APPENDIX-A

CHEMICAL COMPOUNDS

1. RIFAMPICIN

Synonyms : rifampin; rifamycin AMP; rifaldazine; rifampicin SV; 3-[[(4-methyl-1-piperazinyl)imino]methyl]rifamycin SV

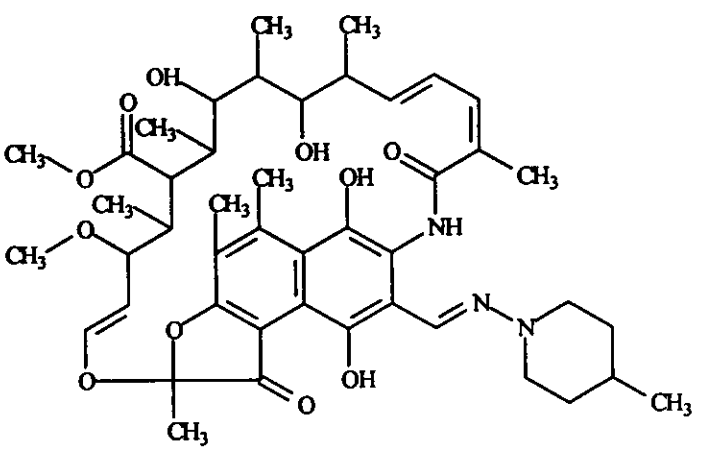
Chemical name : 2,7-(epoxypentadeca[1,11,13]trienimino)naphtha[2,1-b]furan-1,11(2H)-dione,5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-methyl-1-piperazinyl)formimidoyl]-21-acetate

Chemical Properties

Molecular formula : $C_{43}H_{58}N_4O_{12}$

Molecular weight : 822.95

Chemical structure :



pKa : 1.7 related to the 4-hydroxy and 7.9 related to the 3-piperazine nitrogen

Physical Properties

Description : Red to orange to red brown crystalline powder or pellets, odorless

Boiling point : Decomposes at 183°C to 188°C

Freezing point : Decomposes

Density : 0.42 g/ml

Solubility : Freely soluble in dimethylformamide, dimethylsulfoxide, methyl chloride. Soluble in tetrahydrofuran, Slightly soluble in ethanol 95% and very slightly soluble in benzene. Practically insoluble in carbon tetrachloride, cyclohexane, n-butanol, propyleneglycol, glycerol and carbowax 400. Solubility of rifampicin is 349 mg/ml in chloroform, 216 mg/ml in dichloromethane, 108 mg/ml in ethyl acetate, 39 mg/ml in dioxane, 16 mg/ml in methanol, 14 mg/ml in acetone, 0.43 mg/ml in n-hexane, 0.33 mg/ml in petroleum ether. Solubility of rifampicin in water is 2.5, 1.3, 2.8, 99.5 mg/ml at pH 7.3, 4.3, 7.5 and 2.0 respectively.

Absorption maximum: The ultraviolet absorption max of rifampicin are 237, 255, 334 and 475 nm (in aqueous phosphate buffer pH 7.38) that have ε are 33200, 32100, 27000, 15400 respectively.

General information

Use : Antibacterial, antitubercular

Mechanism of action: Rifampicin affects mainly gram-positive bacteria. Gram-negative bacteria are much less sensitive to rifampicin. Gram-negative bacteria possess an outer membrane that is probably too great a barrier for the transport of rifampicin into the cell. Rifampicin's bactericidal effect is caused by the inhibition of RNA synthesis in bacteria. The antibiotic interacts with RNA polymerase, thus

inhibiting the synthesis for long RNA strands. Rifampicin's binding sites lie on the beta-subunit of the enzyme. The antibiotic, however, does not bind to the isolated subunit but only to the complete holo-enzyme. Rifampicin does not interact with eukaryotic RNA polymerases. It is, however, active against RNA polymerases present in chloroplasts and mitochondria. This makes rifampicin a toxic agent for plant and mammal cells. Resistance to rifampicin can to build up rapidly and is based on change in the bacterial RNA polymerases.

