



## Medicinal forms for children

# Characteristics of children population

- Help is often required during administration of medicines
- Sensitive towards drugs and route of administration

# Children age categories



- newborns (0-28 days)
  - prematurely born (before pregnancy week 38)
  - born in date (in 38-42 week)
  - carried over (after week 42)
- nursling (1-12 months)



- **children (1-12 years)**
  - toddlers (1-3 years)
  - preschoolers (3-5 years)
  - school age (6-12 years)
- **adolescents (teenage, adolescents)**  
**(13-18 years)**

# Pharmacotherapy complications

- Missing medicines for children - about only  $\frac{1}{4}$  of medicines have pediatric indications
  - Absence of clinical studies
    - High cost
    - Complicated ethically
    - Uncertain profit
  - Missing info about suitability
  - Missing info about dosage
  - Hazardous excipients

# Pharmacotherapy complications

- Low amount of children dosage forms
- Insufficient amount of application and dosage tools
- Minimal amount of controlled release preparations for kids
- Insufficient offering of medicines incorporated to already existing children dosage forms

# Demands on children medicine

- Low dosing frequency
  - compliance of children patients
  - compliance of parents/assistance
- Dosage forms covering broad dosage range (suitability for more age categories)

# Demands on children medicine

- **Easy dosing**
  - For patients in given age category
  - For parents, medical personnel
- **Suitable administration properties**
  - minimum of unpleasant sensation



