heat according to USP compendial limits.[19] No change of HPLC chromatogram peaks shape and no color change was observed as shown in Figures 3 f-h, respectively.

Epinephrine, levalbuterol, tobramycin and colistin demonstrated greater than 10 % reductions from initial concentration. Moderate degradation of colistin (~22%) was indicated by decrease in peak height and area (Table 1 and Figure 2). No color change was observed and no change in peak shape was noted (Figure 3 b).

Epinephrine stability was reduced at 50°C, demonstrated by decrease in height and area (~40%), as shown in Table 1 and Figure 3 c.

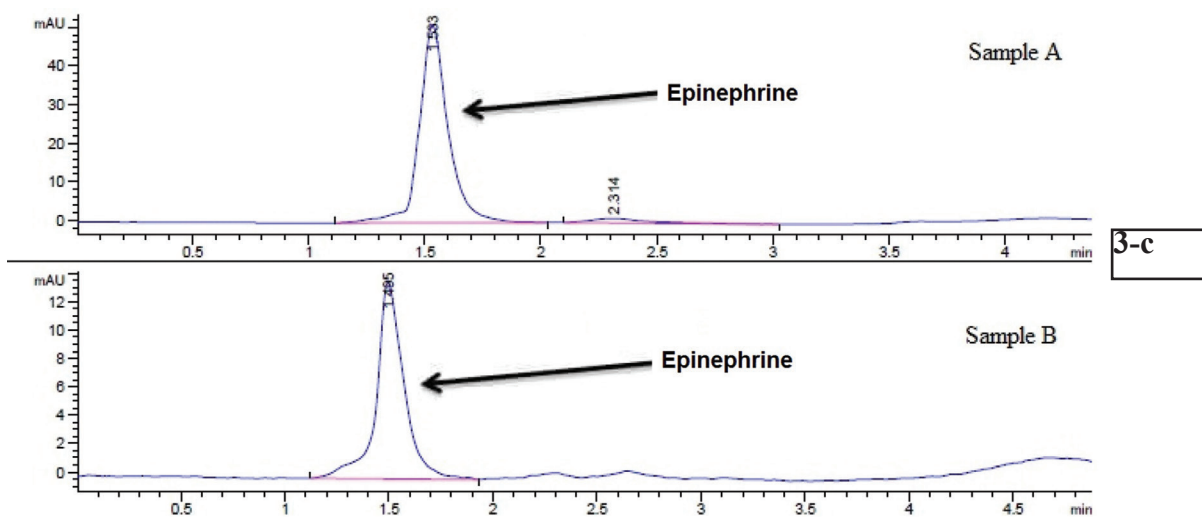
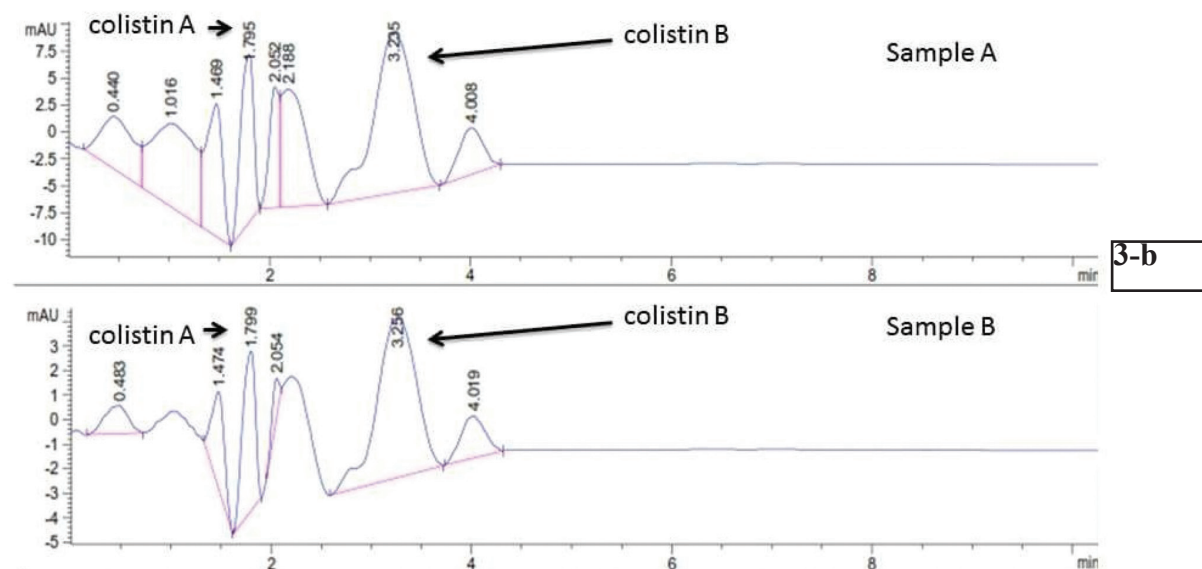
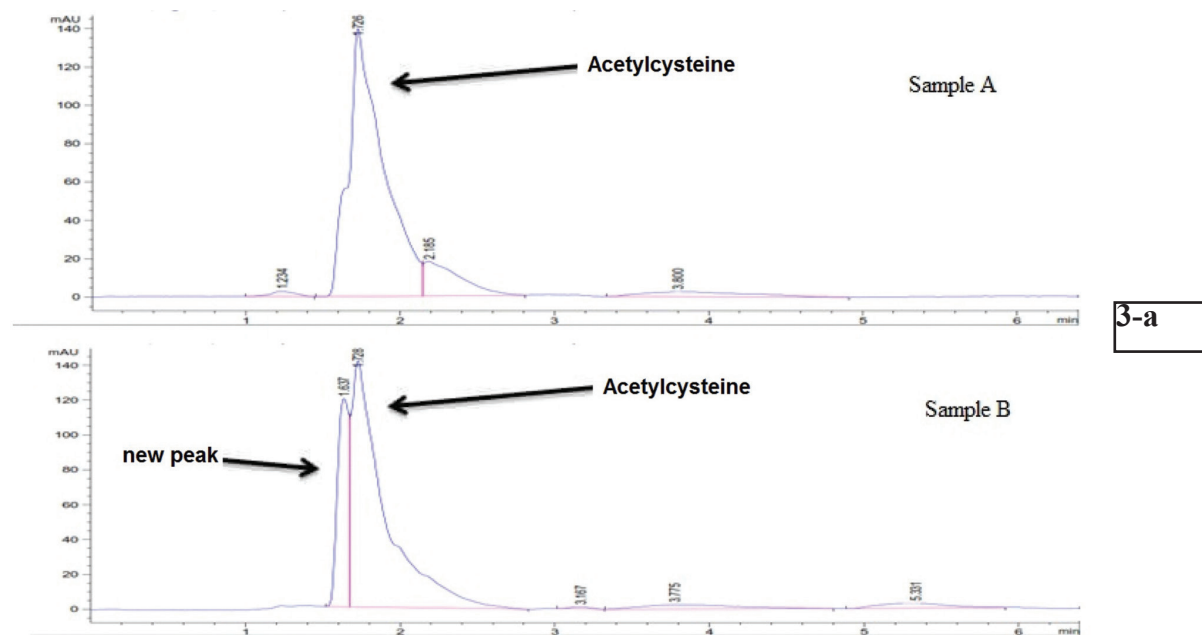
A significant decrease in levalbuterol height and