Stability :

Stability as powder

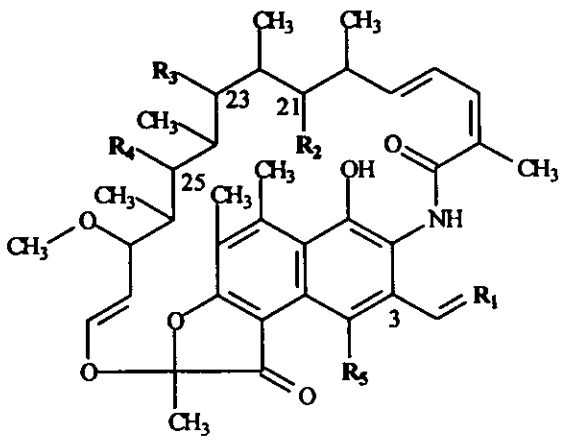
Rifampicin is very stability in an the solid state in sealed containers at room temperature, as described in Table A-1. Rifampicin in the solid state is stable also at temperatures up to 70°C.

Stability in solution

The stability of rifampicin in an aqueous solution has been widely investigated. Chemical structures of rifampicin and its degradates are shown in Figure A.1. Two major antimicrobial decomposition products exist, namely, 3-formylrifamycin SV and rifampicin quinine. Hydrolysis of the 4-methylaminopiperazine moiety in an acidic medium results in 3-formylrifamycin SV, whereas rifampicin quinine is formed in an alkaline medium in the presence of oxygen. Conversly, 25-desacetylrifampicin is reportedly formed in an alkaline medium in the absence of oxygen. 25-Desacetyl-21-acetylrifampicin and 25-desacetyl-23-acetylrifampicin are formed sequentially from 25-desacetylrifampicin and, unlike other indentified decomposition products, have negligible antimicrobial activity.

Table A.1 Stability of rifampicin in the solid state at room temperature

Drug and degrade substance	Starting	12 months	21 months	30 months	41 months
rifampicin	95%	101.1%	99.0%	100.2%	97.3%
3-formylrifamycin SV	traces	traces	traces	traces	traces
rifampicin quinone	absent	1-1.5%	1.5-2%	1.5-2%	2.5-3%
rifampicin N-oxide	traces	1-1.5%	1-1.5%	1-1.5%	1-1.5%
25-desacetyl-21-acetylrifampicin	absent	traces	traces	traces	0.5-1%
25-desacetylrifampicin	0.5-1%	1.5-2%	1.5-2%	1-1.5%	1-1.5%
25-desacetyl-23-acetylrifampicin	absent	absent	absent	traces	traces



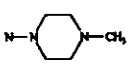
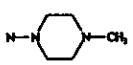
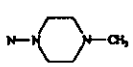
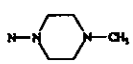
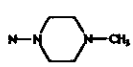
Analyte	R_1	R_2	R_3	R_4	R_5
rifampicin		OH	OH	CH_3COO	OH
3-formylrifamycin SV	O	OH	OH	CH_3COO	OH
rifampicin quinone		OH	OH	CH_3COO	=O
25-desacetylrifampicin		OH	OH	OH	OH
25-desacetyl-21-acetylrifampicin		CH_3COO	OH	OH	OH
25-desacetyl-23-acetylrifampicin		OH	CH_3COO	OH	OH

Figure A.1 Structural features of rifampicin and its decomposition products in aqueous solution

2. ISONIAZID

Synonym : isonicotinic acid hydrazide; isonicotinylhydrazide; isonicotinyl hydrazide; isonicotinylhydrazine; tubazid; isoniazidum; isoniazide

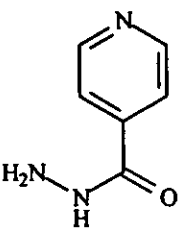
Chemical name : 4-pyridinecarboxylic acid hydrazide; pyridine-4-carboxyhydrazide; pyridine-γ-carboxylic acid hydrazide

Chemical Properties

Molecular formula : $C_6H_7N_3O$

Molecular weight : 137.14

Chemical structure :



Physical Properties

Description : Colorless or white crystalline powder which is odorless and has at first a slightly sweet and then bitter taste.

Freezing point : 174.4°C

Melting point : 170-174°C

Density : 0.68 g/ml

Vapor Pressure : Negligible

Solubility : 14 g of isoniazid are soluble in 100 ml of water at 25°C. 26 g of isoniazid are soluble in 100 ml of water at 40°C. Solubility of isoniazid in ethanol,

boiling ethanol and chloroform are 20 mg/ml, 100 mg/ml and 1 mg/ml, respectively. Isoniazid is very slightly soluble in ethyl ether and insoluble in benzene.

