INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION
国际创新药学院

Pharmaceutical Excipients in Solution Dosage Forms I & II

Course BSc(Pharm) & BSc (ATT)

Year 2024-2025 II

Module Medicines Pharmaceutics 2

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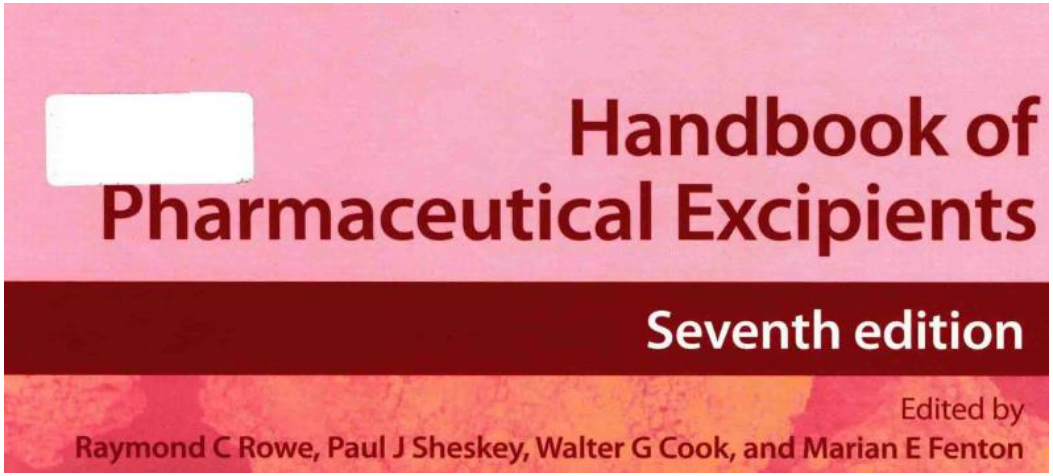
LEARNING OUTCOMES

1. Acknowledge the quality attributes and regulatory control of pharmaceutical excipients
2. Describe the functions of each group and each excipient class with particular reference to oral solution dosage forms

RECOMMENDED READING

This book is a handbook, not for reading!

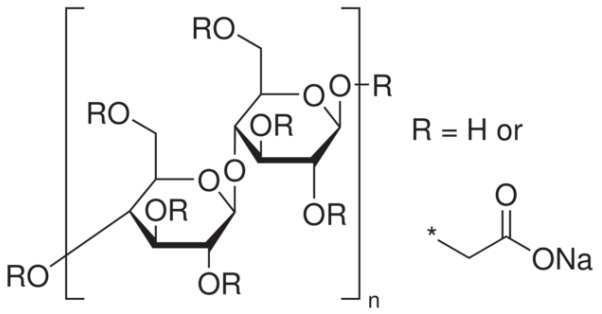


EXCIPIENTS

The constituents of a pharmaceutical form apart from the active substance
(EMEA/CHMP/QWP/396951/2006)

EXCIPIENT SPECIFICATIONS

- Excipients can (and do) have several different functions depending on the grade, physical form, quantity, use conditions
  - E.g. carboxymethyl cellulose羧甲基纤维素 functions as a viscosity enhancer, gelling agent, disintegrant, binder, emulsifier, flocculant絮凝剂, tablet matrix