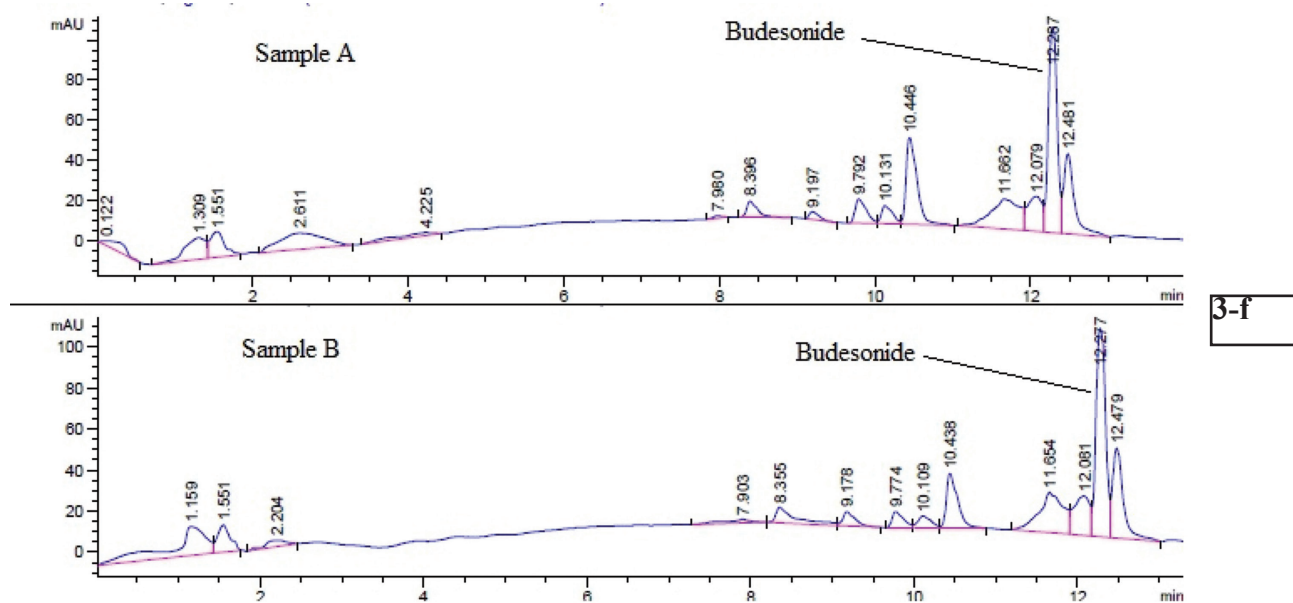
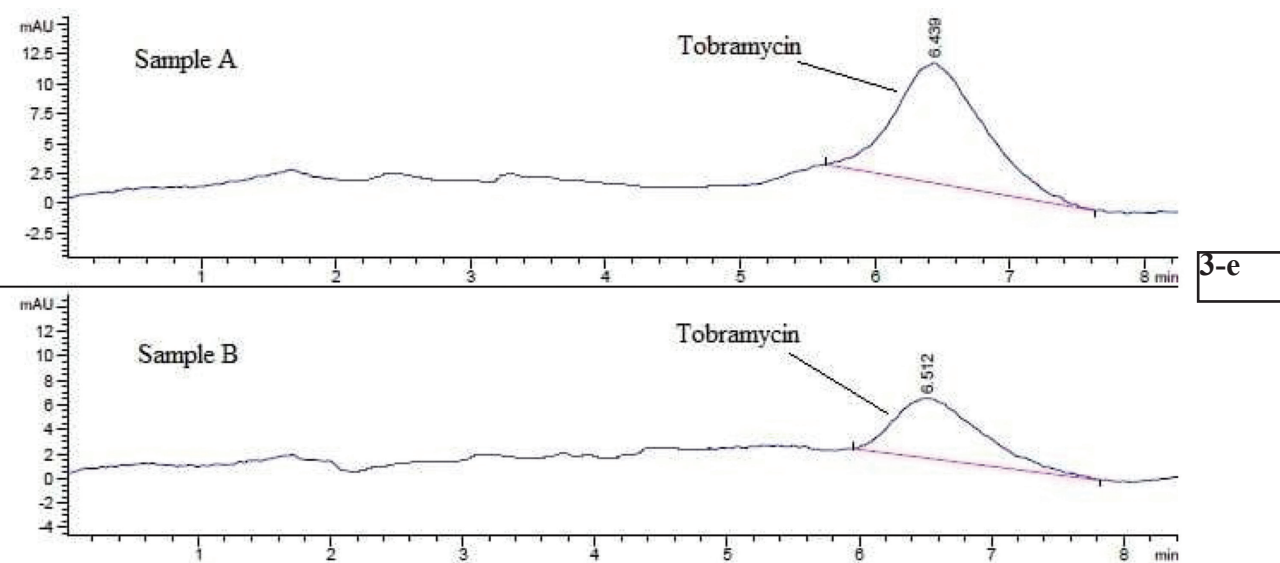
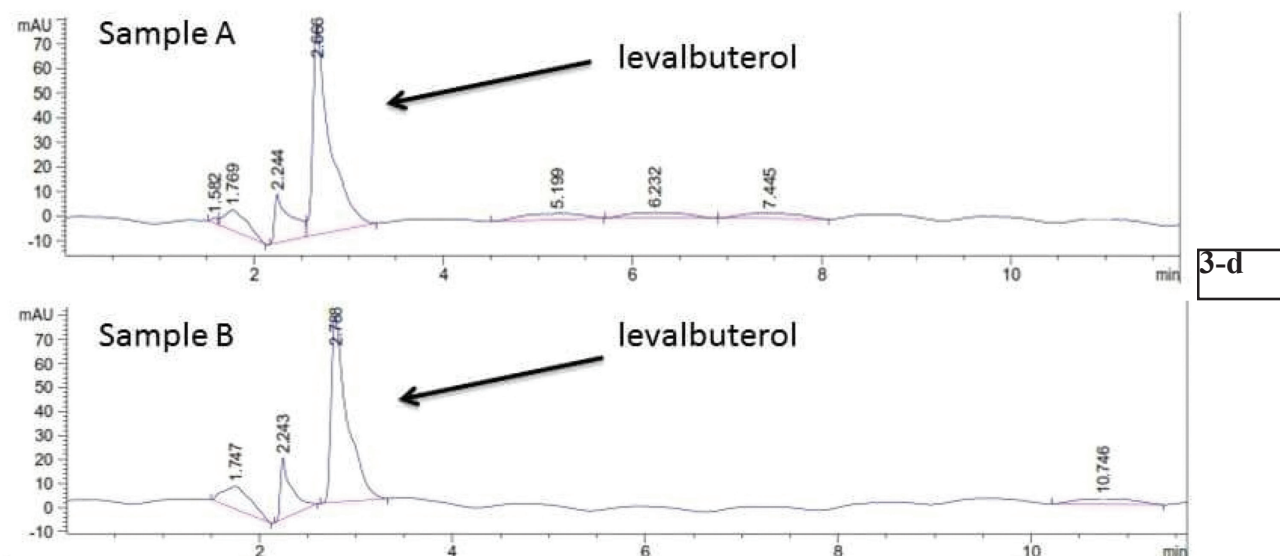
area was also observed (> 10%) but no change was noted in peak shape as shown in Table 1 and Figure 3 d, suggesting very mild degradation of levalbuterol compared to that of colistin and epinephrine. No color change was observed.