pH : 1% aqueous solution 5.5 to 6.5

Refraction index : 1.5502

Flash point : 190°C

General Information

Use : Antibacterial, antactinomycotic agent

Mechanism of action: Isoniazid has a powerful bactericidal activity against replicating tubercle bacilli but little or no activity against near dormant bacilli. Isoniazid inhibits the mycolic acid cell wall synthesis via oxygen-dependant pathways, such as the catalase-peroxidase reaction. It reaches therapeutic concentrations is serum, cerebrospinal fluid, and within caseous granulomas

Stability : The stability of isoniazid has been studied extensively in solution and in various pharmaceutical preparations. Of particular interest is the reaction of the hydrazine group with naturally occurring aldehydes and ketones such as sugars or ketoacids and the complexation of isoniazid with metal ions. Non-ionic chelating material can largely prevent the degradation of isoniazid when neutral and alkaline solutions are autoclaved. Cu (II) and Mn (II) ions accelerated the degradation of isoniazid in the presence of hydrogen peroxide. Isoniazid is stable for several weeks in buffered aqueous solutions at pH values below 8. Alkaline hydrolysis under aerobic conditions yields a mixture of isonicotinic acid, isonicotinamide and 1, 2 diisonicotinoyl hydrazine plus small amounts of unidentified products. Under anaerobic conditions isonicotinic acid and 1, 2 diisonicotinoyl hydrazine were the

principal products. When EDTA was added to the reaction mixture only isonicotinic acid was formed. First order kinetics was followed.

Isoniazid underwent slow oxidation in the aqueous solution, but in the presence of sucrose the isoniazid reacted with the aldohexoses formed on inversion. The reaction with sucrose could be inhibited by the addition of 0.3% sodium citrate. Isoniazid in syrup formulations undergoes hydrazone formation with the free glucose that is present. Absorption of this hydrazone is impared. So, suggest the use of sorbitol as replacement for sucrose.

3. TREHALOSE

Synonyms : Diglucose; mycose

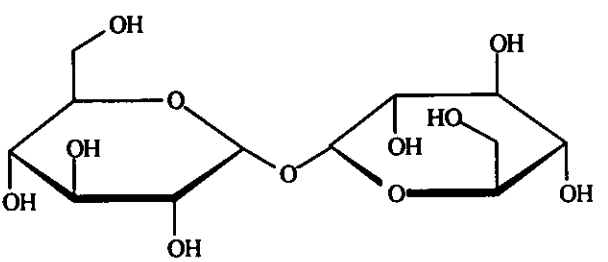
Chemical name : α-D-Glucopyranosyl-α-D-glucopyranoside

Chemical Properties

Molecular formula : $C_{12}H_{22}O_{11}$

Molecular weight : 340.30

Chemical structure :



Physical Properties

Description : Trehalose is disaccharide, two sample sugars one molecule. In trehalose (as maltose), the two sugars are both glucose. Trehalose, like maltose, is 45% as sweet as sugar. Trehalose is a white, odorless, sweet-tasting powder.

Trehalose is a non-reducing sugar with similar chemical structure and characteristics to those of sucrose. It does not brown like sugar, and has a very low hygroscopicity (moisture attraction), so it stays free flowing and dry. In trehalose, one glucose molecule is upside-down relative to the other. In maltose, the two glucose molecules are in the same orientation. This small difference is reflected in the properties of trehalose. It does not brown when heated, it does not promote bacterial growth or tooth decay as much as maltose or sugar, and it is less attractive to moisture. Trehalose is found in mushrooms, honey, baker's yeast, bread, beer, and seafood.

Melting point : 96.5-97.5°C (dihydrate)

203-210.5°C (anhydrous)

Solubility : 68.9 g/100 g of water at 20°C. Soluble in hot alcohol and insoluble in ether

Specific rotation : +178°

T_g : 79°C

Heat of fusion : 57.8 kJ mol^{-1} (dihydrate)

53.4 kJ mol^{-1} (anhydrous)

Hygroscopicity : <1% (% weight gain at 25°C) Trehalose is stable up to 94% relative humidity. The low hygroscopic nature of trehalose dehydrate results in a free-flowing stable dry product.

Relative sweetness : 45% of sucrose

General Information

Use : Trehalose is used in food as a sweetener, a stabilizer and thickener, and a flavor enhancer. It is also used as a cryopreservative additive, where it protects cells from the effects of freezing and drying. In addition to the use in food

products, other distinctive properties of trehalose such as its skin moisture retaining effect and stabilizing effect on bioactive substances will undoubtedly open up new avenues for its uses in such fields as cosmetics and pharmaceuticals.