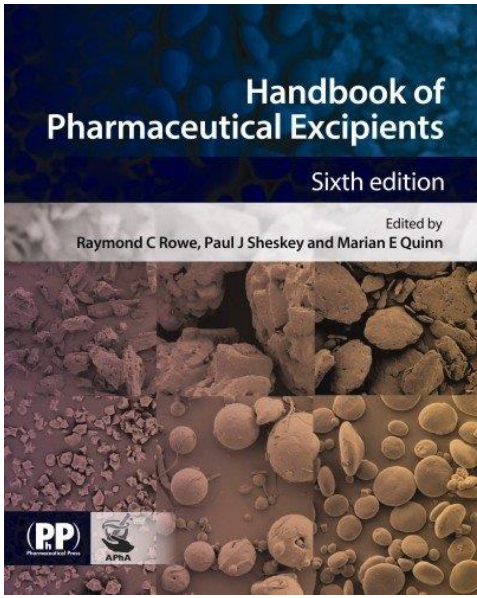


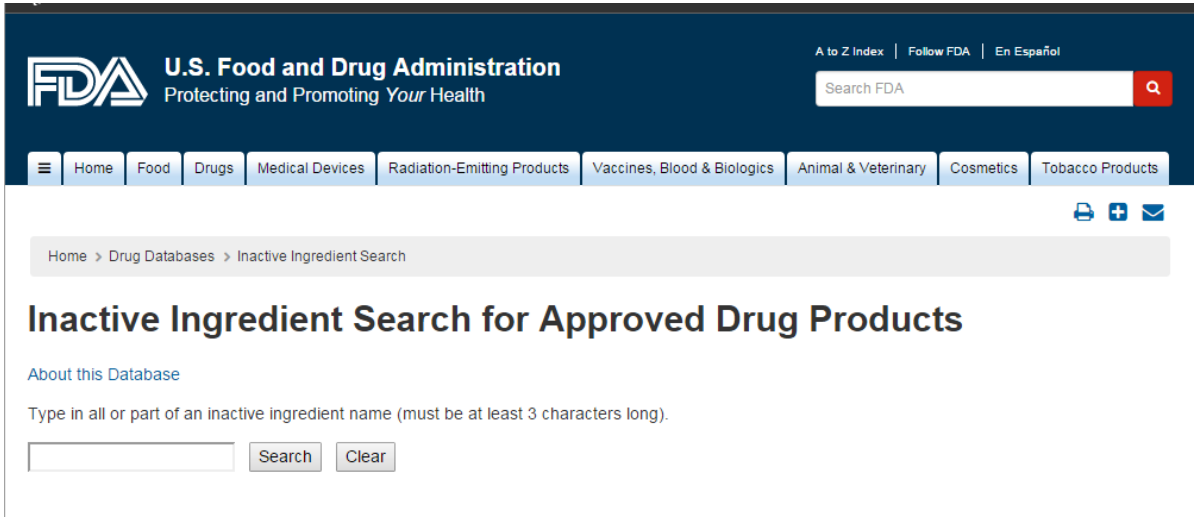
- A wide range of excipient specifications are available in each regulatory jurisdiction (within National Formulary)

- Where a monograph专著 is not present, one must be developed with supporting documentation on safety and effectiveness

INFORMATION SOURCES ON EXCIPIENTS

USP
NF





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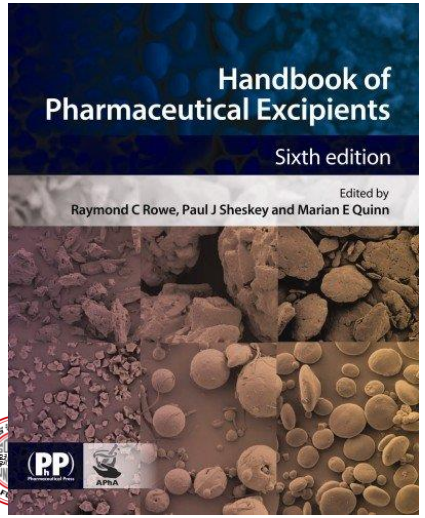
HANDBOOK OF PHARMACEUTICAL EXCIPIENTS

- Monographs on 250 excipients
- Nonproprietary, chemical and commercial names
- Empirical formulas and molecular weights
- Chemical and physical properties
- Incompatibilities and interactions with other excipients and drugs
- Regulatory status
- Applications in pharmaceutical science
- Maximum acceptable daily intake



IDEAL EXCIPIENT ATTRIBUTES

- Chemically and physically stable
- Low microbial content
- Compatible with drug and other excipients
- Compatible with packaging
- Non toxic and safe for human consumption
- Inexpensive, easy to source
- Palatable
- Low or no odour
- Non-sensitising
- Ease to process

EXCIPIENT SOURCES

- **Natural sources**
  - Mineral oil
  - Water
  - Surfactants (lecithin卵磷脂)

- **Semi-synthetic**
  - Cellulose derivatives
  - PEGylated coconut oil 椰子油

- **Synthetic**
  - Surfactants (poloxamer聚羟亚烃)

EXCIPIENTS REQUIRED IN SOLUTION DOSE FORMULATION

Excipient class	Sub-group
Solvent	Aqueous Non-aqueous

Excipient class	Sub-group
Solubility and permeability enhancers	Cosolvents Acidifiers/basifiers Buffers Surfactants (solubilisers) Surfactants (penetration) Complexing agents

Excipient class	Sub-group
Patient compliance	Sialagogues催涎剂 Colouring (dyes) Sweeteners Flavorant食用香料 Viscosifiers Tonicity adjustment

Excipient class	Sub-group
Manufacturing & processing	Wetting agents Levigating agent研磨剂 Clarifiers澄清剂 Glidants助流剂

Excipient class	Sub-group
Antimicrobial preservatives	Antifungal Antibacterials
Chemical preservatives	Antioxidants Air displacement agent Buffers
Physical stability	Antiadsorbents Humectants保湿剂 Surface action Precipitation inhibitors

SOLVENTS

- **SOLVENT**: Used to dissolve another substance in preparation of a solution. Used to prepare solution dosage forms that contain drug in an easily measured unit that is easily swallowed and ready to move across biological membranes
  - Water is a unique solvent
  - Several grades are available

TYPE OF WATER	USE
Purified water	Used for the preparation of medicines that do not have to be sterile or apyrogenic（无热原的）
Highly purified water	Used for the preparation of medicines where water of high biological quality is needed, except where water for injection is required
Water for injection	Used for medicines for parenteral administration (must be pyrogen free)
Sterilised water for injection	Used for medicines for parenteral delivery

COSOLVENTS

- **COSOLVENTS**: Water miscible solvent used to increase the lipophilicity of a solvent. Water is the solvent of choice, but when drug solubility is too low to permit a dissolution in a convenient dose (~5mL), cosolvents are used.