A decrease in tobramycin height (to 67.58% of initial concentration) and area (to 82.47%) was observed, as shown in Table 1 and Figure 3 e, suggesting degradation of tobramycin.

A new peak was observed in chromatogram of sample B for acetylcysteine as shown in Figure 3 a. However, no significant difference was observed in area or height of acetylcysteine samples A and B (decrease in sample B was less than 10%) as shown in Table 1 and Figure 2.

A color change was observed in two drugs. acetylcysteine changed from colorless to brownish yellow and epinephrine changed from clear to brown.





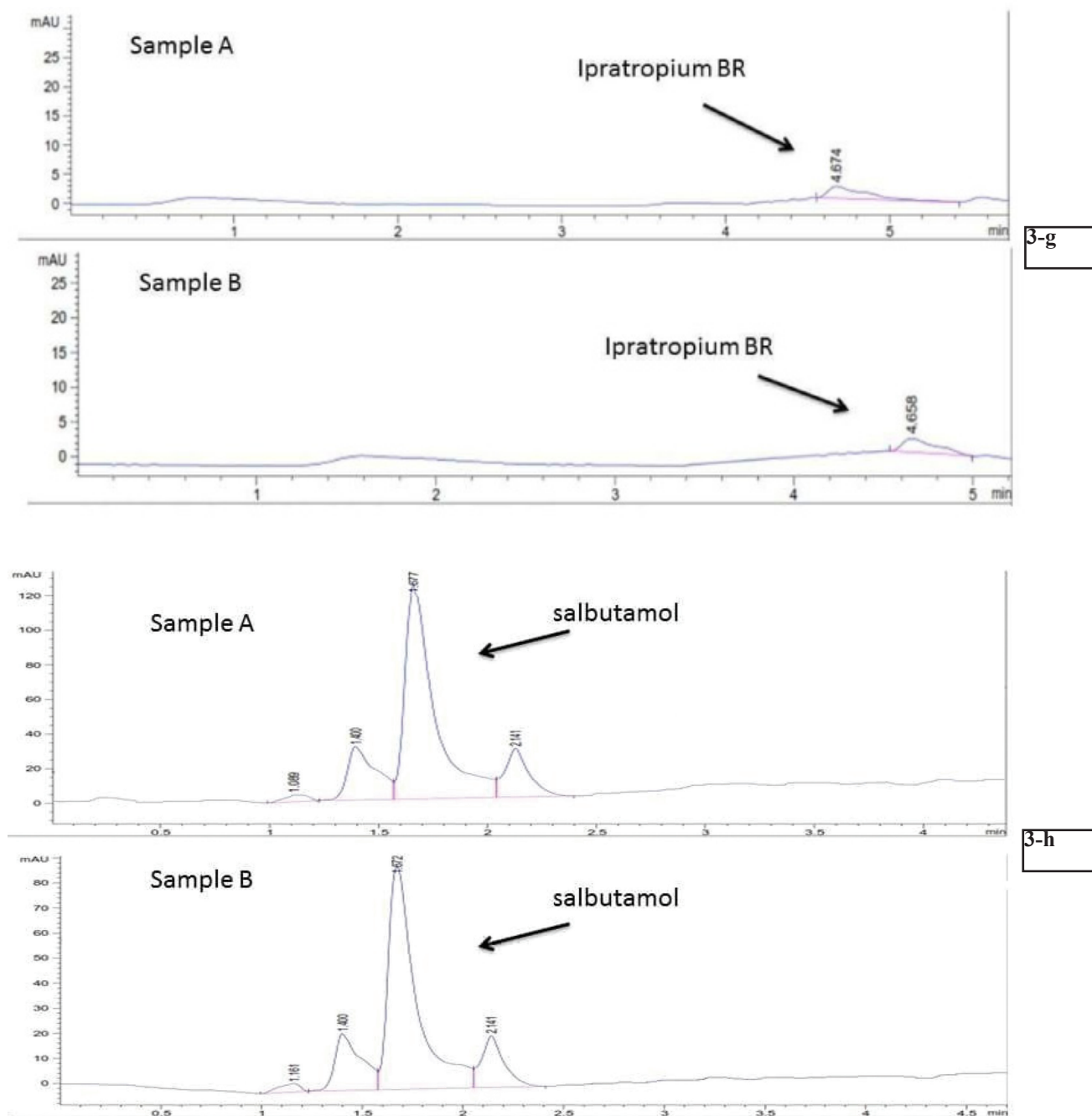


Figure 3. Chromatogram of samples A and B of (a) acetylcysteine (b) colistin; (c) epinephrine; (d) levalbuterol; (e) tobramycin; (f) budesonide; (g) ipratropium and (h) salbutamol

Discussion

Gas delivered to patients requiring ventilatory support is typically anhydrous, containing no water vapor. Heated humidification is common method to increase temperature and water content of inhaled gas to Body Pressure Temperature Saturated (BPTS) conditions and helps prevent damage to airway mucosa from exposure to cold dry gas [1,20].

Aerosol particles deposited in humidifier or ventilator circuit are subject to heat and humidity for prolonged periods, typically up to 7 days (manufacturer recommended change interval for many humidifiers and circuits). Degradation of common inhaled

medications have been reported when exposed to different temperatures e.g. colistin, [21] epinephrine [22-24] and tobramycin [25]. From present study, it is clear that different formulations degrade at different rates.

According to US Pharmacopeia XXXIIX, difference between samples pre and post exposure should be considered significant if sample integrity retained was less than 90% (USP compendial limits $100 \pm 10\%$) [19]. While all drugs studied showed some level of degradation, acetylcysteine, budesonide, ipratropium bromide and salbutamol had less than 10 % degradation. This is consistent with reports of degradation with both ipratropium bromide and salbutamol after 1 month at 54°C [26,27].