Stability : Trehalose is stable under low pH conditions stability of solution > 99% in pH 3.5-10 at 100°C for 24 hours) where other disaccharides typically undergo various reactions, such as hydrolysis into their component monosaccharides. This minimizes caramelization and browing wich are typical of low pH systems that undergo that processing. The heat stability of solution > 99% at 120°C for 90 minutes.

4. MANNOSE

Synonyms : Seminose; carubinose

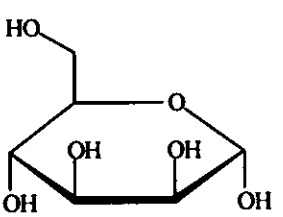
Chemical name : α-D-Mannose

Chemical Properties

Molecular formula : $C_6H_{12}O_6$

Molecular weight : 180.16

Chemical structure :



pKa : 11.98 (18°C)

Physical Properties

Description : α-Form is crystals from methanol. D-mannose is a simple sugar. Chemically, it is closely related (a stereoisomer) to glucose. It is a naturally

occurring sugar found in cranberry and pine apple juice. Reduces Fehling's solution and is fermented by yeast.

Melting point : 133°C

Specific rotation : +29.3° to +14.2° (water)

T_g : 30°C

Solubility : 1 g dissolves in 0.4 ml of water, 120 ml methanol, 250 ml absolute ethanol, 35 ml pyridine.

5. α-LACTOSE

Synonyms : 4-(β-D-galactosido)-D-glucose; milk sugar; saccharum lactis

Chemical name : 4-O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose anhydrous; 4-O-β-D-Galactopyranosyl-(1→4)-α-D glucopyranose monohydrate

Chemical properties

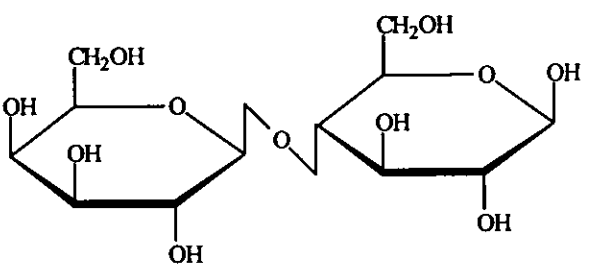
Molecular formula : $C_{12}H_{22}O_{11}$ (anhydrous)

$C_{12}H_{22}O_{11}.H_2O$ (monohydrate)

Molecular weight : 342.30 (anhydrous)

360.31 (monohydrate)

Chemical structure :



Physical Properties

Description : White to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 15% as sweet as sucrose, while β-lactose is sweeter than α-form. Several different forms of lactose are commercially available : anhydrous α-lactose, α-lactose monohydrate, and to a lesser extent, anhydrous β-lactose which a typically contains 70% anhydrous β-lactose and 30% anhydrous α-lactose.

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)

$\mathbf{T_g}$: 101°C

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

Solubility : 1 g of lactose dissolves in 4.63 ml of water, in 3.14 ml of water at 40°C, in 2.04 ml of water at 50°C, in 1.68 ml of water at 60°C and in 1.07 ml of water at 80°C. Lactose is very slightly soluble in alcohol. Lactose is practically insoluble in chloroform, ethanol and ether.

General Information

Use : Lactose is widely used as a filler or diluent in tablets, capsules, and to a more limited extent in lyophilized products and infant feed formulas.

Stability : Under humid conditions (80% relative humidity and above), mold growth may occur. Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp condition. The purity of different lactoses can vary and color evaluation may thus be important, particularly if white tablets are being formulated.

6. CHOLESTEROL

Synonyms : Cholesterin

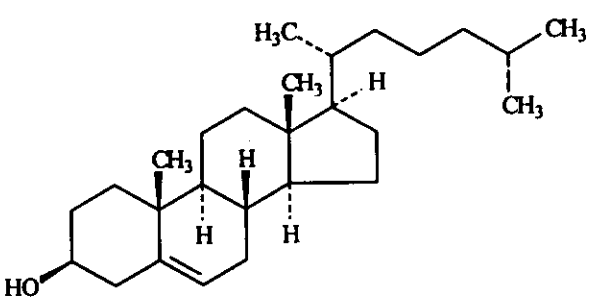
Chemical name : Choles-5-en-3β-ol

Chemical Properties

Molecular formula : $C_{27}H_{36}O$

Molecular weight : 386.66

Chemical structure :



Physical Properties

Description : White or faintly yellow, almost odorless, pearly leaflets, needles, powder or granules. On prolonged exposure to light and air cholesterol acquires a yellow to tan color.