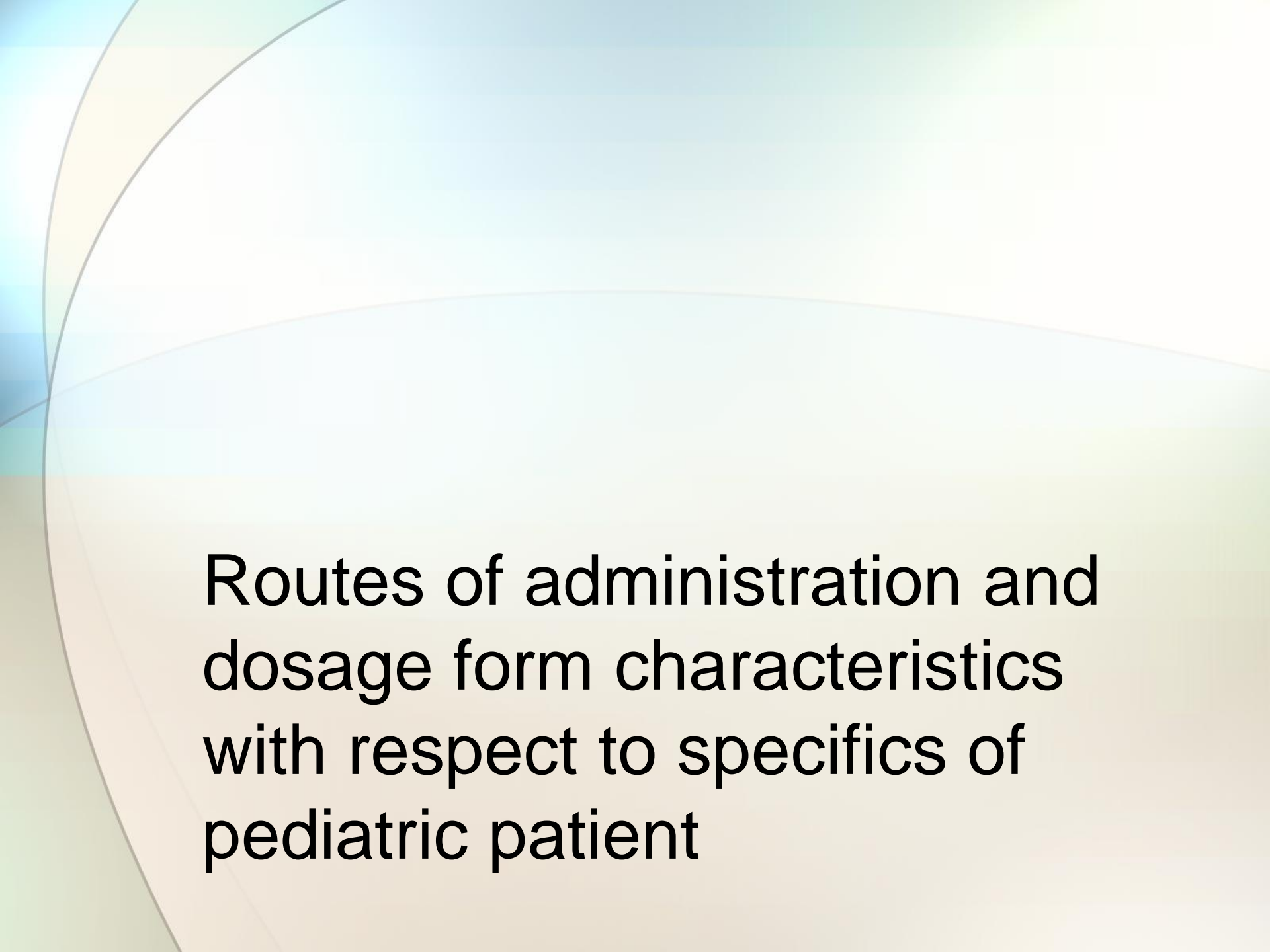
# Demands on children medicine

- Acceptable organoleptic properties
  - taste (!) - number of taste cells decreases with age
  - scent, colour, consistency, overall look



# Demands on children medicine

- Suitable excipients
  - Maximal restriction of pigments, antimicrobial and antioxidant substances,
  - Medicines without
    - sacharose
    - lactose
    - gluten
- Acceptable price



Routes of administration and dosage form characteristics with respect to specifics of pediatric patient

# Elemental routes of administration

- Peroral
- Oral
- Parenteral
- Inhalation
- Topical (dermal, eye, nasal, ear)
- Transdermal
- Rectal
- Vaginal



# Oral medicines

# Use

- Suitable for all age categories
  - If correct dosage form is chosen
- Majority of today's pediatric medicines
- Least applied in newborns (especially prematurely born)
  - Less predictable absorption
  - Worse applicability

Dosage form (oral, partially oral)	Newborns		Nurslings, toddlers do 2 let	Older toddlers, preschoolers (3-5 let)	School age (6-11/12 years)	Adolescents (12/13-18 years)
	prematurely	regular				
Solutions, drops	2	4	5	5	4	4
Suspension, emulsion	2	3	4	5	4	4
Effervescent DF	2	4	5	5	4	4
Powders, microforms	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Orodispersible DF	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5

Younger categories: 1 - not applicable, 2 - applicable with reservations. 3 - applicable, not preferred, 4 - well applicable, 5 - best and preferred application

Older categories: 1 - not acceptable, 2 - acceptable with reservations, 3 - acceptable, 4 - preferred, 5 - DF of first choice

# Liquid dosage forms



- Advantages

- Quicker effect than solid dosage forms
- Allow administration in patients not able to swallow solid dosage
- Allow better dosage adjustment



# Liquid dosage forms

- Disadvantages
  - Require special dosing tools and ability to use them
  - Large volume, heavier, less transportable
  - May irritate digestive tract
  - Not suitable to patients with indigestion(nausea, vomit)

# Liquid dosage forms

- Disadvantages
  - Need of adjustment of organoleptic properties (taste, scent, consistency etc.)
  - Need of stabilizers
  - Lower stability, shorter expiration
  - Often they need more strict storage condition (eg. fridge)

# Liquid dosage forms

- Dosage forms
  - multidose
    - solutions
    - syrups
    - suspensions
    - emulsions
    - oral drops



# Liquid dosage forms

- Dosage forms
  - Single dose (usually OTC)



# Liquid dosage forms excipients

- Solvents
  - Lipophilic solvents - vegetable oil - no restrictions with exception of groundnut oil (Arachidis oleum - solvent for i/m injections)
    - Use of groundnut oil in childhood leads to hypersensitivity in later age

