International Journal of Pharmaceutics, 63 (1990) 17–22
Elsevier

IJP 02101

Decomposition of salbutamol in aqueous solutions. I. The effect of pH, temperature and drug concentration

Liisa Mälkki and Seija Tammilehto

Pharmaceutical Chemistry Division, Department of Pharmacy, University of Helsinki, Helsinki (Finland)

(Received 10 January 1990)
(Accepted 28 January 1990)

Key words: Salbutamol (sulfate); Decomposition kinetics; HPLC assay; pH-rate profile; Arrhenius plot

Summary

The decomposition of salbutamol sulphate (albuterol sulphate) was studied in the pH range 1.9–8.8 at 65°C. The decomposed salbutamol sulphate solutions were discoloured and contained a precipitate. Depending on the pH of the solution, one to four major and several minor decomposition products were formed. The rate of decomposition was followed by RP-HPLC with UV detection. The decomposition of salbutamol in aqueous solution obeyed apparent first-order kinetics with respect to salbutamol sulphate. The reaction rate increased with increasing initial drug concentration and elevated temperatures. The maximum stability of salbutamol in aqueous solution occurred at a pH of about 3.5.

Introduction

Salbutamol sulphate (albuterol sulphate), the hemisulphate of 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(*tert*-butylamino)ethanol, is a β_2-selective adrenoreceptor agonist which is used as a bronchodilator and in the prevention of premature labour. Salbutamol is recommended to be kept in a well-closed container and protected from light (BP, 1988; Reynolds et al., 1989). As a salicyl alcohol derivative it shows a relatively high stability compared to that of adrenergic catecholamines.

The first report of salbutamol stability in solution was from Wall and Sunderland (1976). The decomposition of salbutamol was studied in a dextrose solution at pH 2.4 and in phosphate buffers of pH 6.9–8.3 at 40–70 °C. The stability decreased with increase in pH and temperature. The decomposition of salbutamol appeared to proceed faster in concentrated solutions (2%) than in dilute solutions (0.02%). This can also be seen from the results of Hakes et al. (1979).

In 5% dextrose and 0.9% sodium chloride solutions, the common vehicles for intravenous medication, salbutamol is stable for up to 24 h at various temperatures (4–8, 20, 30, 45 °C) (Roberts, 1982; Bhalla et al., 1986).

The influence of some sugars (glucose, sucrose and fructose) on the stability of salbutamol varies with varying solution pH (Hakes et al., 1980). At pH 7.0 (70 °C) glucose accelerated the decomposition of salbutamol in contrast to sucrose, which had no effect. At pH 3.5 (70 °C) both sugars accelerated the reaction to a similar extent by the hydrolysis of sucrose in acidic solution. Fructose

Correspondence: L. Mälkki, Pharmaceutical Chemistry Division, Department of Pharmacy, University of Helsinki, Fabianinkatu 35, SF-00170 Helsinki, Finland.

had the same effect on the stability of salbutamol as glucose. The extent of decomposition increased with increasing sugar concentration. Salbutamol syrups containing saccharin remained undegraded at 55 °C for 3 months (Sequeira and Zupon, 1985).

The effect of two antioxidants, thiourea and sodium metabisulphite, on the stability of salbutamol has been studied in commercial preparations and aqueous and buffered solutions (pH 4.5–7.0) at about 60 °C (Valdés Santurio and Vega Eguino, 1985) and in aerosol solutions (pH 3.5) at 25–65 °C (Valdés Santurio and Vega Eguino, 1986). Thiourea proved to be a better antioxidant than sodium metabisulphite.

Analytical techniques used in stability studies include fluorometry (Wall and Sunderland, 1976), colorimetry (Wall and Sunderland, 1976; Valdés and Vega, 1985; Bhalla et al., 1986; Valdés and Vega, 1986) and high-performance liquid chromatography (Hakes et al., 1979, 1980; Roberts, 1982; Iacono et al., 1987). The fluorometric and colorimetric methods are not necessarily specific, because the unidentified decomposition products may react with the reagent used in the method.