Boiling point : 360°C

Density : 1.052 g/ml for anhydrous form

Dielectric constant : 5.41

Melting point : 147-150°C

Specific rotation : -39.5° (2% w/v solution in chloroform)

-31.5° (2% w/v solution in ether)

Solubility : Cholesterol is insoluble in acetone and vegetable oils. It is practically insoluble in water. Cholesterol 1 g is soluble in 7 ml of benzene, 4.5 ml of chloroform, 2.8 ml in ether, 52 ml in hexane and 19 ml in isopropyl myristate. In addition, cholesterol 1 g were dissolve in 147 ml of ethanol at 0°C, 78 ml of ethanol at 20°C, 29 ml of ethanol at 40°C, 19 ml of ethanol at 50°C, 13 ml of ethanol at 60°C. 1 g of cholesterol were dissolve in 294 ml of methanol at 0°C, 153 ml of methanol at 20°C, 53 ml of methanol at 40°C, 34 ml of methanol at 50°C, 23 ml of methanol at 60°C.

General Information

Use : Cholesterol is used in cosmetics and topical pharmaceutical formulations at concentrations between 0.3-5.0% w/w as an emulsifying agent. It imparts water-absorbing powder to an ointment and has an emollient activity. Cholesterol additionally has a physiological role and is used for prepare novel drug delivery systems such as liposome.

Manufacture : Principal sterol of the higher animals. Found in all body tissues, especially in the brain, spinal cord, and in animal fats or oils. Main constituent of gallstones. The commercial material is normally obtained from the spinal cord of cattle by extraction with petroleum ethers but may also be obtained from wool fat. Purification is normally accomplished by repeated bromination. Cholesterol may also be produced by entirely synthetic means.

7. LECITHIN

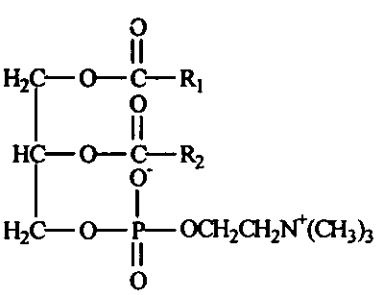
Synonyms : Phosphatidylcholine; lecithol; egg lecithin; mixed soybean phosphatides; ovolecithin; soy bean lecithin; soy bean phospholipids; vegetable lecithin

Chemical Properties

Molecular weight : The molecular weight of lecithin varies. The USPNF XVII describes lecithin as a complex mixture of acetone-insoluble phosphatides, which consist chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol, combined with various amounts of other substances such as triglycerides, fatty acids and carbohydrates as separated from a crude vegetable oil source.

The composition of lecithin and hence its physical properties varies enormously depending upon the source of the lecithin and the degree of purification. Egg lecithin, for example, contains 69% phosphatidylcholine and 24% phosphatidylethanolamine, while soybean lecithin contains 21% phosphatidylcholine, 22% phosphatidylethanolamine and 19% phosphatidylinositol, along with other compounds.

Chemical structure :



α-phosphatidylcholine

Where, R1 and R2 are fatty acids which may be different or identical.

Physical Properties

Descriptions : Lecithins vary greatly in their physical form, from viscous semiliquids to powders, depending upon the free fatty acid content. They may also vary in color from brown to light yellow, depending upon whether they are bleached or unbleached.

Lecithins have practically no odor. Those derived from vegetable sources have a bland or nut-like taste, similar to soybean oil.

Density : 0.97 g/ml for liquid lecithin

0.5 g/ml for powdered lecithin

Iodine number : 95-100 for liquid lecithin

82-88 for powdered lecithin

Isoelectric point : ≈ 3.5

Saponification value : 196

Solubility : lecithins are soluble in aliphatic and aromatic hydrocarbons, halogenated hydrocarbons, mineral oil and fatty acids. They are practically insoluble in cold vegetable and animal oils, polar solvents and water. When mixed with water however, lecithins hydrate to form emulsions.

General Information

Use : Lecithins are used in a wide variety of pharmaceutical applications. They are also used in cosmetics and food products. Lecithins are mainly used in pharmaceutical products as dispersing, emulsifying and stabilizing agent and are included in intramuscular and intravenous injections, parenteral nutrition formulations and topical products, such as creams and ointments.