Concerns regarding the use of cosolvents

- Toxicity
- Irritancy (刺激)
- Sensitising potential
- Flammability
- Cost
- Stability
- Compatibility with other ingredients
- Internal v External Use
- Parenteral Use

COSOLVENTS: ALCOHOLS

- **Ethanol**: The most common organic solvent in pharma solutions
  - Route: oral, topical and parenteral
  - Pharmacological actions
  - Cooling on evaporation
  - Restrictions on use in paediatrics
- **Propylene glycol丙二醇**: is a polyhydric alcohol (2 hydroxyl groups)
  - Route: oral, topical, parenteral and otic
- **Glycerol丙三醇**: contains three hydroxyl groups per molecule
  - Route: oral, rectal and parenteral
- **Low Mw PEGs**: Polyethoxylates (formula $HOCH_2(C_2H_2O)CH_2OH$)
  - Route: oral or parenteral dosage forms

OTHER SOLVENTS OF INTEREST (FIXED OILS, ESTERS, & MISC)

- **Fixed oils固定油**: non-volatile oils of vegetative origin. Commonly triglycerides of fatty acids derived from seeds, fruit, pit/stone/kernel（核）of plants (e.g. olive, corn, sesame芝麻, arachis花生, soya大豆, castor蓖麻).

- **Esters:** For example ethyl oleate**油酸乙酯**(lower viscosity, synthetic oil used in IM injections), ethyl ethanoate乙酸乙酯, benzyl benzoate苯甲酸苄酯

- **Dimethyl sulfoxide（DMSO）**: Application in topical applications. For example as a carrier of idoxuridine碘苷and as a penetration enhancer and solubiliser.

- **Glycofurol四甘醇**: cosolvent for IM and IV

- **Ethyl ether乙醚**: cosolvent with ethanol in collodions火棉胶

pH MODIFIERS AND BUFFERS

- **Acidifiers酸化剂**: Substance that provide H^+ to adjust pH to acid condition. Used to alter pH to alter solubility and permeability.
- **Alkalizers碱化剂**: Substances that provide OH^- to adjust pH to basic condition. Used to alter pH to alter solubility and permeability.
- **Buffers**: Buffers provide an optimal pH range and resist change upon dilution or addition of acid or alkali

EXAMPLES

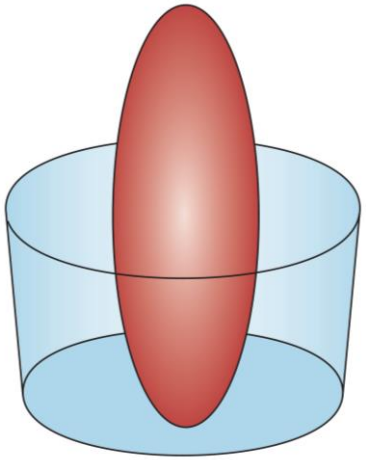
- Citric acid
- Acetic acid
- Hydrochloric acid
- Sulfuric acid
- ammonia solution
- Ammonium acetate
- Potassium hydroxide
- Sodium hydroxide
- Sodium bicarbonate
- Sodium borate,
- Sodium carbonate

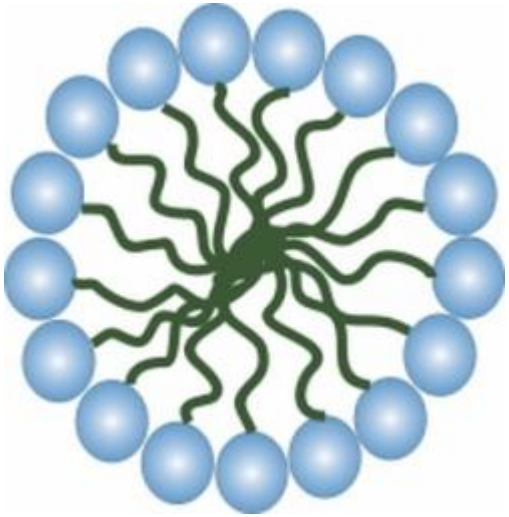
SOLUBILISERS (SURFACTANTS AND INCLUSION COMPLEXES)

- **SOLUBILISERS增溶剂**: Increase the apparent solubility of a drug in water so that the dose is contained in a more manageable size unit and the drug is readily moved across membranes

