

APPENDIX-A

CHEMICAL COMPOUNDS

1. Salbutamol

Synonyms : Salbutamol; Albuterol; AH 3365; Sch 13949W

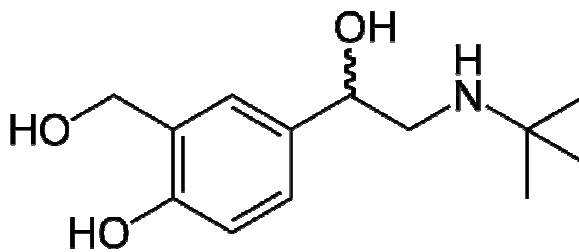
Chemical name : 2-(hydroxymethyl)-4-[1-hydroxy-2-(tert-butylamino)ethyl]phenol

Chemical properties

Molecular formula : C₁₃H₂₁NO₃

Molecular weight : 239.31

Chemical structure :



pKa : 5.9 for salbutamol

pKa₁=9.3, pKa₂=10.3 for salbutamol sulfate

Physical Properties

Description : White crystalline powder from ethanol-ethyl acetate or ethyl acetate-cyclohexane. The powder is odorless and almost tasteless.

Melting point : 157-158°C

Solubility : Salbutamol is soluble 1 in 70 of water and 1 in 25 ethanol, slightly soluble in ether.

Absorption maximum : The salbutamol showed a clear negative cotton effect at 276-280 nm. At a lower wavelength, 220-230 nm, the curves tended towards a further negative peak although this was somewhat masked by the high aromatic absorption.

General information

Use : Prevent or relief asthma symptom, symptom relief during maintenance therapy of asthma and other conditions with reversible airways obstruction (including COPD)

Mechanism of action : Salbutamol binds to β_2 -adrenergic receptors with a higher affinity than β_1 -receptors. In the airway, activation of β_2 -receptors results in relaxation of bronchial smooth muscle resulting in a bronchodilation.

Metabolism, Absorption and Excretion : Salbutamol is readily absorbed from the gastrointestinal tract, it is metabolized inside wall-gut about 50% after oral administration. After absorption the drug was transformed again with liver enzyme "sulfatase". Its effect occurs within 15 minutes and lasts for about 14

hours. When given by inhalation, its effect occurs within 5 minutes. The drug is excreted in urine in about 24 hours, 50% of the dose administered by mouth or 30% of the dose by inhalation is excreted within 4 hours. About 80% of the tritium-labelled salbutamol given orally, intravenously or by aerosol is excreted in urine within three days. The peak-plasma concentration of salbutamol and its metabolites is 5.1-11.7 $\mu\text{g}\%$ at 2.5-3 hours after an oral dose (4 mg of salbutamol). Salbutamol was extensively metabolized to a polar metabolite in humans, which possessed spectral and chemical properties different from the parent drug. The metabolite is a conjugate which was not hydrolysed by β -glucuronidase, sulphatase, ketodase or β -glucosidase.

2. α Lactose

Synonyms : 4-(β -D-galactosido)-D-glucose; Milk Sugar; Lactin; Lactobiose; Saccharum Lactin

Chemical name : 4-O- β -D-galactopyranosyl- α -D-glucopyranose

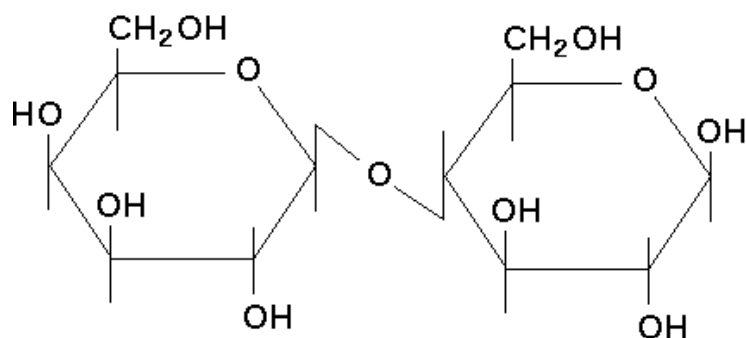
Chemical properties

Molecular formula : $\text{C}_{12}\text{H}_{22}\text{O}_{11}$ (anhydrous)

