INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION
国际创新药学院

Solution Dosage Forms

Course BSc(Pharm) & BSc (ATT)

Year 2024-2025 II

Module Medicines：Pharmaceutics 2

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LEARNING OUTCOMES

1. State the advantages and disadvantages of solution dosage forms
2. Describe the different types of solutions used in pharmaceutical science
3. Outline the how solutions are prepared both extemporaneously and by manufacturing with emphasis on quality
4. Distinguish between shelf life and use by date
5. Quote the shelf life of solutions and the relevant storage temperature

CONSTITUENTS OF SOLUTIONS

Can be conventional small molecular or larger biomolecules including peptides, proteins or nucleic acids

Water alone does not dissolve many drug compounds to a sufficient degree to form a solution

Key functions in solution dosage forms include improving solubility, improved absorption, stability, buffering, colouring, flavour enhancement, optimisation of use conditions

SOLUTION DOSAGE FORM

ADVANTAGES

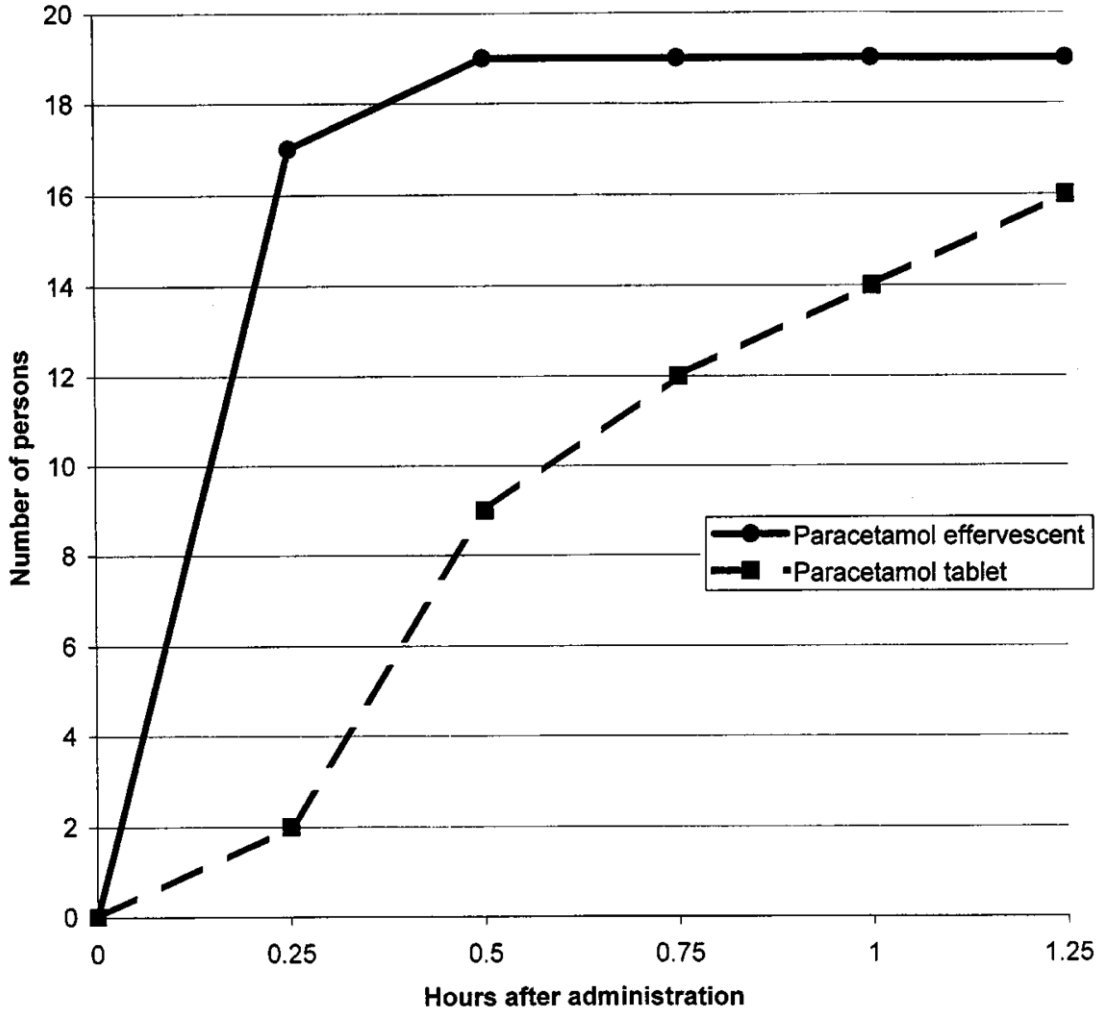
- Easier to swallow than tablets or capsules
- Readily absorbed in the GI tract, rapid onset
- Easy to administer for children, geriatics (老年人) or chronic conditions（慢性病）that impede oral swallow reflex（吞咽反射）
- Flexible dose adjustment
- Consistent dosing (no requirement to shake the dosage form)
- Can reduce GI irritation