The aim of the present study was to collect qualitative and quantitative data in order to obtain more detailed knowledge on the decomposition of salbutamol in aqueous solution as a function of pH, temperature and drug concentration.

Materials and Methods

Materials

Salbutamol sulphate was kindly supplied by Leiras (Turku, Finland). The identity and purity of the substance were verified by TLC and HPLC and by UV, IR and ^{1}H-NMR and ^{13}C-NMR spectra. All chemicals used were of analytical grade. Water was purified on an Alpha-Q Water Purification system (Millipore).

Apparatus

The decomposition experiments were carried out in a temperature oven (Memmert). pH values were measured with a PHM83 Autocal pH meter (Radiometer). Precoated 0.2 mm silica gel 60 F_{254} aluminium plates (Merck) were used in TLC studies. The HPLC system consisted of an LKB 2150 HPLC pump, an LKB 2151 variable-wavelength monitor operating at 265 nm and a D-2000 chromatointegrator (Hitachi, Merck). Samples were injected using a Rheodyne 7125 injector with a 20 µl loop. The analytical column used was a LiChrosorb RP-18 column (250 × 4 mm i.d., particle size 10 µm).

Stability studies

Aliquots (3 ml) of the 0.018–0.072 M salbutamol sulphate solutions prepared in Britton-Robinson buffers (Brezina and Zuman, 1958) were dispensed into 10 ml glass vials. The ionic strength of the solutions was adjusted with potassium chloride.

The vials were tightly sealed and covered with aluminium foil. They were placed in a preheated temperature oven at 55, 65, 75 or 85 °C (±2 °C).

At appropriate time intervals at least duplicate samples were removed from the oven and the pH value of each sample was determined.

The rate of decomposition was followed by HPLC. The mobile phase consisted of a mixture of acetonitrile and 0.02 M sodium dihydrogen phosphate buffer (pH 3.0 with phosphoric acid) containing 750 µl triethylamine/1 l buffer (3 : 97 v/v). The mobile phase was filtered and bubbled with helium before use. The flow rate was 1.8 ml/min. For the HPLC analysis 0.25–1.0 ml of the sample solution and 1.0 ml of the internal standard solution (orciprenaline sulphate (metaproterenol sulphate) 1.3 mg/ml in water) were diluted to exactly 10 ml. The solutions were filtered through a 0.45 µm disposable filter (Spartan 30/B) before injection into the liquid chromatograph. All samples were injected in triplicate.

For the quantification of salbutamol, a calibration graph was constructed in the range 0.2–2.0 mM by plotting peak area ratios of salbutamol to the internal standard vs salbutamol concentration.

The decomposition was also monitored by TLC using ammonia : water : 2-propanol : ethyl acetate 4 : 16 : 30 : 50 (A, BP, 1988) as eluent. A mixture of methanol : ammonia 100 : 1.5 (B) and an organic layer of 1-butanol : water : acetic acid 4 : 5 : 1 (C) were used as eluents in preliminary TLC studies.

Results and Discussion

Qualitative experiments

The stability of salbutamol sulphate solutions was studied in light-protected glass vials in the presence of air. The solutions were discolored from yellow to brownish red, the development of colour being more pronounced in alkaline solutions. On prolonged storage at elevated temperatures a precipitate was formed, which was insoluble in water and in common organic solvents. It dissolved in dilute sodium hydroxide solution like the precipitate formed by the degradation of epinephrine and phenylephrine (Al Taii et al., 1982). The precipitate may be a polymer containing a phenolic hydroxyl group.