# Liquid dosage forms excipients

- hydrophilic solvent - **water** - basic solvent
  - Purified water - in most cases
  - Water for injection - IPM for newborns, requirement in prematurely born children (aseptic preparation needed)
- other hydrophilic solvents
  - ethanol
  - glycerol
  - Propylene glycol
  - macrogol

# Liquid dosage forms excipients

- **ethanol** - toxic for children, just small amount can be used as co-solvent, eventually solvent in dosing by drops; maximum caution in newborns, nurslings and toddlers
  - symptoms of intoxication at blood concentration 25 mg/100 ml
  - concentration 25 mg/100 ml - oral administration 20 ml 10% solution to children with weight 13,6 kg (30 lbs)
  - Limit concentration for one dose

# Liquid dosage forms excipients

## – ethanol

### – Recommendation for manufacturers:

- max. 10% ethanol concentration for age over 12y
- max. 5% ethanol concentration for age 6-12 y
- max. 0,5% ethanol concentration for age under 6y (FDA - no ethanol at all)





# Liquid dosage forms excipients

- **glycerol** - sweetish taste, in small amount as a co-solvent it usually has no adverse effect, it should not be used as a solvent
  - hygroscopic - withdraws water,
  - Strongly hypertonic, in higher dose irritates digestive tract
  - Diarrhea, electrolytic imbalance

# Liquid dosage forms excipients

## - propylene glycol

- three times less toxic than ethanol, should be used as little as possible, particularly in neonates and infants
- 4 years is considered a contraindication to oral propylene glycol solutions
  - may cause CNS depression, tachycardia, lactic acidosis, gastrointestinal discomfort, renal toxicity, haemolysis
  - complications can occur even after application to a larger area of the skin, particularly the damaged parts

# Liquid dosage forms excipients

- macrogol (polyethylene glycol)
  - used also in treatment of constipation in children, suitable for long-term therapy
  - can be considered safe, but higher doses can cause diarrhea

# Liquid dosage forms excipients

- Sweeteners

- natural and modified

- Saccharose (sucrose)

- the most commonly used sweetener

- Not suitable for diabetics

- promotes tooth decay

- in infants can cause gastrointestinal problems

- dextrose (glucose)

- rarely used

- Fructose

- is more suitable for diabetics than sucrose (used relatively little)

# Liquid dosage forms excipients

- Lactose

- as sweetener should not be used  
a little sweetness  
lactose intolerance

- Sorbitol

- Has calories, trouble in diabetics (must be counted against the total daily dose hydrocarbons)  
among hyperosmotic laxatives; cause diarrhea at a dose of 9 g, in susceptible individuals, even at low doses, low risk of tooth decay

# Liquid dosage forms excipients

- mannitol, xylitol
  - like sorbitol can cause diarrhea when used in higher doses
- stevia
  - insufficiently researched in children
- Synthetic sweeteners (FDA approved)
  - Aspartam
    - unsuitable for patients with phenylketonuria
    - may cause headaches
    - may cause neuropsychiatric problems
    - may develop hypersensitivity

# Liquid dosage forms excipients

- sacharin
  - non-caloric, 300 times sweeter than sucrose
  - suitable for diabetics
  - It leaves a bad taste in the mouth
  - may cause allergy, cross allergy in patients allergic to sulfonamides
  - unconfirmed risk of bladder cancer (?)
  - It is not very suitable for the pediatric population and pregnant women

# Liquid dosage forms excipients

- Sucralose
  - newest artificial sweetener approved by the FDA
  - single synthetic sweetener made from sucrose molecule by substituting chlorine (chloride)
  - 600x sweeter than sucrose
  - highly stable and compatible
  - Unlike other synthetic sweeteners is minimally absorbed (85% is not absorbed), the absorbed part (15%) is excreted by urine unchanged
- acesulfam
- neotam



# Liquid dosage forms excipients

- Dyes

- Use should be sporadical
- Natural dyes
  - carotenoids, chlorophyll and others
    - preferred
    - low stability