DISADVANTAGES

- Bulky
- Rapid onset can result in more frequent dosing
- Inconvenient for transport and storage
- More sensitive to chemical degradation
- Susceptible to microbial contamination
- Taste

ONSET: ORAL SOLUTION VERSUS TABLET

- Number of patients reaching a therapeutic concentration of paracetamol (70mcg/mL) from a solution versus a tablet



SOLUTION DOSAGE FORMS

- Solution are historically categorised by the nature of the formulation or traditional names relating to the solvent system

Waters
Spirits (醑xǔ剂)
Elixirs (酏yǐ剂)
Syrups (糖浆)

AROMATIC WATERS AND SPIRITS

Aromatic waters: Saturated aqueous solutions of volatile oils or other aromatic or volatile substances

- Manufactured as concentrated waters (e.g. peppermint (1:40), anise洋茴香 (1:100), chloroform氯仿 (1:40)
- Clear saturated aqueous solutions, but if the solvent is alcohol they are referred to as spirits

Spirits (醑xǔ剂): Alcoholic or hydroalcoholic solution (60%+) of volatile substance

ELIXIRS

Elixirs (酏y剂): Oral solutions that contain alcohol as a cosolvent

- Clear, fluidic solutions where active is solubilised by cosolvency with alcohols
- Self preserving over 15%
- Very significant safety concerns in paediatric medicines

Model drugs in elixer dosage forms

Paracetamol

Diazepam

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SYRUPS

Syrups: Oral aqueous solutions containing high concentrations of sucrose or other sugars.

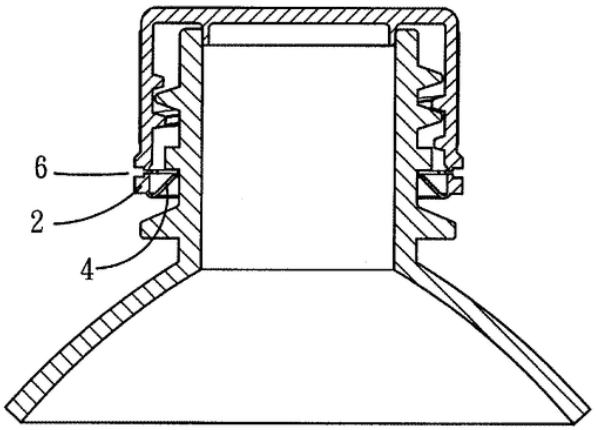
- Simple syrup BP contains 66.6% sucrose in purified water.
- High sugars concentrations are bacteriostatic（抑制细菌的）

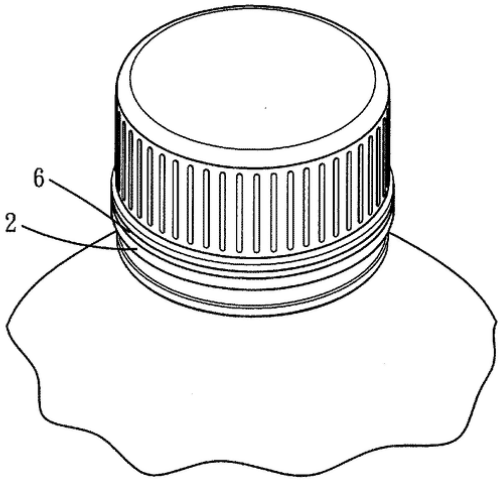
PROBLEMS

- Very high sugar concentrations can influence the solubility of other constituents of the dosage form
- Susceptible to surface dilution
- Invert syrup (果葡糖浆) is a mixture of glucose and fructose (果糖) (hydrolysed sucrose)
- Dilution of sucrose can produce an environment for microbial propagation
- Tooth decay
- Not suitable for diabetics (糖尿病患者)