$\text{C}_{12}\text{H}_{22}\text{O}_{11} \cdot \text{H}_2\text{O}$ (monohydrate)

Molecular weight : 342.30 (anhydrous)

360.31 (monohydrate)

Chemical structure :**Physical Properties**

Description : Lactose is a white, or creamy white, hard crystalline material, which is readily milled into a powder. It is odorless, has slightly taste, and tends to absorb odors from the atmosphere. The material can be spray-dried, yielding a granular, highly flowable material.

Density : 1.540 (α -lactose monohydrate)

1.589 (anhydrous β -lactose)

Melting point : 201-202°C (α -lactose monohydrate)

223°C (anhydrous α -lactose)

252.2°C (anhydrous β -lactose)

T_g : 101°C

Specific rotation : +54.8° to +55.5° for anhydrous lactose, as 10% w/v

Solubility : Lactose has a solubility of 1 in 4.63 measured %w/v. This translates to 0.216g of lactose dissolving readily in 1mL of water. The solubility of lactose in water is 18.9049 g at 25 °C, 25.1484 g at 40 °C and 37.2149 g at 60 °C per 100 g solution. Its solubility in ethanol is 0.0111 g at 40 °C and 0.0270 g at 60 °C per 100 g solution.

General Information

Use : Lactose is one of the most commonly used excipients in direct compression formulations. The compound is normally used as a diluents, whose purpose is to make up the required bulk of a solid dosage form when the amount of drug itself is not adequate. Lactose is probably the most widely diluents in tablet formation, since it is found to be stable in the presence of many drug substances. Anhydrous lactose is particularly useful since it can be purified to such a degree that it dose not undergo the Maillard reaction, which leads to browning and discoloration.

Stability : When stored in adequately sealed containers, anhydrous lactose is a very stable material. Its normal high stability and purity have led to the widespread use of lactose as one of the most important pharmaceutical excipients. In the solid state, exposure to high relative humidity can lead to formation of the α -lactose monohydrate form, and to the growth of mold.

Acidic hydrolysis of lactose will convert lactose into equal amounts of glucose and galactose. Lactose may also be oxidized with bromine water, yielding an acid which hydrolyses to galactose and gluconic acid.

In the solution phase, the anomeric composition of lactose changes with time, ultimately ending up as 35% α -lactose and 65% β -lactose. Equilibrium can be reached instantly through the addition of dilute ammonia to the lactose solution.

APPENDIX-B

AERODYNAMIC ASSESMENT OF FINE PARTICLES

1. **ANDERSEN CASCADE IMPACTOR (ACI)** (Adapted from BP, 2001 ; Mitchell and Nagel, 2004 ; USP 25, 2002)

ACI is assembled from several stages with progressively decreasing cut sizes (Figure B.1), so that an incoming aerosol is size separated into the same number of fractions as there are 8 stages. For inhaler testing, it is desirable to have at least 5 stages with d_{50} values located within the critical range from 0.5 to 5 μm aerodynamic diameter. There is a link between the cut sizes of individual impactor stages and the likely deposition sites in the respiratory tract of the particles that are size-separated, but it is important to appreciate that diagrams, such as Figure B.2, which relates to the Andersen 8-stage impactor, are only a guide, since the constant flow rate through an ACI does not simulate the continuously varying flow rate associated with the respiratory cycle. Size ranges appropriate to these and other ACIs occasionally used for inhaler testing that are based on published calibration data, are summarized in Table B.1.