Lecithins are also used as a base for suppository, to reduce the blittleness of suppositories and have been investigated for their absorption enhancing properties in intranasal insulin formulations. Lecithins are also commonly used as a component of the bilayer have been used to encapsulate drug substances and their potential as novel delivery systems has been investigated.

Method of manufacture: Lecithins are essential components of cell membranes and may thus in principle be obtained from a wide variety of living matter. In practice however, lecithin are usually obtained from vegetable products such as soybean, peanut, cottonseed, sunflower, rapeseed, corn or groundnut oil. Soybean lecithin is the most commercially important vegetable lecithin. Lecithin obtained from eggs is also commercially important and was the first lecithin to be discovered.

Vegetable lecithins are obtained as a by-producted in the vegetable oil refining process. Polar lipids are extracted with hexane and after removal of the solvent a crude vegetable oil obtained. Lecithin is then removed from the crude oil by water extraction. Following drying the lecithin may then be further purified. With egg lecithin, a different manufacturing process must be used since the lecithin in egg yolks is more tightly bound to protein than in vegetable sources. Egg lecithin is thus obtained by solvent extraction from liquid egg yolks using acetone or from freeze dried egg yolks using ethanol. Synthetic lecithins may also be producted.

Stability : Lecthins decompose at extreme pH. They are also hygroscopic and subject to microbial degradation. When heated, lecithins oxidize, darken and decompose. Temperatures of 160-180°C will cause degradation within 24 hours. Fluid, or waxy, lecithin grades should be stored at room temperature or above; temperatures below 10°C may cause separation.

APPENDIX-B

AERODYNAMIC ASSESMENT OF FINE PARTICLES

1. TWIN STAGE IMPINGER (TSI) (Adapted from BP, 1998)

This apparatus is Apparatus A in BP. The apparatus is shown in Figure B.1 (see also Table B.1).

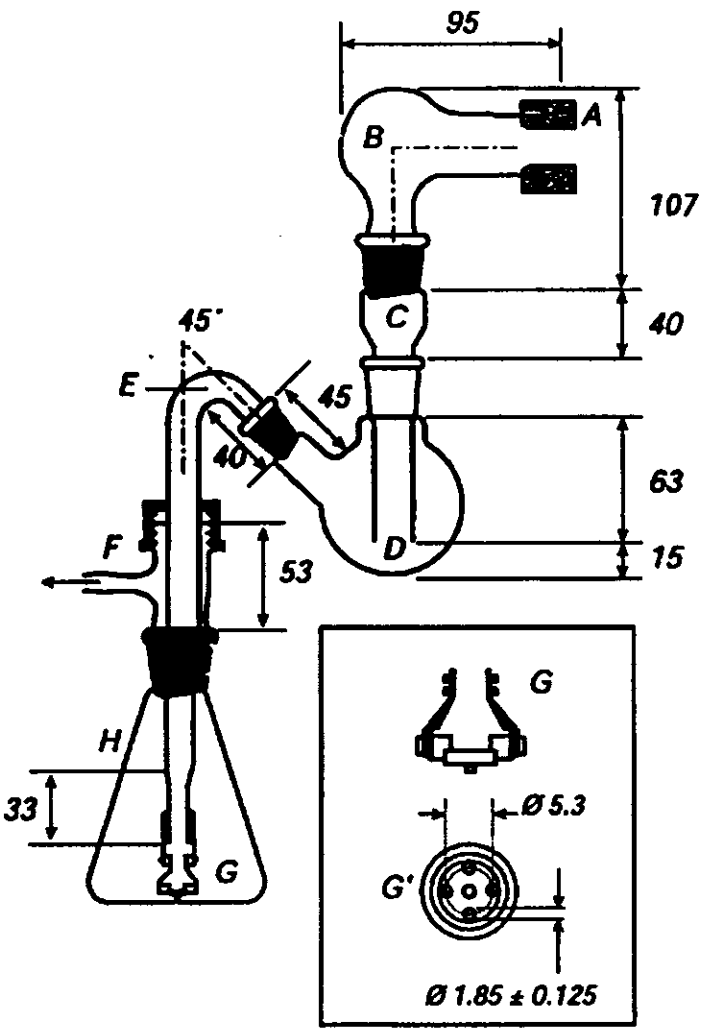


Figure B.1 Twin stage impinger for the aerodynamic assessment of fine particles (dimension in mm)