CAPLOCKING IN SOLUTIONS

- Cap-locking involves recrystallisation in the cap threads at the bottle cap interface and makes opening the bottle difficult after prolonged periods of non-use.
- Sorbitol (山梨醇), glycerol and other polyhydric alcohols (多元醇) prevent this phenomena and therefore are commonly added to syrups to prevent such crystal formation
- Common in syrups





OTHER TERMS USED FOR SOLUTIONS

- **Linctus (止咳糖浆)**: Are viscous oral liquids that may contain one or more active ingredient in solution. Typically high sucrose concentration, and alcohol. Used in the treatment or relief of cough and intended to be sipped or swallowed slowly
- **Mixture**: Solutions (or suspensions) containing one or more active ingredients dissolved, suspended or dispersed in a suitable vehicle.
- **Mouthwashes:** are typically solution dosage forms intended for cleansing the oral cavity
- **Gargles (漱口剂)**: Typically aqueous solutions containing antiseptics (防腐剂), antibiotics, anaesthetics (麻醉剂) used to treat the pharynx (咽喉) by forcing air from the lungs through the gargle that is held in the throat
- **Oral drops**: Are oral solutions (oral suspensions) which are administered in small volumes using a suitable measuring device.

SOLUTION DOSAGE FORMS

- Solution dosage forms are today commonly classified by the intended route of administration

Oral Solution
Otic (耳部) Solution
Ocular solution
Nasal solution
Inhaled solution
Rectal solution
Vaginal solutions
Injectable solutions

SOLUTION DOSAGE FORMS BY ROUTE

ROUTE	INFORMATION ON SOLUTIONS BY ROUTE
ORAL	•Used for both local and systemic delivery •Oral solutions are commonly 5mL (or multiples thereof) • Delivery spoon, cup, syringe •Commonly packaged in reclosable amber bottles, child-resistant closure •Must be palatable and visually appealing •Solution pH is commonly 7.0 but values range between 2.0-9.0 •Viscosity should be > water to ensure accurate pourability •Tight control over solvent selection (water, ethanol, PG, glycerol)
PARENTERAL	•Injectable routes of administration, Must be sterile, pyrogen free, •pH as close to physiological as possible but pH 3-9 can be tolerated •Preservatives used in multidose, but very tightly controlled regulations on use • IV are aqueous solutions •IM or SC can be aqueous or non-aqueous •Large volume parenterals must be isotonic