EXAMPLES

- Cyclodextrins环糊精
- Polyoxyethylene castor oil蓖麻油乳化剂
- Poloxamer聚羟亚烃
- Polysorbates聚山梨醇酯





MANUFACTURING AND PROCESSING

- **Wetting agent**: Permits hydrophobic powders to displace air and be wetted by water. Wetting agents can be required in manufacturing to facilitate processing (e.g. polysorbates, sodium lauryl sulphate, polyoxyl-40 stearate)
- **Levigating agent研磨剂**: Liquid or semi-solid used to facilitate the reduction of the particle size of a powder by grinding on an ointment slab (mineral oil, glycerol, propylene glycol)
- **Clarifiers澄清剂**: Filter aids that adsorbed any undissolved solid particles which are subsequently removed by filtration leaving a clear solution (e.g. silica)
- **Humectants保湿剂**: A substance added to a formulation to prevent evaporation through a lowering of the vapour pressure of the solution (glycerol, propylene glycol, sorbitol)
- **Bulking agents 膨胀剂for freeze drying**: Protect drug from freeze concentration during lyophilisation of solutions for reconstitution (trehalose 海藻糖, mannitol甘露醇, glycine甘氨酸)

HUMECTANTS

- **Humectants**: Substances added to a liquid product to prevent evaporation and ultimately drying out. They interact with the solvent to reduce the vapour pressure (colligative property) maintaining levels of water.
- **EXAMPLES**
- Glycerol
- Propylene glycol
- Sorbitol山梨醇
- PEG300

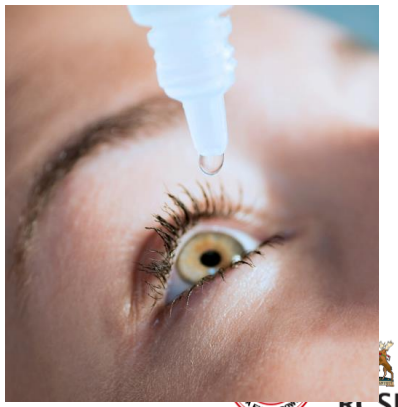
- *Crystallisation and cap-locking can be minimised by humectants.*

CLARIFIERS

- **Clarifiers**: Substances added to a solution during manufacturing to bind and assist the removal of substances (commonly insoluble particulates) in order to assist the clarification of the solution. This ensures a product that show a high degree of clarity.
  - E.g. clarification of tinctures酊剂, aqueous and alcoholic extracts, mouthwashes, removal of particulates from ophthalmic solutions

EXAMPLES

Crospovidone 交聚维酮



PRESERVATION

Substances which are used to extend the shelf-life of medicines by respectively retarding 减缓 the oxidation of active ingredients and excipients and by reducing microbial proliferation

- Commonly used in multidose aqueous preparation
- Activity influences by active, excipients and the container
- Some formulations have antimicrobial activity themselves (syrups, elixirs)
- Anhydrous 无水的 products like ointment
- An assumption must not be made that antimicrobial solutions are self preserving, as few are extensively broad spectrum to kill moulds, fungi and all bacterial species
- Mold霉菌, yeast and bacteria favour slightly basic conditions

PRESERVATIVE SELECTION CRITERIA

- Non-toxic, non-irritant, non-sensitising
- Robust inhibition of bacterial growth in use conditions
- Broad spectrum
- Soluble
- Compatible with other ingredients
- Active over a wide pH range
- Must penetrate bacteria
- Chemical stability
- Compatible with container

No single preservative satisfy all of these criteria. It is estimated that as few as 8 preservatives are in common use in the UK

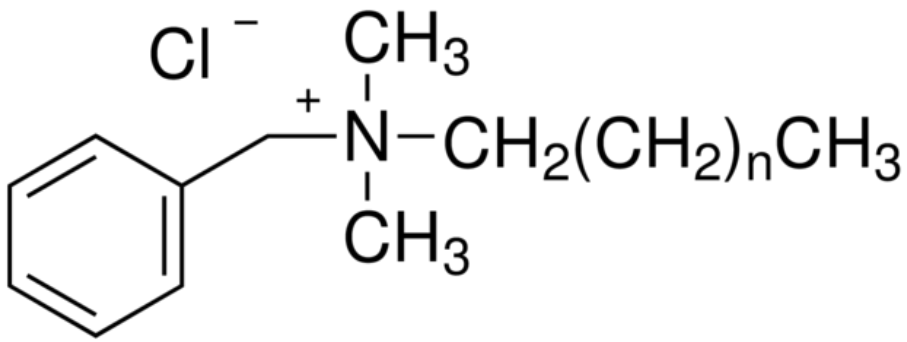
PRESERVATIVES

KEY PRESERVATIVES	KEY ROUTE
Parabens对羟苯甲酸酯	oral, parenteral
Benzalknium chloride苯扎氯铵	ophthalmic
Benzoic acid苯甲酸	oral
Benzyl alcohol苯甲醇	parenteral
Sorbic acid山梨酸	oral