# Liquid dosage forms excipients

- Synthetic dyes should not be used at all
  - allergy
  - Adverse effect not dependent on concentration
  - Azo dyes = unacceptable

# Liquid dosage forms excipients

## - Synthetic dyes

- most risky azo dyes(E102 - tartrazine, E104 - quinoline yellow, E110 - SY yellow, E122 - azorubine, E124 - cochineal red A, E129 - Allura AC yellow)
  - connection with disturbances of concentration in children
  - tartrazine (yellow) is also dangerous for people sensitive to aspirin

# Liquid dosage forms excipients

- Antimicrobial agents
  - the emergence of side effects depends on the concentration; more sensitive are children born prematurely and low weight born children
    - benzoic acid and benzoate - hypersensitivity (urticaria, atopic dermatitis), possible influence of the activity and concentration in children
    - sorbic acid and salts - hypersensitivity

# Liquid dosage forms excipients

- Parabens - hypersensitivity, allergic reactions  
the most widely used group of antimicrobial agents
  - In pharmacy available methyl and propyl paraben
  - for new applications and marketing authorization for pediatric oral fluids is accepted only methylparaben (or. ethylparaben), referring to the elimination of propylparaben: a limit for the ADI (Acceptable Daily Intake) in European food legislation - the negative impact of propylparaben on reproduction when administered in juvenile animals (impaired development of testicles)
  - parabens should not be added to the compositions for long term use
  - Propyl parabene not even for short-term use

# Liquid dosage forms excipients

- benzalkonium chloride - bronchoconstriction, especially after inhalation among asthmatics
- benzyl alcohol - particularly toxic (i / v) for premature infants and infants with low birth weight
  - Better not to use in children under 4 years old

# Liquid dosage forms excipients

- thiomersal - hypersensitivity, accumulation of mercury in organism (risk of toxicity)
- formerly used in children vaccines; currently withdrawn because of possible toxicity (associated with childhood autism)  
Recommendation: Do not use in young children at all

# Taste adjustment of liquid preparations

- Flavoring agents
  - Flavors and aromas

Basic taste of preparation	Overlapping flavor
Acid	Cherry, lemon, lime, tangerine, orange, strawberry
Alkaline	Banana, caramel, cherry, licorice, passion fruit, peach
Bitter	Cherry, chocolate, grapefruit, licorice, strawberry, peach, raspberry, tutti-frutti
Sweet	Caramel, grapefruit, lemon, orange, vanilla
Salty	Banana, caramel, cream, chocolate, grapefruit, vanilla



# Taste adjustment of liquid preparations

Disease, health status	Taste
Pain, fever, allergies, infections	Cherry, strawberry, banana, caramel
Lack of vitamins (multivitamin preparations)	Black currant, lemon, lime, tangerine, orange
Indigestion (antacids)	Lemon, lime, orange, peppermint

- FLAVORx system

- Suitable for both IP and industry
- the list of recommended ingredients for a variety of medicines



# Taste adjustment of liquid preparations

- Dosing tools
  - Suitable dosing tool



- syringes, prefilled syringes



- calibrated dropper



- measuring cups, dosing spoons



# - Dosing scoops for infants



# - Special dosing bottle



Patented-Design Nipple

Medication is delivered directly to the child's mouth, keeping it separate from bottle contents

Patented-Design Nipple

Works with child's natural desire to feed and helps improve medication acceptance

Isolated Channel

Medication is kept completely separate from bottle contents

Isolated Channel

Because it doesn't mix with bottle contents, medication is delivered without dilution or contamination

Controlled Plunger

Medication is delivered at a controlled rate

Controlled Plunger

Accurate and complete dosing is ensured for total peace of mind



ReliaDose®



# Examples of liquid IP medicines

Rp.

Coffeini 1,0  
Ac. citrici monohydr. 1,094  
Aq. pro inj. ad 100,0  
M.f.sol.

Indication: apnea in preterm infants

Rp.

Sacharosi 2,5  
Aq. pro inj. ad 10,0  
M.f.sol.

Indication: analgesic prior to minor painful performance (0.2 ml on tongue)

# Examples of liquid IP medicines

Rp.