Table B.1 Details of TSI

Item	Description	Identifying Code[1]	Dimentions[2] mm
Mouthpiece adapter	Moulded rubber adapter for actuator mouthpiece	A	
Throat	Modified rouded-bottomed flask	B	50 ml
	groung-glass inlet socket		29/32
	ground-glass outlet cone		24/29
Neck	Modified glass adaptor	C	
	ground-glass inlet socket		24/29
	ground-glass outlet cone		24/29
	Lower outlet section of precision-bore glass tubing		
	bore diameter		14
	Selected-bore light-wall glass tubing		
	external diameter		17
Upper impingement chamber	Modified round-bottomed flask	D	100 ml
	ground-glass inlet socket		24/29
	ground-glass outlet cone		24/29
Coupling tube	Medium wall glass tubing	E	
	groung-glass cone		24/23
	Bent section and upper vertical section		
	external diameter		13
	Lower vertical section		
	external diameter		8
Screwthread, side-arm adapter	Plastic screw cap	F	28/13
	Silicone rubber ring		28/11
	PTFE washer		28/11
	Glass screwhead, *treadsize*		28
	Side-arm outlet to vacuum pume,		
	minimum bore diameter		5
Lower jet assembly	Modified polypropylene[3] filter holder connected to lower vertical section of coupling tube PTFE tubing	G	
	Acetal circular disc with the centres of four jets arranged on a projected circle of diameter 5.3 mm with an integral jet spacer peg	G′	10
	peg diameter		2
	peg protrusion		2
Lower impingement chamber	Conical flask	H	250 ml
	ground-glass inlet socket		24/29

[1]On Figure B.1

[2]Dimention of ground-glass sockets and cones are specified in terms of the ISO designation in accordance with British Standard 572 : 1960. Quickfit apparatus is suitable.

[3]A modified Millipore Swinnex 13 polypropylene filter holder is suitable.

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.3, 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 cascade impactors occasionally used for inhaler testing that are based on published calibration data, are summarized in Tables B.2.

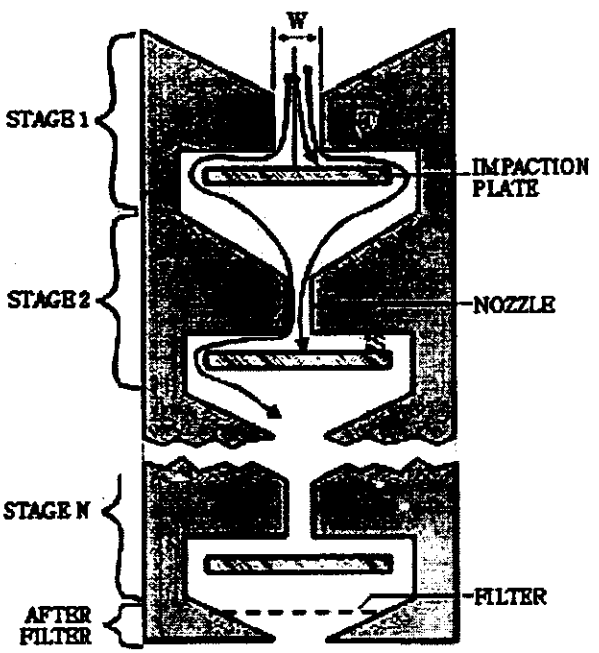


Figure B.2 Schematic representation of the principle of operation of cascade impactor

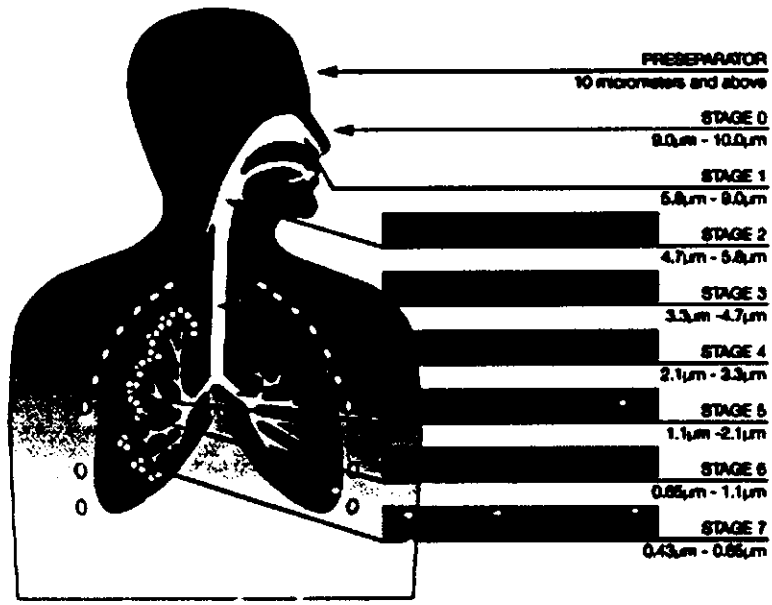


Figure B.3 Relationship between Andersen 8-stage cascade impactor cut sizes at 28.3 l/min and likely particle deposition in the respiratory tract

Table B.2 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)		
	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 Figure B.4 (see also Table B.3). Other suitable induction ports may also be used.