	Concentration (%)		
Preservative	Liquids	Parenterals	Ophthalmic/ Nasal/Otic Products
Alcohol/ethanol	15–20		
Benzalkonium chloride	0.004–0.02	0.01	0.013
Benzethonium chloride	0.004–0.02	0.01	0.01
Benzoic acid and salts[a]	0.1–0.3		
Sodium benzoate	0.1–0.3		
Benzyl alcohol	1.0–3.0	2.0	
Boric acid and salts	0.5–1		
Cetylpyridinium chloride	0.01–0.02		
Cetyltrimethyl ammonium bromide	—		
Chlorobutanol[b]	0.3–0.5	0.25–0.5	
Chlorocresol	0.05–0.1	0.1–0.3	
Cresol	0.3–0.5		
Imidazolidinyl urea	—		
Metacresol		0.1–0.3	
Myristylgamma picolinium chloride		0.17	
Nitromersol	0.001–0.1		
Parabens[c]	0.001–0.2	0.02–0.2	0.1
Benzyl			
Butyl		0.015	
Methyl		0.1–0.2	
Propyl		0.02–0.2	
Phenol[d]	0.2–0.5		
o-Phenyl phenol	0.005–0.01		
β-phenylethyl alcohol	0.2–1		
Phenylmercuric acetate/nitrate	0.002–0.005	0.002	0.004
Sorbic acid and salts	0.05–0.2		
Thimerosal	0.001–0.1	0.01	0.01

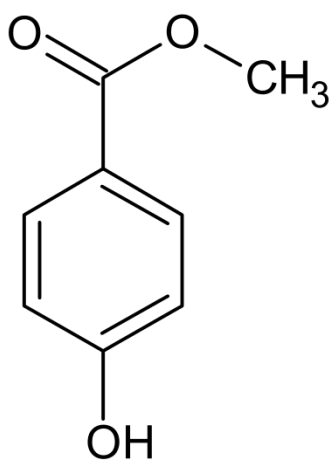
QUATERNARY AMMONIUM COMPOUNDS

- Benzalkonium chloride苯扎氯铵: Common preservative in external preparations
  - Active over a wide pH range
  - Incompatible with anionic substances
  - Perturbation of bacterial membranes
  - Safety considerations (irritation of skin and mucous membranes)



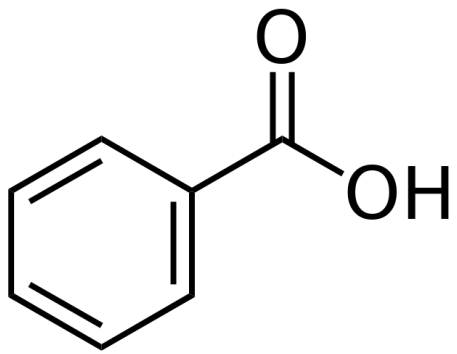
PARABENS 对羟苯甲酸酯

- A collection of structurally similar alkyl esters of p-hydroxybenzoic acid (methyl, ethyl, butyl, propyl derivatives)
  - Activity increases with increasing alkyl chain length
  - Solubility decreases as R group increases in size
  - Soluble Na salts available
  - Mixtures commonly used; synergistic effects (2:1 Methyl and Propyl)
  - Chelating agents increase activity e.g. disodium edetate乙二胺四乙酸盐
- **METHYL PARABEN 甲基对羟基苯甲酸酯**
  - Active between pH 4-9 (activity decreasing at high pH in ionised form)
  - Can be autoclaved in aqueous solutions
  - Incompatible with non-ionic surfactants
  - Discoloured 脱色 by iron
  - May sorb to certain plastics



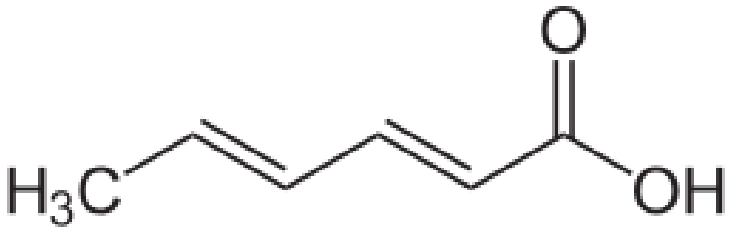
BENZOIC ACID苯甲酸

- Antibacterial and antifungal activity
- Active only in the unionised form (<pH 4)
- Only sparingly soluble in water
- Potential for allergy
- Exhibits a number of incompatibilities



SORBIC ACID 山梨酸

- Antibacterial and antifungal properties
- Predominantly used in oral and topical preparations
- Optimal activity at pH 4.5 and inactive above pH 6
- Synergistic effects with other preservatives or glycols (3-5%)
- Sensitive to oxidation and toxic by-products (Malondialdehyde)
- Moulds can detoxify (decarboxylation脱羧反应)