Chloral hydras	4,0
Sirupus simplex	20,0
Methylcellul. sol. 1,5% ad	106,0
M.f.sol.	(100 ml)

Indication: sedative

Rp.

Sotalol hydrochloridi	0,50
Acidi citrici monohydr.	0,08
Kalii sorbatis	0,10
Sirupi simplicis	20,00
Aqua purificata	
Aq. pro inj. ad	105,00
M.f.sol.	(100 ml)

Indi: antiarrhythmics III. class

# Examples of liquid IP medicines

Rp.

Ac. citrici monohydr. 14,0

Natrii citratis dihydr. 5,0

Kalii citratis monohydr. 5,0

(Sirupi simplici 30,0)

Aq. purificata 100,0 g

M.f. sol.

Indication : metabolic acidosis

Rp.

Propranolol hydrochlorid 0,2

Acidum citricum monohydr. 0,84

Natrium hydrogenphos.\* 0,74

Natrium benzoas 0,05

Sirupus simplex 64,0

Aqua purificata ad 114,0 g

M.f. sol.

Indication: arrhythmia, hypertension

# Solid dosage forms



- Classic tablets

- For various age category with the expectation of the youngest children
- For kids who are able to swallow them
- conventional tablets can be halved or even crushed; they can be administered with food or liquid
  - risk of incorrect dosing
  - Ideally, crushing and dosing should be performed at the pharmacy
- Risk of incompatibilities

# Solid dosage forms

- Classic capsules
  - Various age categories
  - Whole capsules (size 1-4) are administered in children who are able to swallow them
  - For little kids, capsule can be opened and the content poured into meal or water
  - Hospital pharmacy - dilution of capsules
    - Capsule for direct administration
    - Capsule as a primary package - pouring out the content

# Solid dosage forms

- Enteric formulations, controlled release formulations
  - CR (controlled release), Dur (duration), EC (enteric coated), LA (long acting), SA (sustained action), SR (sustained release) etc.
  - Classic systems (tablets, capsules) - patient has to be able to swallow the medicine
  - Matrices can be halved; never crushed

# Solid dosage forms

- Tablets for suspension preparation



# Solid dosage forms

Pills, grained powders  
served with liquid or food





# Example of IP powders

Rp.

Calcii gluconatis 0,1

Calcii hydrogenphosphatis 0,11

M.f.pulv.

D.t.d.No X (decem)

Administration: capsule content is poured out into milk

Indication: mineral supplement

Rp.

Natrii chloridi 2,6

Kalii chloridi 1,5

Natrii citratis dihydr. 2,9

Glucosi anhydricus 13,5)

M.f. plv.

D.S.: Dissolve in 1000 ml of water

Indication: rehydratation

# Solid dosage forms

- Grained powders or microforms in hard capsules (sprinkles, sprinkle powders)
  - just prior to the administration content is poured on spoon with food or liquid



- Older kids can swallow whole capsule

# IP example (weighed out commercial product)

Rp.

Omeprazoli 0,002 (0,03, ...)

M.f.cps.

D.t.d.No

Administration: pellet spill from the capsule into fruit juice or juice to drink within 20 minutes.

Omeprazole - proton pump inhibitor

- decomposes in acidic medium
- available in capsules filled with acid resistant pellets (Helicid, Ortanol)
- Prepared by weighing poured out pellets into capsules (do not crush or perform using a razor)

# Solid dosage forms

- Dispersible grained powders and microforms
  - For suspension preparation

# IP example

Rp.

Omeprazoli 0,2

Natrii hydrogencarbonatis  
sol. 8,4% ad 100,0 ml

M.f.susp.