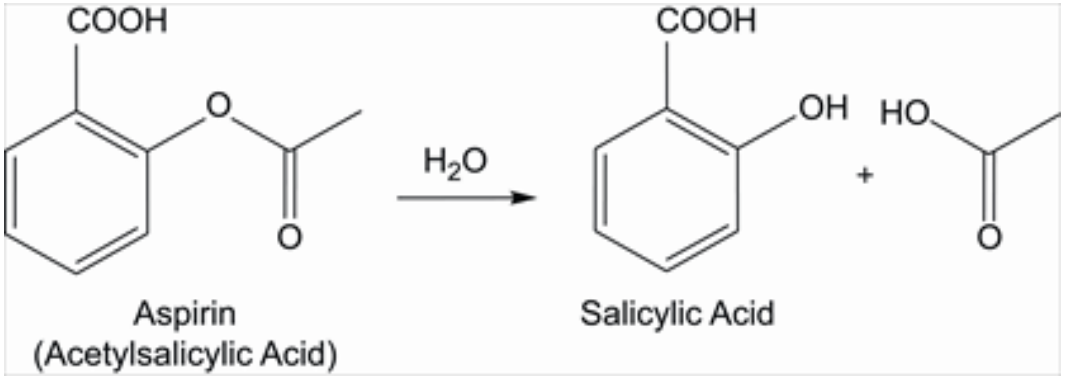
SOLUTION DOSAGE FORMS BY ROUTE

ROUTE	INFORMATION ON SOLUTIONS BY ROUTE
TOPICAL	•Used for both local and systemic delivery •Formulations can be viscous (to flow and adhere to the skins) but not tacky •Vehicle can be aqueous or non-aqueous •Commonly used in parasiticides and antimicrobials •**Lotions**: Solutions (or other dispersions) for external application without friction •**Liniment**: An alcoholic or oily solution (or emulsion) designed to be rubbed into skin •**Paints and tinctures**: Concentrated aqueous or alcoholic antimicrobial solutions •**Collodion**: Solution of a polymer (usually pyroxylin) in a volatile organic solvent (alcohol ether mix). •**Ungual and Transungual solutions**: are used to treat nail infections
OTIC	•Solution instilled to remove wax, deliver antiinfectives, analgesics, or NSIADS •May be aqueous or non-aqueous solvents (e.g. PG, water, glycerin, arachis oil) •Residence time enhanced with viscosity enhancing polymers/viscous solvents •No requirement for isotonicity
OCULAR	•Treatment of local and selected intraocular disorders •Commonly aqueous solutions, must be sterile, isotonic in large volumes •Eye lotions are solutions for rinsing/bathing the eye or impregnating dressings •Multidose preparations require preservation •pH must be carefully balanced (eye can tolderate pH2-9 but will quickly adjust) •Viscosity is important in residence time (common viscosity of 15-25mPa s)

CASE DRUGS IN SOLUTION

DRUG	OFFICIAL SOLUTION FORM(S)	USE	COMMENT
Aspirin	—	Analgesic, antipyretic	Poor aq stability
Ethanol	Parenteral solution Oral solution Topical solution	Antidote and excipient Antidote and excipient Cooling action and excipient	
NaCl	Parenteral solution Ocular solution Oral rehydration salts Nasal drop	Rehydration and excipient Eye rinse and excipient Electrolyte replacement	—
Ferrous sulphate	Oral solution Parenteral solution	Dietary supplement Iron deficiency	—
Glucose	Parenteral solution Oral solution	Dietary supplement & excipient Electrolyte replacement	—
Paracetamol	Oral solution Parenteral solution (as prodrug)	Analgesic	—
Caffeine	Oral solution Parenteral solution	Constriction of blood vessels Primary apnoea	—
Diazepam	Oral solution Parenteral solution Rectal solution	Various (e.g. Anxiety)	—

CHEMICAL DEGRADATION IN SOLUTION
HYDROLYSIS



- The acetyl ester in aspirin is hydrolyzed to acetic acid and salicylic acid in the presence of moisture, but in a dry environment the hydrolysis of aspirin is negligible.
  The aspirin hydrolysis rate increases in direct proportion to the water vapour pressure in an environment.

MULTIDOSE VERSUS SINGLE DOSE SOLUTIONS

Drug: Chloramphenicol
Volume: 400µL minim
Dose: 30-50 µL
Route: ocular
Type: Unit dose

Drug: Adrenaline
Volume: 3mL
Dose 2-3mL
Route: IM
Type: Unit dose

Drug: paracetamol (Dozol)
Volume: 110mL
Dose 5-20mL
Route: Oral
Type: multidose

Drug: Permethrin
Volume: 59mL
Route: topical
Type: Unit/multi dose

MANUFACTURING OF SOLUTIONS

- The manufacturing process for liquid preparations for oral use should meet the requirements of **Good Manufacturing Practice (GMP)**.
- GMPs provide quality systems that assure proper design, monitoring, and control of manufacturing processes and facilities.
- Good Manufacturing Practice is enforced regulatory agencies (e.g. FDA, HPRA) in an and jurisdiction where the manufactuerer wishes to market a pharmaceutical product.

QUALITY OF MATERIALS (DRUG AND EXCPIENTS)
UNIFORMITY OF MASS (FILL)
UNIFORMITY OF DOSE
APPEARANCE (CLARITY, COLOUR)
ODOUR
pH
CLARITY
MICROBIAL QUALITY (ACCEPTANCE CRITERIA)
CHEMICAL STABILITY (DRUG AND EXCPIENTS)
PHYSICAL STABILITY (LABEL CONDITIONS)
PRESERVATIVE SELECTION (SAFETY ASSURANCE)
STABILITY TESTING
MANUFACTURING CONTROLS
CONTAINER QUALITY
VISUAL INSPECTION TESTING

FDA GUIDANCE ON CURRENT GMP
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm

WHY EXTEMPORANEOUSLY COMPOUND SOLUTIONS?