The reduction of integrity and concomitant degradation of drugs is used to determine potency and purity of active drug prior to administration, and is considered in determining shelf life.

While our findings of reduced concentration with formulations tested is of interest they likely do not translate to increased risk to patient, as drug deposited in humidifier or tubing would not be re-nebulised or otherwise administered to patient. Greater concern lies in any potentially toxic by-product that might be “out gassed” or carried as vapor to patient.

Previous reports have noted slow degradation and color changes of acetylcysteine in number of condition [28-30]. Presence of additional peaks observed with acetylcysteine, suggests new by-product which was not part of original formulation approved for inhalation. While this change may be benign it should remain suspect as possible toxic change until additional inhalation toxic studies are performed.

Of drugs we studied, only epinephrine has been associated with ability to be therapeutically administered as vapors as well as aerosol. Leung and colleagues recently reported that dissolving epinephrine in water feeding humidifier (Vapotherm, Stevensville, Maryland, USA) could produce clinical therapeutic response in children [31]. Similar effects have not been documented for any of other seven drugs studied here.

Much of recent literature on effect of heat on epinephrine has been focused on its storage in emergency vehicles in exceptionally warm climates where temperatures can exceed 50°C for extended period of time. Gammon et al reported that epinephrine (1 mg/mL) was kept for 12 weeks at 70°C, with no degradation.[26] This would support that our 1 week storage at 50°C likely did not produce substantial toxic by product [26].

Methods of heated humidification could have direct influence on drug delivery to patient. Previous use of bubble cascade humidifiers were found to produce micro-aerosols which could carry pathogens from contaminated humidifier reservoirs, resulting in practices such as daily changes of humidifier chambers and ventilator circuits [32,33]. Such micro-aerosols could potentially carry dissolved drug and its by-products from humidifier to ventilated patient. In contrast, both Passover and wick heated humidifiers do not generate micro-aerosols, removing aerosol as vector of transmission. This was pivotal to practice changes allowing extension of ventilator circuit change requirements to 7 days and beyond [34-36]. Consequently, any drug or bacteria depositing in reservoir of these humidifiers will not be re-nebulized.

Clinicians have expressed concern when they observe color change in humidifier after administration of epinephrine. Potential hazard with drug rainout during mechanical ventilation is not isolated to placement of nebulizer before humidifier. It is likely that same changes in color occur with rainout in ventilator circuit, with aerosol generator placement after humidifier, which may not be visible to caregiver. Either way, with possible exception of acetylcysteine, our findings suggest that aerosolized drug accumulation in ventilator circuit or humidifier does not pose increased risk after exposure to heat over 7 days.

There were some limitations of the study. We did not assay drug

taken directly from heated humidifier or ventilator circuit, nor from water vapors emitted from humidifier or circuit. Such testing would be of interest for future studies, but was beyond scope of this project.

Additional testing of potential harmful by-products of acetylcysteine after exposure to heat and humidity over time may provide greater insights as to importance of our observations.

Drug-drug interactions occur between drugs in humidifier solution, producing by-products with no benefit to patient or with potentially harmful effects if inhaled as aerosol. These combinations were beyond scope of our study and further research in this area is warranted.

Conclusions

Our analysis of commonly inhaled medications subjected to 50°C for 7 days, simulating heat exposure in heated humidifier demonstrated no evidence to suggest any toxic effect. Discoloration was noted in 2 drugs (epinephrine and acetylcysteine) but only acetylcysteine showed a sign of by-product formation via HPLC. We recommend changing the humidifier water more frequently to avoid any possible inhalation of any formed by-products.

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Conflict of Interest

Dr. Fink is CSO of Aerogen Pharma Corp. and has consulted for Aerogen Ltd, Aradis, Ansun, Bayer and Quark. Ms. Dail works with Aerogen Ltd. No other conflict of Interest and no competing financial interests exist. The rest of the authors have no Conflict of Interest and no competing financial interests exist.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Financial Disclosure

The financial support for this study was provided by the investigators themselves.

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