Omeprazole - proton pump inhibitor

- decomposes in acidic medium
- available in capsules filled with acid resistant pellets (Helicid, Ortanol)
- Suspension is prepared by spontaneous swelling of the pellets (Ortanol)

# Solid dosage forms

- Jelly bears
  - MP and IP



# Solid dosage forms

- Ice cream with medication
  - MP and IP



# ORAL CAVITY/MUCOSA MEDICATIONS





# Use

- Both local and systemic effect
- All age categories
  - With condition of well chosen DF
  - Systemic effect medications from certain age
  - Usually application by an adult is needed

# Liquid (solutions, sprays)

- separately from a certain age (usually not less than school)
- little children - assistance by an adult person
- more often for local effect



# IP examples

Rp.

Nystatini                    2 mil. I.U.

Glyceroli 85%            0,6

Methylcellulosi sol. 1,5%

ad 20,0

M.f.susp.

D.S. to wipe 3-6x daily

Note .: isotonic suspension  
for newborns

Rp.

Nystatini                    1 mil. I.U.

Glyceroli 85%        ad 20,0

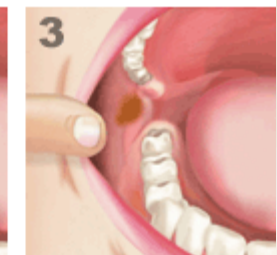
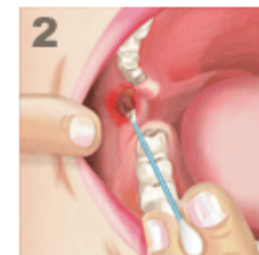
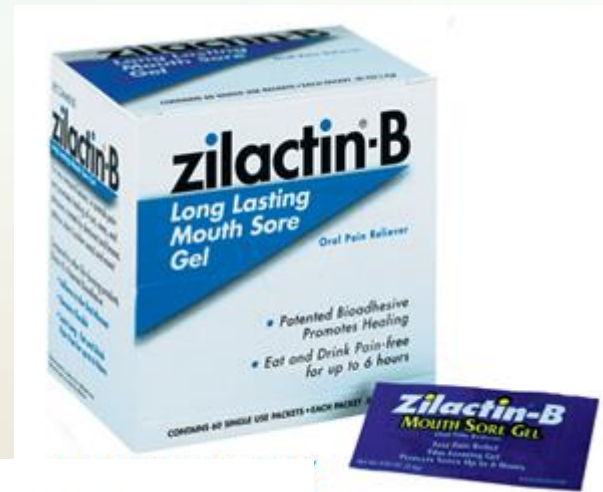
M.f.susp.

D.S. to wipe oral cavity 3-  
6x daily

Note .: not suitable for  
newborns because of  
hyperosmolarity

# Semisolid preparations

- Local effect
- Mainly hydrophilic gels



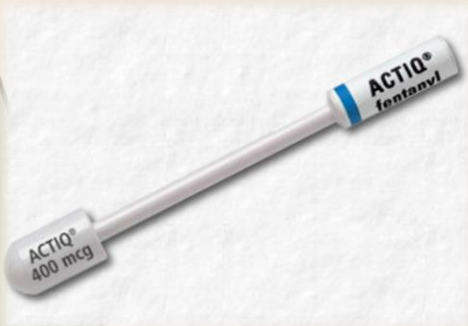
# Solid preparations

- Usually with an assistance
  - tampons (local effect)