Eluent A was used in TLC studies, since it resulted in the clear separation of the parent drug from its decomposition products. TLC experiments revealed the product formation to depend on the pH of the solution. In basic solution there were three main compounds at $R_f = 0.50$, 0.56 and 0.65 and several trace compounds ($R_f < 0.46$) with the remaining salbutamol at $R_f = 0.46$. In addition, in acidic solution (pH < 7) one major compound ($R_f = 0.24$) was formed, which differed from those obtained in basic solution. The decomposition products were detected under UV light (254 nm) and by spraying with diazotised *p*-nitroaniline. Red spots formed by the reagent indicated that the decomposition products had retained their phenolic character. None displayed a positive reaction with 2,4-dinitrophenylhydrazine (for aldehydes). HPLC analysis (Fig. 1) confirmed the results obtained in TLC. The structures of the decomposition products remain to be elucidated.

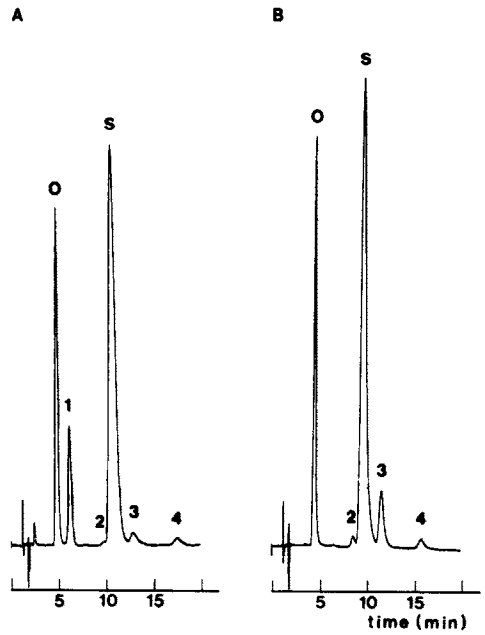

Fig. 1. Chromatograms of partly decomposed salbutamol sulphate solutions at (A) pH 2.2, (B) pH 8.8. Temperature, 65 ± 2 °C. Peak O, internal standard; peak S, salbutamol; peaks 1–4, decomposition products.

Analytical procedure

The decomposition of salbutamol in aqueous solution was followed with HPLC. In previous stability studies, reversed-phase columns were used with the mobile phase containing the ion-pair component in 20% acetonitrile (Hakes et al., 1979,

TABLE 1

Day-to-day reproducibility of retention times by injections of replicate samples (n = 6) of decomposed salbutamol sulphate solutions

Compound	Retention time (min), RSD (%)			
	Day 1	Day 2	Day 3	Mean
Salbutamol	9.33(0.17)	9.54(0.16)	9.33(0.37)	9.40(1.29)
Orciprenaline	4.40(0.19)	4.43(0.12)	4.34(0.32)	4.39(1.04)
Peak 1	5.65(0.30)	5.61(0.31)	5.50(0.14)	5.59(1.39)
2	8.75(0.15)	8.48(0.41)	8.45(0.70)	8.56(1.93)
3	11.68(0.21)	11.29(0.32)	11.26(0.51)	11.41(2.05)
4	15.96(0.19)	15.47(0.51)	15.47(0.52)	15.63(1.81)

1980) or methanol and phosphate buffer, pH 3.0 (Iacono et al., 1987) and with UV detection. The mobile phase used in this study was a slightly modified phase reported in the literature for salbutamol (Agostini et al., 1982; Hutchings et al., 1983; Miller and Greenblatt, 1986; Bannon et al., 1988). Triethylamine was added to the mobile phase to improve the peak shape.

The mean retention times for salbutamol, orciprenaline and the major decomposition products at a flow rate of 1.8 ml/min are listed in Table 1. The capacity factors varied between 2.38 and 11.02 ($t_0 = 1.3$ min as determined using sodium nitrate). The column resolutions (R_s) were greater than 1.27. The calibration graph of salbutamol sulphate showed excellent linearity ($y = 2.0904x - 0.0394$, $r = 1.000$) in the concentration range of interest (0.2–2.0 mM). The precision of the HPLC method was determined by repetitive injections ($n = 6$) of aqueous salbutamol sulphate solution (0.2 and 2.0 mM) and the relative standard deviations were found to be 1.33 and 0.63%, respectively. The mean recovery of salbutamol was 101.4% (RSD = ±1.76%, $n = 12$). The relative standard deviations for parallel decomposed salbutamol sulphate samples ($n = 6$) varied between 1.55 and 6.08%.