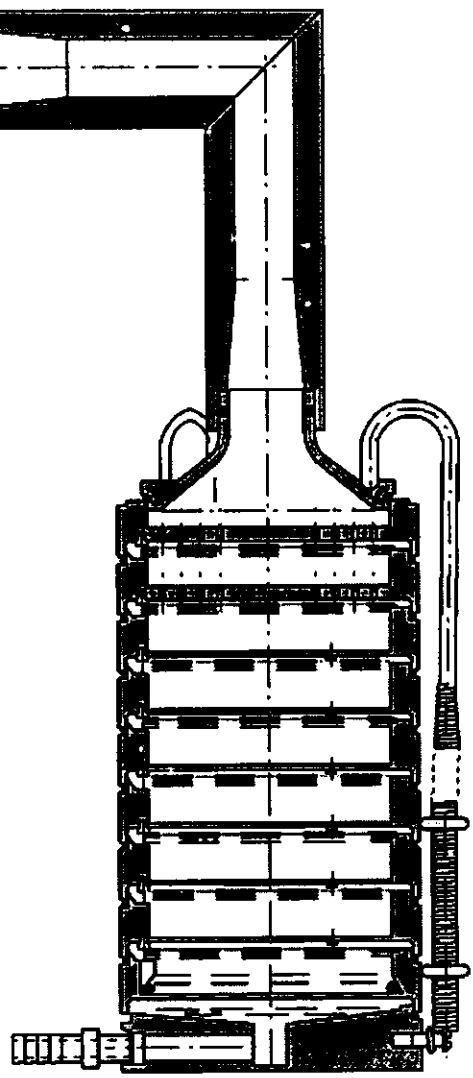


Figure B.4 ACI for the aerodynamic assessment of fine particles (Dimensions in mm)

Table B.3 Component units of ACI

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

Procedure for powder inhalers

If necessary, coat each plate with a 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 a suitable adaptor. Switch on the pump for 5 seconds. Switch off the pump and remove the inhaler. Repeat for a further nine discharges. Dismantle the apparatus.

The preseparator in this study is shown in Figure B.5. It is used for prevent the particle bounce and air re-entrainment (Mitchell *et al.*, 1988). The particles smaller than 8.6 μm do not reach the first stage. This can lead to some inaccuracies in the resulting particle size distribution; therefore, the preseparator performance is a very important issue in cascade impaction of dry powder aerosols.

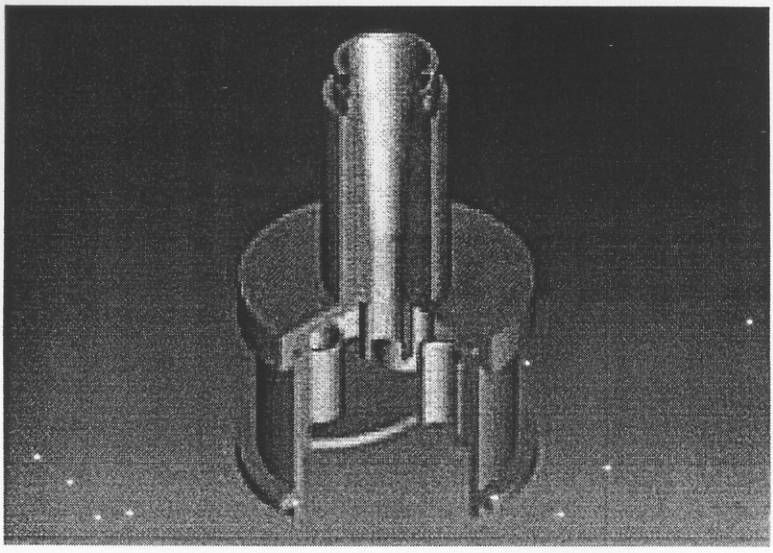


Figure B.5 The preseparator of ACI (Adapted from Mitchell and Nagel, 2004)