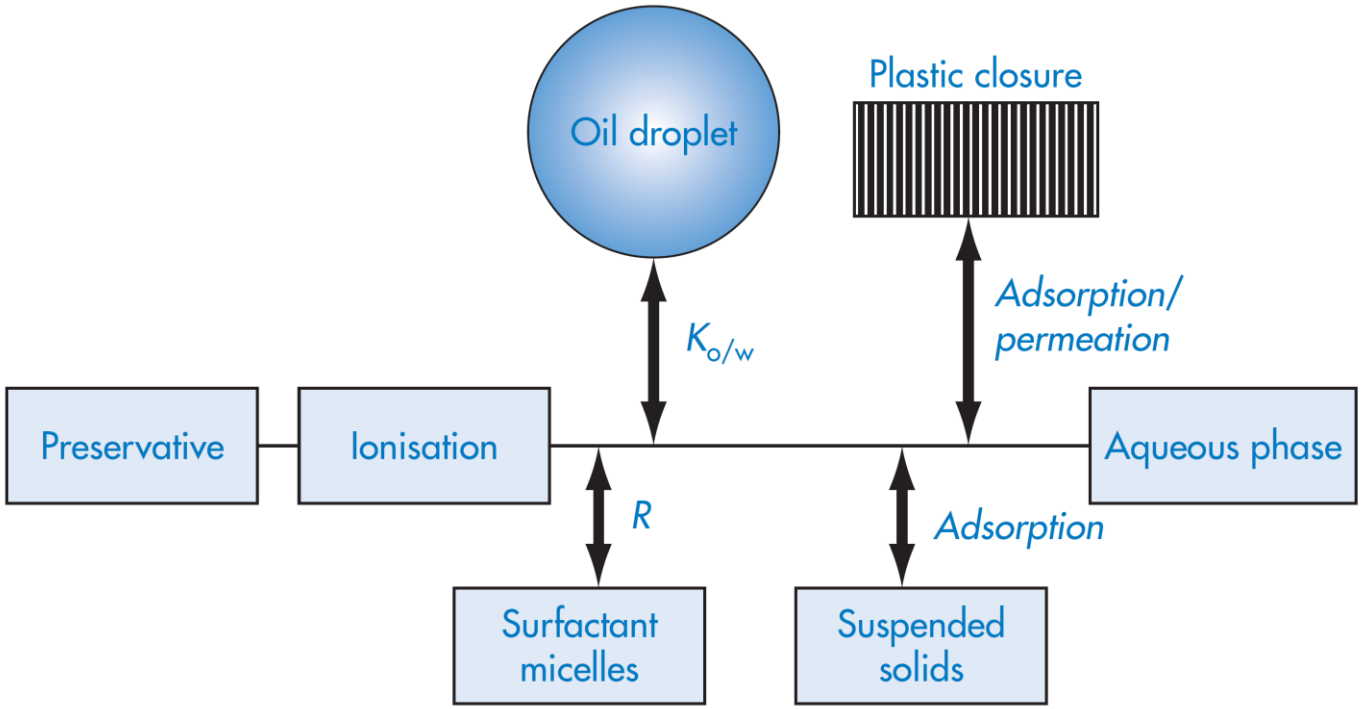
PRESERVATIVE EFFICACY TESTING (EP TEST)

- A product development test applied to a formulated medicine in its final container to determine whether it is protected against microbial spoilage微生物腐败.
- Performed over individual preservative testing to ensure there are no interactions in the dosage form
- Following inoculation of a microbial challenge (10^5-10^6 cells), samples are withdrawn periodically, and survival is measured at t= 0 h, 6h, 24h, 48 h 7 days, 14 days, 28 days.
- Criteria of acceptance vary dependent on type of formulation
- 1000-fold decrease in microbial content for injectables after 24 h

TEST ORGANISMS

Pseudomonas aeruginosa铜绿假单胞菌
Staphylococcus aureus 金黄色葡萄球菌
Candida albicans 白色念珠菌
Aspergillus brasiliensis 巴西曲霉
Zygosacchromyces Rouxii鲁氏接合酵母

THE FATE OF PRESERVATIVES IN PHARMACEUTICAL PRODUCTS



Substance	% Propylparaben bound
Methyl cellulose甲基纤维素	13%
PVP聚乙烯吡咯烷酮	36%
PEG sorbitol monooleate 山梨糖单油酸酯	90%