Degradation kinetics

The kinetics were investigated at elevated temperatures (55–85 °C), since the decomposition rates of salbutamol at lower temperatures were too slow to obtain reliable kinetic data. Under all conditions studied, the decomposition of salbutamol sulphate followed apparent first-order kinetics ($r > 0.981$; except pH 3.5, $r = 0.823$). The rate constants were determined from the slopes of the straight lines obtained by plotting the logarithm of the residual salbutamol concentration vs time. The half-lives were calculated from the equation $t_{1/2} = 0.693/k_{obs}$ and shelf-lives from the equation $t_{90} = 0.105/k_{obs}$.

Britton-Robinson buffer solutions were used throughout the entire pH range in order to avoid possible effects of different buffer species. The pH-rate profile is sigmoidal (Fig. 2). The shape of the profile at pH > 7 can be explained by changes in ionization states ($pK_a = 9.3$ for the amino group

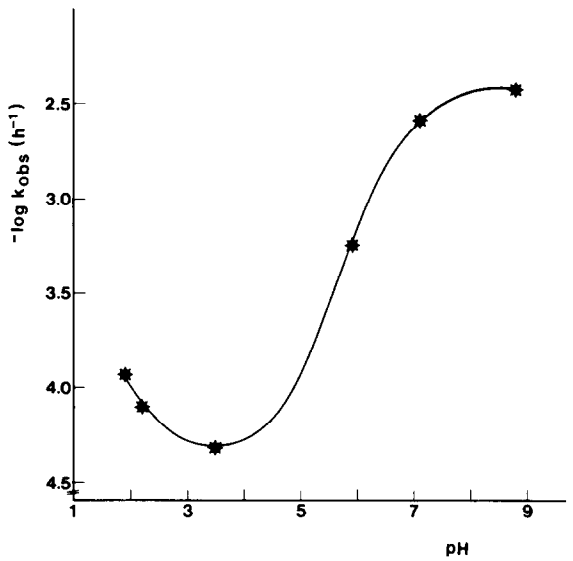

Fig. 2. pH-rate profile for the decomposition of salbutamol sulphate (0.036 M solution) at constant ionic strength and 65 ± 2 °C.

and $pK_a = 10.3$ for the phenolic group; Moffat et al., 1986). Salbutamol proved to be most stable at a pH of about 3.5, which is in agreement with the observation of Hakes et al. (1980). Drugs undergoing oxidative degradation have maximum stabilities usually in the pH range 3–4 (Lachman et al., 1986). The half-lives varied from 7.6 to 605.3 days for the decomposition of salbutamol sulphate within the pH range 1.9–8.8 at 65 ± 2.0 °C (Table 2).

The effect of drug concentration (0.018–0.072 M) was studied at pH 8.8 and 65 ± 2 °C. The decomposition rate of salbutamol increased with

TABLE 2

Decomposition rates, half-lives and shelf-lives of salbutamol sulphate (0.036 M solution) at different pH values and a temperature of 65 °C

pH	k_{obs} (h^{-1})	$t_{1/2}$ (d)	t_{90} (d)	r
1.9	1.18×10^{-4}	244.7	37.1	0.9956
2.2	7.74×10^{-5}	373.1	56.5	0.9818
3.5	4.77×10^{-5}	605.3	91.7	0.8230
5.9	5.82×10^{-4}	49.6	7.5	0.9817
7.1	2.60×10^{-3}	11.1	1.7	0.9948
8.8	3.82×10^{-3}	7.6	1.1	0.9942

increasing initial concentration of salbutamol (Fig. 3). Discoloration of the solution, as well as formation of the precipitate, showed an acceleration in rate in concentrated solution, probably indicating faster polymer formation. Also, the HPLC peaks of the decomposition products diminished more rapidly in concentrated as compared to dilute solutions with the decomposition proceeding further. The reaction order as determined by the half-life method was 1.4, which is similar to that reported by Hakes et al. (1979), suggesting the possibility of variation in the reaction mechanisms in concentrated and dilute solutions.