- No commercially available formulation
- Paediatrics, geriatric
- Liquids are used to avoid non-compliance (e.g. incarcerated patients)
- Permits enteral feeding
- Improved control over dose

EXTEMPORANEOUS COMPOUNDING OF SOLUTIONS

General method

The following general method should be used in the preparation of a solution:

1. Write out the formula either from the prescription (unofficial) or from an official text (official).
2. Calculate the quantities required for each ingredient in the formula to produce the required final volume. Remember, it is not usual to calculate for an overage of product in the case of solutions as it is relatively easy to transfer the entire final contents of the conical measure. Additionally, as far as is practically possible, the product will be assembled in the final measure, thus reducing any transference losses.
3. Complete all sections of the product worksheet.
4. Prepare a suitable label.
5. Weigh all solids.
6. Identify the soluble solids and calculate the quantity of vehicle required to dissolve the solids fully. If more than one solid is to be dissolved, they are dissolved one by one, in order of solubility (i.e. the least soluble first). In almost all cases, dissolution will take place in a glass (or occasionally plastic) beaker, not a conical measure. Remember that the solubility of the soluble solids will be dependent on the vehicle used.
7. Transfer the appropriate amount of vehicle to a glass beaker.
8. If necessary, transfer the solid to a glass mortar and use the glass pestle to reduce particle size to aid dissolution (Figure 2.1).
9. Transfer the solid to the beaker and stir to aid dissolution. If a mortar and pestle have been used to reduce particle size, ensure that the mortar is rinsed with a little vehicle to ensure complete transfer of the powders.
10. When all the solid(s) has/have dissolved, transfer the solution to the conical measure that will be used to hold the final solution.
11. Rinse out the beaker in which the solution was made with a portion of the vehicle and transfer the rinsings to the conical measure.
12. Add any remaining liquid ingredients to the conical measure and stir.
13. Make up to final volume with remaining vehicle.
14. Transfer to a suitable container, label and dispense to the patient.

EXTEMPORANOU

ROUTE	TACTILE NATURE	VOLUME	EXAMPLES
INTERNAL	Amber **flat** medical bottle	50mL, 100mL, 150mL, 200, mL, 300mL, 500mL	Syrups Mixtures Linctuses Elixirs Decongestants
	Amber **round** medical bottle with dropper	10mL	Paediatric drops
EXTERNAL	Amber **fluted** medical bottle		Applications Collodions Enemas Gargles Liniments Lotions
	Amber **fluted** medical bottle	10mL	Ear drops Nose drops

EXTEMPORANEOUS SOLUTIONS OF IMPORTANCE

EXTEMPORANEOUS DISPENSING ACTIVITY (BY THE NUMBER OF UNITS DISPENSED IN YORKSHIRE, THE NORTH EAST AND LONDON (12 MONTH ACTIVITY SURVEYED 2005-2006)

EXTEMPORANEOUS SOLUTIONS	NO OF PRESCRIPTIONS	RISK GROUPING (based on clinical risk and technical risk)
Sodium chloride oral liquid	621	High
St Mark's solution	60	Medium
Captopril oral liquid	246	Medium
Clonidine hydrochloride oral liquid	266	Medium
Morphine sulphate oral liquid	475	Very high
Warfarin oral liquid	131	High
Levothyroxine oral liquid	880	Medium

ORGANOLEPTIC PROPERTIES

- Modern medicines must be acceptable to the patient, particularly those that are chronic prophylactic properties.
- Many drugs are unpalatable and visually unpleasing, which is a key concern for oral medications
- Taste bud respond rapidly to sweet, sour, bitter, acid materials that are in solution, which is unavoidable for solution dosage forms
- Water insoluble forms are not possible for solution dosage forms
- Taste masking in the form of sweeteners and flavour enhancers
- Taste of the drug must be matched to specific flavours to ensure masking
  - Citrus flavours mask acidic or sour drugs
  - Children prefer sweet tastes
- Colours can improve colour, mask a colour change, or complement flavour (citrus, yellow; strawberry red)
- Some ingredients have a cooling sensation (e.g. sorbitol) which can improve mouth feel

PSYCHORHEOLOGY

Psychorheology: Study of the psychological and sensory characteristics of a material as a result of its rheological properties

- A field advanced by the food industry
- Manipulation of fluid viscosity can improve palatability by reducing the contact of solution drugs with taste buds (decreasing diffusivity)

TEXTURE

Mouth feel

Grittiness

Viscosity

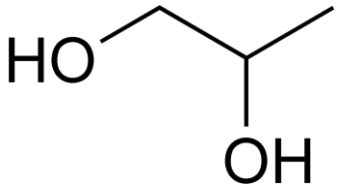
SOLUTIONS IN PAEDIATRICS

- In most cases pharmaceutical manufacturers to not licence medicines for children and therefore adult doses are diluted by first dissolving (solutions) or suspending drug particles (suspensions) in vehicle and administered in a convenient liquid dosage form