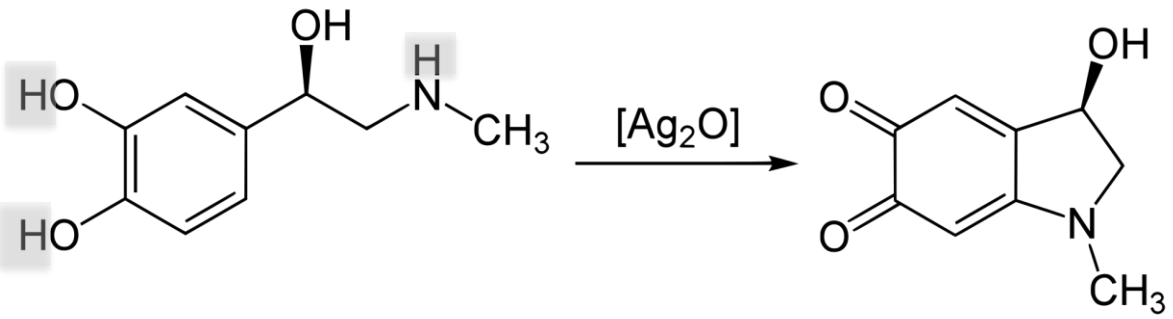
Propylparaben:
对羟基苯甲酸丙酯（防腐剂）

CHEMICAL PRESERVATION
OXIDATION

oxygen
8
O
15.999

- In pharmaceutics, we simplify the definition of oxidation to

An increase in the carbon to oxygen ratio
OR
A decrease in the carbon-to-hydrogen ratio



- **ANTIOXIDANT**: Substances added to minimise or retard oxidative processes that occur with some drugs or excipients on exposure to oxygen or in the presence of free radicals. These processes are often catalysed by light, temperature, H^+ ion concentration, presence of trace metals or peroxides.

ANTIOXIDANT CATEGORISATION

- **True antioxidants**: substances added to a formulation to rapidly react with free radicals (quenching) as they are formed thereby blocking reaction propagation

- **Reducing antioxidants**: substances added to a formulation that are more readily oxidised than the drug/excipient that requires protection (lower redox potential)

- **Synergists**: enhance the activity of antioxidants

ANTIOXIDANTS

ANTIOXIDANT	USE CONCENTRATION	MODE
Ascorbic acid	0.02-0.1%	REDUCING
Citric acid	0.005-0.01%	CHELATION/SYNERGY
EDTA	0.02-0.1%	CHELATION/SYNERGY
Sodium bisulphite	0.05-1%	REDUCING
Sodium metabisulphite	0.02-0.5%	REDUCING
D-α-Tocopherol	0.05-0.5%	TRUE
Acetylcysteine	0.1-0.5%	TRUE
Cysteine	0.1-0.5%	TRUE
Propyl gallate	0.001-0.15%	TRUE
Butylated hydroxyanisole	0.005-0.02%	TRUE
Butylated hydroxytoluene	0.005-0.02%	TRUE

FLAVOURS, SWEETENERS AND COLOURS

- Optimising taste, smell and sight, texture and even sound is a critical component in patient compliance, especially oral liquid dosage forms

FLAVOURS IN ADULTS, CHILDREN AND ELDERLY

- **CHILDREN**: Prefer sweet tastes and do not respond well to bitter tastes (butterscotch, citrus, berry vanilla)

- **ADULTS**: Accept reasonable levels of bitterness and in drug products (wine, spice, cherry chocolate, anise). Almost any flavour can be used in adults.

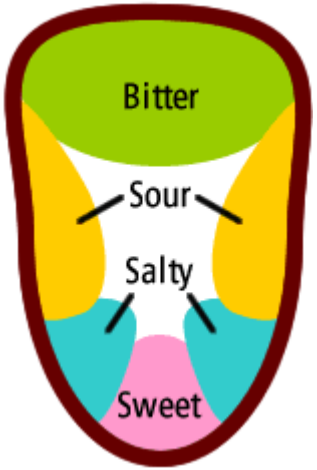
- *Some illnesses impair senses…..*

CORRELATION BETWEEN CHEMICAL PROPERTIES AND TASTE

TASTE	CHEMICAL PROPERTY
SOUR	H^+
SALTY	Simultaneous presence of anions and cations
BITTER	High Mw organic species
SWEET	Polyhydroxyl 多羟基compounds, polyhydrogenated compounds, alpha amino acids

ILLUSTRATING FLAVOUR AND TASTE

Solution Strength	Sweet (% sucrose)	Sour (% citric acid)	Salty (% NaCl)	Bitter (% caffeine)
Slight	5	0.05	0.4	0.05
Moderate	10	0.10	0.7	0.10
Strong	15	0.20	1.0	0.20



FLAVOUR AND TASTE

- **Flavourant食用香料**: A substance that imparts a pleasant flavour and often odour to a preparation.

What is considered an acceptable taste….