The influence of temperature on the decomposition rate of salbutamol sulphate was studied in the range 55–85 °C at pH 8.8. An Arrhenius plot of the log of the observed rate constant as a function of the reciprocial of the absolute temperature was linear with a correlation coefficient of $r = 0.996$ (Fig. 4). The activation energy (E_a) for the decomposition of a 1.0% salbutamol sulphate solution at pH 8.8 over the temperature range 55–85 °C was 132 kJ mol^{-1}. The activation energy of a 0.5% solution at pH 9.0 has been reported to be 101 kJ mol^{-1} (Hakes et al., 1979). If the reaction mechanism remains unaltered, the rate constant and shelf-life of a 1.0% salbutamol sulphate solution at pH 8.8 and room temperature (25 °C) are 7.14×10^{-6} h^{-1} and 1.7 years, respectively.

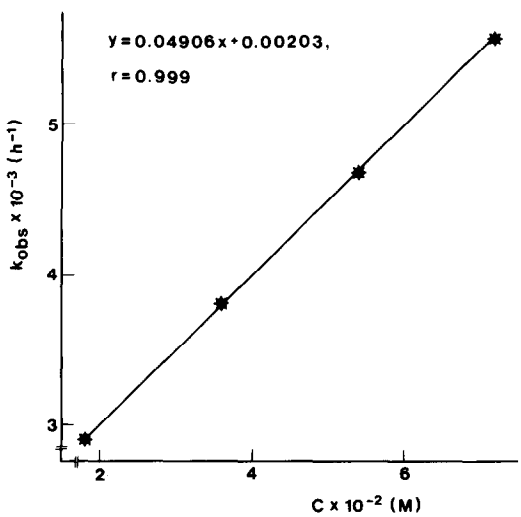

Fig. 3. Effect of drug concentration on the decomposition rate of salbutamol sulphate at pH 8.8 and 65 ± 2 °C.

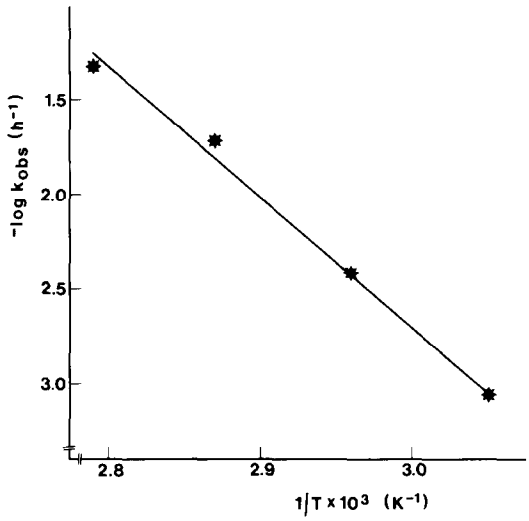

Fig. 4. Arrhenius plot for the decomposition of salbutamol sulphate (0.036 M solution) at pH 8.8 and constant ionic strength.

Acknowledgements

We are grateful to Leiras for the generous gift of salbutamol sulphate. Financial support provided by the Pharmacal Research Foundation, Finland, is gratefully acknowledged.

References

Agostini, O., Chiari, A. and Baffoni, D.C., Simultaneous high-performance liquid chromatographic determination of salbutamol sulphate, theophylline, and saccharin in a hydroalcoholic formulation. *Boll. Chim. Farm.*, 121 (1982) 612–618.