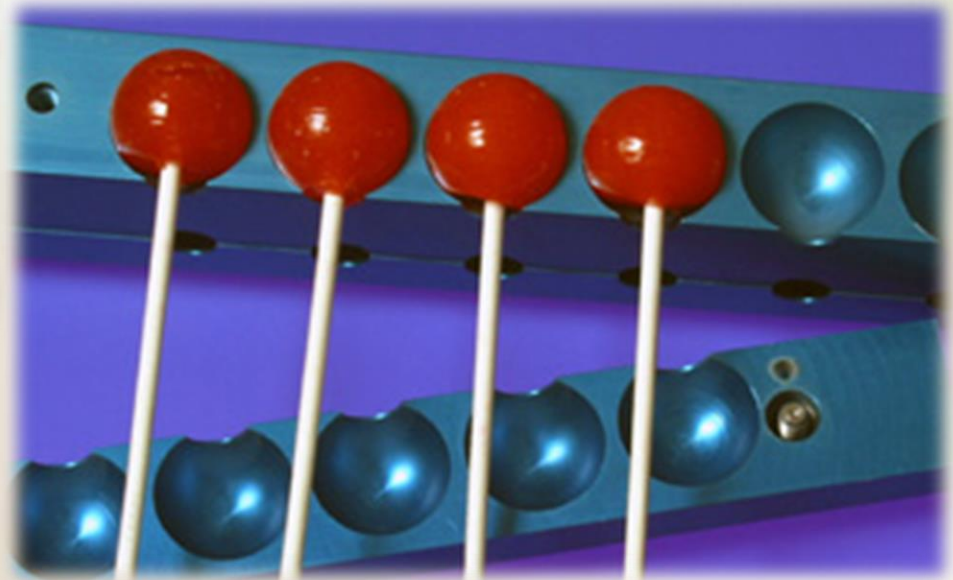
# Solid preparations

- buccal, sublingual tablets
- lozenges, strip, films
- lollipops
  - IP
  - Industry:
    - Actiq with fentanyl
    - Chloraseptic - (thrush)



# Solid Preparations

- lollipops
  - Pouring into moulds





# PARENTERAL ADMINISTRATION



# Use

- Suitable for all ages
- Not very popular in children
  - for seriously ill children; an IV administration is preferred (or. i / v administration via a central catheter) from repeated injections into the muscle
- Injections
  - subcutaneous (solutions, suspensions)
  - intramuscular (solutions, emulsions, suspensions)
  - intravenous (water solutions, o/w emulsions)
- Infusion (water solution, o/w emulsion)
- Implants



Dosage form	Newborns		Nurslings, toddlers do 2 let	Older toddlers, preschoolers (3-5 let)	School age (6-11/12 years)	Adoles- cents (12/13- 18 years)
	prematurely	regular				
Injection i/v and infusions	5	4	4	4	4	3
Injection i/m	3	3	3	4	4	3
Injections s/c	4	4	4	4	4	3
Pumps	5	4	4	4	4	3

Younger categories: 1 - not applicable, 2 - applicable with reservations. 3 - applicable, not preferred, 4 - well applicable, 5 - best and preferred application

Older categories: 1 - not acceptable, 2 - acceptable with reservations, 3 - acceptable, 4 - preferred, 5 - DF of first choice

# **INHALATION DOSAGE FORMS**

# Use

- Suitability for a particular age category determines:
  - Mechanism of aerosol creation
  - Used equipment for inhalation device,
  - respiratory capacity of the patient.
- At the lower age categories administration requires the assistance of an adult

Mechanism of aerosol creation	Newborns		Nurslings, toddlers do 2 let	Older toddlers, preschoolers (3-5 let)	School age (6-11/12 years)	Adolescents (12/13-18 years)
	prematurely	regular				
Jet sprays (nebulizers)	2	3	4	5	4	3
Metered dose inhaler (MDI)	1	3	4	5	4	4
Dry powder inhaler (DPI)	1	1	3	4	5	5

Younger categories: 1 - not applicable, 2 - applicable with reservations. 3 - applicable, not preferred, 4 - well applicable, 5 - best and preferred application

Older categories: 1 - not acceptable, 2 - acceptable with reservations, 3 - acceptable, 4 - preferred, 5 - DF of first choice

- **Aerosols from jet nebulizers**

- Suitable for all ages: infants and toddlers are in need of mask,
- toddlers and older children: cooperation in the presence of adults
- older children: standalone application



- **MDI - metered dose inhaler**
  - Suitable from age since child is able to cooperate; in younger dosing aids are needed
    - spacers



- **DPI - dry powder inhalers**
  - only suitable for ages with sufficient respiratory capacity

# IP examples

Rp.

Amiloridi hydrochl. 0,006

Natrii chloridi 0,18

Aq. pro inj. ad 20,0

M.f.sol.

Sterilisetur!

D.t.d. No XV (quindecim)

Note .: the treatment of cystic fibrosis

Rp.

Natrii chloridi 9,0 (7,55; 21,0)

Aq. pro inj. ad 300,0

M.f.sol.