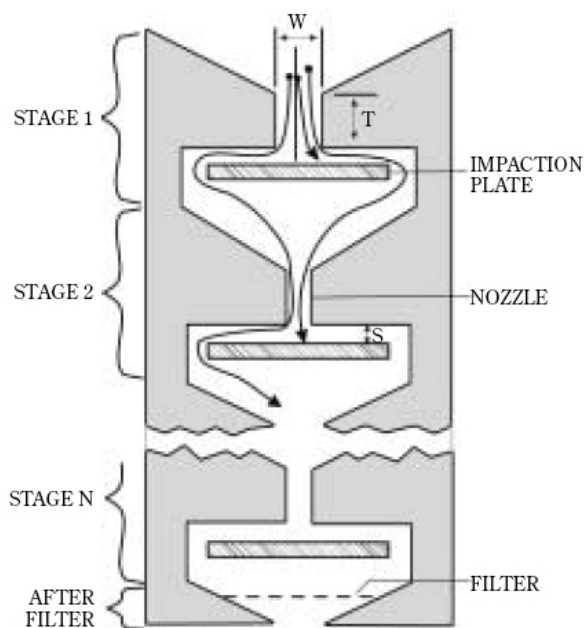


Figure B.1 Schematic of a multi-stage impactor, showing the separation of progressively finer particles as the aerosol passes through successive stages to the after filter

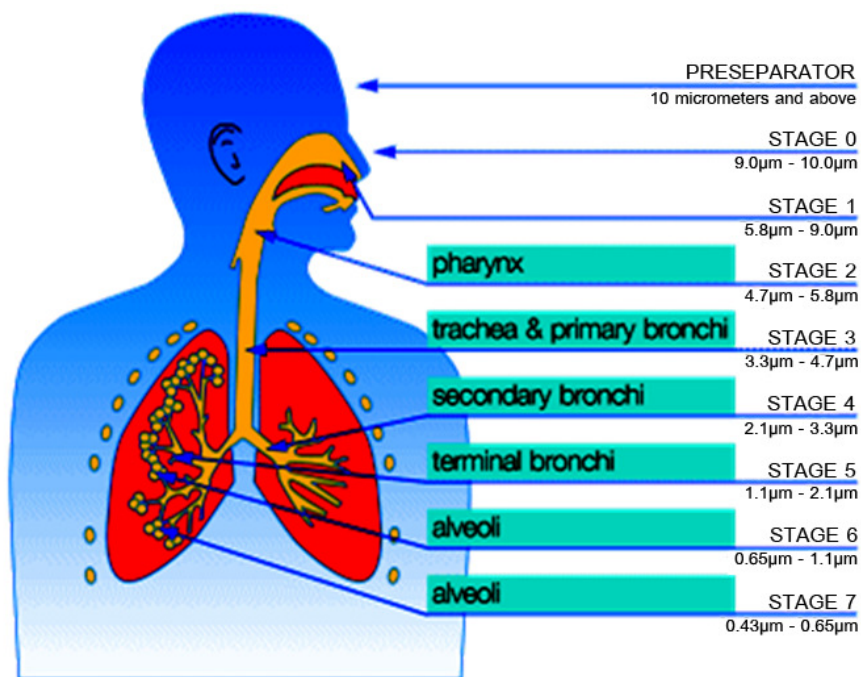


Figure B.2 Relationship between Andersen 8-stage cascade impactor cut sizes at 28.3 L min^{-1} and likely particle deposition in the respiratory tract

Table B.1 Stage D_{50} values (μm) for the various configurations of the Andersen 8 stage cascade impactor at different flow rates

Stage	Flow Rate (L min^{-1})		
	28.3	60	90
-2	Not used	Not used	8.0
-1	Not used	8.6	6.5
0	9.0	6.5	5.2
1	5.8	4.4	3.5
2	4.7	3.2	2.6
3	3.3	1.9	1.7
4	2.1	1.2	1.0
5	1.1	0.55	0.22
6	0.7	0.26	Not used
7	0.1	Not used	Not used

ACI is Apparatus D in BP or Apparatus 3 for DPIs in USP. Suitable configurations of a multistage cascade impactor, for which the following text applies, are given in Table B.2. Other suitable ports may also be used.