Al Taii, R.A.A., Stanford, J.B. and Sugden, J.K., Some aspects of the photolysis of aqueous solutions of phenylephrine hydrochloride. *Pharm. Acta Helv.*, 57 (1982) 56–60.

Bannon, Y.B., Corish, J., Corrigan, O.I. and Masterson, J.G., Iontophoretically induced transdermal delivery of salbutamol. *Drug Dev. Ind. Pharm.*, 14 (1988) 2151–2166.

Bhalla, H.L., Dias, L. and Sanzgiri, Y.D., Studies in intravenous admixtures. I: Stability and compatibility of salbutamol sulphate in LVP fluids and drug additives. *Indian Drugs*, 23 (1986) 358–363.

Brezina, M. and Zuman, P., *Polarography in Medicine, Bio-*

chemistry, and Pharmacy, Interscience, New York, 1958, p. 731.

British Pharmacopoeia, Her Majesty's Stationery Office, London, 1988, p. 497.

Hakes, L.B., Corby, T.C. and Meakin, B.J., The stability of salbutamol solution. *J. Pharm. Pharmacol.*, 31 (suppl.) (1979) 25P.

Hakes, L.B., Meakin, B.J. and Winterborn, I.K., The effect of sugars on the stability of salbutamol sulphate solutions. *J. Pharm. Pharmacol.*, 32 (suppl.) (1980) 49P.

Hutchings, M.J., Paull, J.D. and Morgan, D.J., Determination of salbutamol in plasma by high-performance liquid chromatography with fluorescence detection. *J. Chromatogr.*, 277 (1983) 423–426.

Iacono, M., Johnson, G.J. and Bury, R.W., An investigation of the compatibility of ipratropium and sodium cromoglycate nebuliser solutions. *Aust. J. Hosp. Pharm.*, 17 (1987) 158–161.

Lachman, L., Deluca, P. and Akers, M.J., Kinetic principles and stability testing. In Lachman, L., Lieberman, H.A. and Kanig, J.L. (Eds), *The Theory and Practice in Industrial Pharmacy*, 3rd edn, Lea & Febiger, Philadelphia, 1986, pp. 760–803.

Miller, L.G. and Greenblatt, D.J., Determination of albuterol in human plasma by high-performance liquid chromatography with fluorescence detection. *J. Chromatogr.*, 381 (1986) 205–208.

Moffat, A.C., Jackson, J.V., Moss, M.S. and Widdop, B., *Clarke's Isolation and Identification of Drugs in Pharmaceuticals, Body Fluids, and Post-mortem Material*, 2nd edn, Pharmaceutical Press, London, 1986, pp. 963–964.

Reynolds, J.E.F., Partitt, K., Parsons, A.V. and Sweetman, S.C., *Martindale, The Extra Pharmacopoeia*, 29th edn, Pharmaceutical Press, London, 1989, pp. 1480–1483.

Roberts, M.J., Salbutamol obstetric injection stability in Hartmann's solution. *Aust. J. Hosp. Pharm.*, 12 (1982) 29–30.

Sequeira, J.A. and Zupon, M.A., Stable pleasant-tasting albuterol sulfate pharmaceutical formulations. *U.S. Patent*, No. 4 499 108 (1985).

Valdés, J.R. and Vega, E., Influencia del metabisulfito de sodio en la estabilidad del sulfato de salbutamol. (I). *Rev. Cubana Farm.*, 19 (1985) 156–172.

Valdés Santurio, J.R. and Vega Eguino, E., Estabilidad del sulfato de salbutamol. Nebulizaciones. (II). *Rev. Cubana Farm.*, 20 (1986) 28–34.

Wall, B.P. and Sunderland, V.B., A preliminary study on the stability of salbutamol in aqueous solution. *Aust. J. Hosp. Pharm.*, 6 (1976) 156–160.