- Solutions enable more accurate dose adjustment based on volume compared with suspensions, but the volume required to dissolve the dose in water is often prohibitive and use of cosolvency is strictly controlled to prevent toxicity

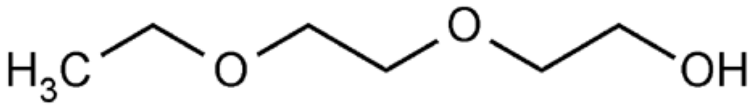
INGREDIENT QUALITY IN SOLUTION DOSAGE FORMS

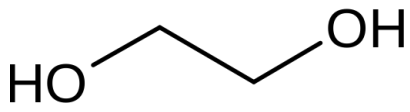
Pharma disasters: propylene glycol vs diethylene glycol



Propylene glycol

A widely used solvent in oral formulation of solutions





Diethylene glycol & Ethylene glycol

Are excellent co-solvents and often cheaper than other glycols, but they are toxic to mammals at very low doses

- ***Many disasters have arisen from the use of DEG and EG in pharmaceutical drug manufacturing***

MYPIKIN BABY TEETHING MIXTUR NIGERIA (2008)

- **<u>84 INFANT DEATHS (2 months to 7 years)</u>**
- Ingestion of tainted teething mixture tainted with DEG
- Nigerian Regulatory Agency (Nigerian National Agency for Food And Drug Administration and Control) traced the ingredient to an unlicenced chemical dealer in Lagos.
- The parent company Barewa Pharma was shut down and 12 people were arrested in connection with the incident

BEYOND USE DATING

- **EXPIRATION DATE**: Is a projection of the length of time the product can be expected, on the basis of accelerated stability studies, to retain its purity and potency (used for commercial products)
- **BEYOND USE DATES**: Is an estimate of the time interval that the compounded preparation can be expected to retain its potency and purity on the basis of general guidelines, literature references or actual real time stability studies using prescribed conditions

- These dates vary greatly depending on the type of solution, the route of administration and the purpose of the medicinal product.
  - Pharmaceutical manufacturers are required to perform stability testing (chemical, physical and biological) and provide such information to patients and healthcare professionals.
  - Extemporaneously compounded formulations are unlicensed medicines and assigning shelf life is often arbitrary, ambiguous and potentially dangerous

- Regulatory agencies (e.g. USP <795>) also provide general guidance on the beyond use dates or the date after which the preparation should not be used

ASIGNING BEYOND USE

- WORD OF MOUTH STABILITY INFORMATION CAN BE DANGEROUS

“We use a 2 week beyond use date for pedicycline in glass, so I guess 10 days should be safe for it in plastic”

“We dispensed monkimycin for one of our patients and just put a date of 10 days on it”

What is wrong here? Word of mouth end use dating is unsafe, unprofessional, unscientific and ill advised. Unless evidence is available to the contrary, beyond use dates for non-sterile products are listed overleaf. Drugs know to decompose require further consideration

USP BEYOND USE DATES RECOMMENDED FOR COMPOUNDED PRODUCTS

FORMULATION	BEYOND USE DATES
NON-AQUEOUS LIQUID AND SOLID FORMULATIONS	Not later than the time remaining until the earliest expiration date of any active pharmaceutical ingredient or 6 months (which ever is less)
WATER CONTAINING ORAL FORMULATIONS	Not later than 14 days when stored at cold temperatures
WATER CONTAINING TOPICAL/DERMAL AND MUCOSAL LIQUID AND SEMI-SOLID FORMULATIONS	30 Days

STORAGE TEMPERATURE

TERM	SPECIFICATIONS
COLD	<8°C
REFRIGERATOR	2-8°C
FREEZER	-10 TO -20°C
COOL	8-15°C
ROOM TEMPERATURE	20-25°C

STORAGE NOTES

- Stability of drugs in liquid form can mostly be increased by decreasing temperature
- Elixirs can precipitate at low temperature
- Oxidisable drugs are often more stable at low temperature
- O2 solubility increases at low temperature
- Time to reach room temperature 3h for 500mL, 20 min for fluid in infusion line

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