Table B.2 Component units of ACI

Item	Description	Identifying code	Dimensions
Mouthpiece adaptor	Moulded rubber adaptor for actuator mouthpiece	A	
Throat	Modified round bottom flask <i>ground-glass inlet socket</i>	B	50 ml 29/32
Adaptor	Plastic tube	C	
Multistage cascade impactor	Manufacturer's description	D	

Procedure for powder inhalers

If necessary, coat each plate with suitable liquid, for example, silicone. Assemble the multistage cascade impactor with a suitable preseparator and ensure that the system is airtight. Connect a pump to the apparatus and, without the inhaler in place, adjust the air flow through the apparatus, as measured at the inlet to the throat, to that prescribed for the apparatus. Switch off the pump.

Prepare the inhaler for use and locate the mouthpiece in the apparatus by means of suitable adaptor. Switch on the pump for 5 seconds. Switch off the pump and remove the inhaler. Dismantle the apparatus.

The preseparator will collect any particles with an aerodynamic size larger than 10 μm and it also prevent particle bounce and re-entrainment (Holzner and Muller, 1995). The preseparator used in this study is shown in Figure B.3. The Andersen preseparator is an impaction chamber with one 0.53 inch diameter inlet orifice and three outlet tubes which are 1 inch above the

impaction surface. The design results in a very low turbulence and allows collection of several grams of particulate matter without the preseparator being overloaded. Therefore, the preseparator performance is a very important issue in cascade impaction of dry powder aerosols.

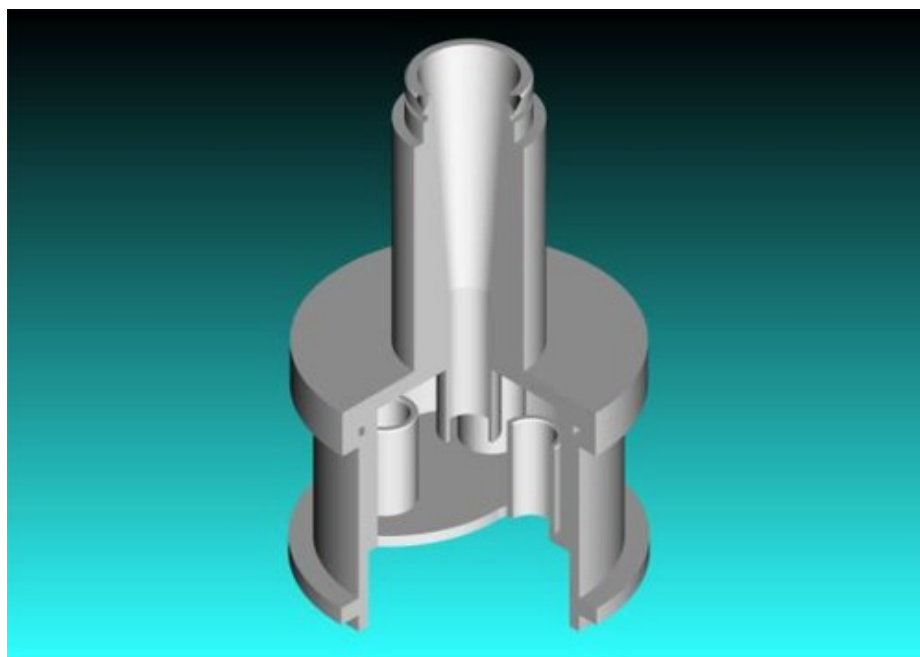


Figure B.3 The preseparator of ACI (Adapted from Mitchell and Nagel, 2004)