Sterilisetur!

Divide in dos. aeq. No XV

Note .: the treatment of cystic fibrosis





# TOPICAL AND TRANSDERMAL MEDICATION

Dosage form	Newborns		Nurslings, toddlers do 2 let	Older toddlers, preschoolers (3-5 let)	School age (6-11/12 years)	Adoles- cents (12/13- 18 years)
	prematurely	regular				
Dermal						
• liquid	4	4	4	5	4	4
• semisolid	4	4	4	5	5	5
Transdermal	1	2	2	4	4	5
Eye:						
• drops	3	4	4	4	5	5
• semisolid	2	3	4	4	4	4
Nasal:						
• drops	3	4	4	4	4	4
• semisolid	2	3	3	4	4	4

Younger categories: 1 - not applicable, 2 - applicable with reservations. 3 - applicable, not preferred, 4 - well applicable, 5 - best and preferred application

Older categories: 1 - not acceptable, 2 - acceptable with reservations, 3 - acceptable, 4 - preferred, 5 - DF of first choice

# Dermal preparation

- Liquid (solutions, suspension, emulsion, shampoo, nail polish)
- Semisolid (ointment, cremes, paste, gels)
- Aerosols and foams
  - allow gentler treatment, better accepted, particularly young patients
- Solid (dusting)

# Příklady IVLP

Rp.

Propranolol hydrochl. 0,3

Aqua purificata 15,0

Neo-aquasorb ad 30,0

D.t.d. crm

Indication.: Infantile  
Hemangioma

Rp.

Ureae 3,0

Ac. Lactici 1,0

Natrii lactatis sol. 50 % 4,0

Glyceroli 85 % 2,0

Dimeticoni 6,0

Aq. purif. 7,0

Cutilan ad 100,0

To salve dry skin

# Dermal preparation

- Application

- In newborns and infants, the preparations should not be applied to a larger area of the skin - risk of undesirable systemic effects

# **RECTAL ADMINISTRATION**

# Application

- All age categories
  - Beneficial for newborns and infants
  - Older children often refuse
- For systemic effect they should be used mainly when it is not possible to use a different application path

# Rectal administration

Dosage form	Newborns		Nurslings, toddlers do 2 let	Older toddlers, preschoolers (3-5 let)	School age (6-11/12 years)	Adoles- cents (12/13- 18 years)
	prematurely	regular				
Suppositoria	4	5	5	4	3	2
Clysmas	5	4	4	3	3	2
Rectal capsules	2	3	4	4	4	3

Younger categories: 1 - not applicable, 2 - applicable with reservations. 3 - applicable, not preferred, 4 - well applicable, 5 - best and preferred application

Older categories: 1 - not acceptable, 2 - acceptable with reservations, 3 - acceptable, 4 - preferred, 5 - DF of first choice



# Rectal administration

- Liquid (enemas- solution and suspension)
  - Special package with adapter



# IP example

Rp.

Chlorali hydratis	5,0
Aq. purificatae	50,0
Methylcellulosi sol 1,5% ad	100,0

M.f.sol.

# Rectal administration

- Semisolids (ointments, gels)
  - special packaging with an application extension



# Rectal administration

- Solid (suppositories, rarely tablets and capsules)
  - suppositories should not be halved
  - macrogol suppositories should be usually moistened before application



# IP example

Rp.

Domperidoni 0,01 (0,02;  
0,03)

Massae ad suppos. q.s.

D.t.d.No

Pozn.: antiemetics

Rp.

Ibuprofeni 0,05 (0,1; 0,2;  
0,4)

Massae ad suppos. q.s.

D.t.d.No

*Special: Closing of ductus  
arteriosus*

# **VAGINAL ADMINISTRATION**

# Application

- For pediatric patients, relatively little applied group of dosage forms
  - adolescent girls (vaginal infections, sometimes contraception)

## IP example

Rp.

Nitrofurantoini 0,01

Massae ad suppos. q.s.

D.t.d.No

THE END



ANNE GEDDES®