- A product that exhibits
  - Immediate flavour identity
  - Rapid and full flavour development
  - Acceptable mouth feel
  - Short after taste
  - No undesirable sensation

HOW TO IMPART AN OPTIMAL TASTE

- **Blending调和**: Use of a flavour that blends with drug taste (orange to mask acid)
- **Overshadowing掩盖**: Use of a flavour with greater intensity (e.g. anise)
- **Physical methods**: Formulating suspension, emulsion, viscosifiers
- **Chemical methods**: Adsorption or complexation of drug
- **Physiological methods**: Cooling sensation of mannitol (caused by the negative heat of solution, desensitisation of taste buds), sialagogue催涎剂action of citric acid

FLAVOURS USED TO MASK BASIC TASTES

Taste	Flavor
Sweet	Vanilla, fruit, grape, bubblegum, berry
Acid/sour	Lemon, lime, orange, cherry, grapefruit, raspberry, acacia
Salty	Nut, butter, butterscotch, spice, maple
Bitter	Licorice (anise), coffee, chocolate, mint, grapefruit, cherry, peach, raspberry, orange, lemon, lime
Oily	Peppermint, anise, wintergreen
Metallic	Berry, mint, grape, marshmallow

EXAMPLES OF FLAVOURS

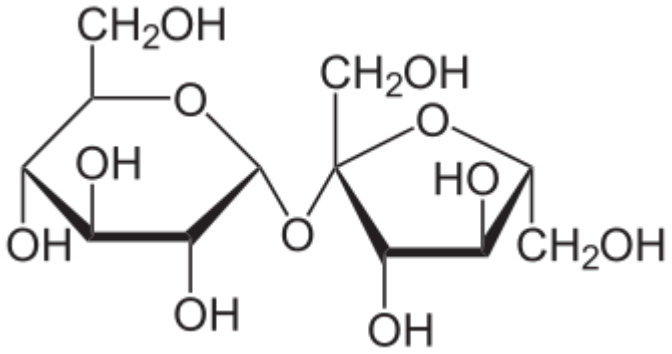
Type	Example	Use conc
Natural	Fruit syrup	
	Glycyrrhizin甘草甜素	
	Mint	
Spice	Cinnamon肉桂	
	Anise茴香	
	Clove丁香	
Artificial	Vanillin香草醛	0.01-0.02
	Citric acid	0.2-2.0
	Ethyl maltol乙基麦芽酚	0.005

SWEETENERS

- **Sweeteners**: Used to impart sweetness on a product

SWEETENER	USE CONC	SWEETNESS	USE	CALORIES	COMMENT
Sucrose	<85%	1	Non-diabetics	YES	Good stability
Aspartame		180-200	Diabetics	NO	Stable at pH 3.4-5
Sorbitol山梨醇	20-70	0.5-0.6	Diabetics	YES	Good stability
Syrup		0.85	Non-diabetics	YES	Good stability
Saccharin糖精	0.02-0.05	500	Diabetics	NO	Strong after taste

SUCROSE AND SYRUP



- Disaccharide二糖 of Fru, Glc
- Long history of use as high concentration syrups (>44% m/m)
- Potential for cap-locking (minimised with polyhydric alcohols)
- Self-preserving at high concentrations
- High temperatures in some production plants can leads to cleavage to fru, glu causes stickiness (but preventing recrystalisation)
- Colourless
- Impart viscosity for pleasing texture in mouth and throat
- Cariogenic
- Masks salty and bitter drugs

SIALAGOGUES

- SIALAGOGUES: Substances added to a formulation to stimulate saliva production. This minimises the residence time of unfavourable drug or excipient tastes

EXAMPLES

- Citric acid
- Fumaric acid富马酸
- Tartaric acid酒石酸

VISCOSITY ENHANCER

- VISCOSITY ENHANCERS: Substances (usually macromolecular colloids) that render preparation more resistant to flow. In solutions they:
  - Optimise dose uniformity (pouring)
  - Improve mouth feel
  - Promote optimal contact with surfaces (e.g. skin, tongue, eye)

EXAMPLES

- Carbomer卡波姆
- Carboxymethyl cellulose羧甲基纤维素钠
- Acacia阿拉伯树胶
- Poloxamer聚羟亚烃
- Povidone聚维酮
- Syrup and polyhydric alcohols

COLOURING

- **Colourant着色剂**: used to impart colour to a solid (lake) or liquid (dye) preparation

- Colour is often selected to match flavour
  - Green for mint
  - Red for Cherry, raspberry, strawberry
- Improves identification
- Masks colour deterioration (if not harmful)
- TYPES: Mineral, Natural or Synthetic
- Patient acceptability concerns
  - If derived from animals
  - If associated with pharmacological actions

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APPENDIX: E-NUMBERS

Table 4.2 E colours and food additives classification

Additives	*E numbers*
Colours	100–181
Preservatives	200–290
Acids, antioxidants, mineral salts	300–390
Vegetal gums, emulsifiers, stabilisers, etc.	400–485, 500–585
Flavour enhancers	620–640
Miscellaneous (contains sweeteners)	>900