Pharmaceutical excipients – an overview including considerations for paediatric dosing

Training workshop:

Pharmaceutical development with focus on paediatric formulations

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Introduction

- **Overview of excipients commonly used in medicines** (particularly in oral dosage forms)
  - **Role of Key Solid Dose Excipients**
  - **Role of Key Solution/Suspension Excipients**
- **Paediatric considerations with regard to excipients**

Excipients – an overview (1)

- **Drug products contain both drug substance (commonly referred to as active pharmaceutical ingredient or API) and excipients. Reasons for this include:**
  - Ease of administration to the target patient population(s) by the intended route
  - Improved dosing compliance
  - Consistency and control of drug bioavailability
  - To enable bioavailability
  - Improved API stability including protection from degradation
  - To ensure a robust and reproducible physical product
- **Excipients are sub-divided into various functional classifications, depending on the role that they are intended to play in the resultant formulation, e.g. in solid dosage forms:**
  - Diluents, e.g. lactose, microcrystalline cellulose
  - Disintegrants, e.g. sodium starch glycolate, croscarmellose sodium
  - Binders, e.g. PVP, HPMC
  - Lubricants, e.g. magnesium stearate
  - Glidants, e.g. colloidal SiO_2

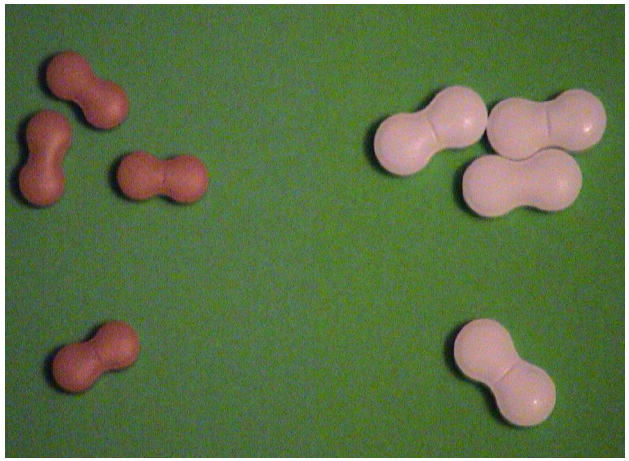
Excipients – an overview (2)

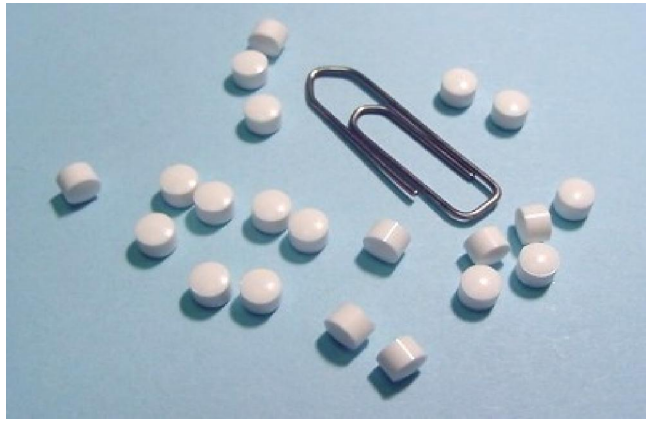
- **Certain excipients can have different functional roles in different formulation types, e.g. lactose; widely used as:**
  - a diluent, filler or bulking agent in tablets and capsules
  - a carrier for dry powder inhalation products (DPIs).

- **Furthermore, individual excipients can have different grades, types and sources depending on those different functional roles….**

- **For example, there are various grades of lactose commercially available that have different physical properties, e.g. flow characteristics & particle size distributions. This permits selection of the most suitable grade for a particular need…….**
  - Wet Granulation: usually, finer grades of lactose are used so that the binder is more efficient and this permits better mixing and granule quality.
  - Direct Compression: in contrast here, spray dried lactose is used as it has good flow properties and is more compressible.
  - For dry powder inhalers: crash-crystallisation fine-milled lactose with a coarser fraction for flow and a finer fraction to enhance API aerosolisation and delivery to the lungs

Solid dosage forms for paediatrics





Diluents (Fillers)

- **Bulking agent**
  - E.g. to make a tablet weight practical for the patient: minimum tablet weight is typically ~50mg.
    Actual API doses can be as low as ~20µg, e.g. for oral steroids.

- **Compression aid**
  - Deforms and/or fragments readily to facilitate robust bonding in tablet compacts, e.g. microcrystalline cellulose.

- **Good bulk powder flow….diluents have a strong influence**
  - Good flow of bulk powders is very important in designing a robust commercial tablet product.

    Favoured combinations: Lactose is an excellent choice of filler in many respects but can exhibit poor flow characteristics, so is often combined with free-flowing microcrystalline cellulose in wet granulation formulations.

Disintegrants

- **As an aid to de-aggregation of solid dosage forms. Disintegrants cause rapid break up (disintegration) of solid dosage forms upon exposure to moisture.**
- **Generally, disintegration is viewed as the first stage in the dissolution process, although dissolution does occur simultaneously with disintegration.**
- **Mode of action:**
  - In many cases water uptake alone will cause disintegration, by rupturing the intra-particle cohesive forces that hold the tablet together and resulting in subsequent disintegration.
  - If swelling occurs simultaneously with water uptake, the channels for penetration are widened by physical rupture and the penetration rate of water into the dosage form increased.

Binders

- **Binders act as an adhesive to 'bind together' powders, granules and tablets to result in the necessary mechanical strength:**
  - As a dry powder with other excipients in dry granulation (roller compaction, slugging) or as an extra-granular excipient in a wet granulation tablet formulation.
  - As a dry powder with other intra-granular excipients in wet granulation. When the granulating fluid is added, the binder may dissolve partially or completely to then exhibit adhesive binding properties in helping granules to form.
  - Most commonly in wet granulation, the binder is added already dissolved in the granulating fluid to enable a more effective and controllable granule formation.
  - **Water** is the most common granulating fluid, very occasionally in a co-solvent system with, e.g. ethanol.

- **Examples:**
  - Dry binders: Pregelatinised starch, cross-linked PVP
  - Solution binders: HPMC, PVP
  - Soluble in water/ethanol mix: PVP

Lubricants

- **Compression lubricants prevent adherence of granule/powder to punch die/faces and promote smooth ejection from the die after compaction:**
  - **Magnesium stearate** is by far the most extensively used tableting lubricant
  - There are alternatives, e.g. stearic acid, sodium stearyl fumarate, sodium behenate
  - Lubricants tend to be hydrophobic, so their levels (typically 0.3 – 2%) need to be optimised:
    - Under-lubricated blends tend to flow poorly and show compression sticking problems
    - Over-lubricated blends can adversely affect tablet hardness and dissolution rate

- **Lubricants can also be used when compression isn't involved, e.g.**
  - In powder blends for filling into capsules to prevent adherence of granule/powder to equipment surfaces and dosator mechanisms
  - Coating the surface of multi-particulate dosage forms (including intermediate product) to inhibit agglomeration of individual particles

Glidants

Most commonly; colloidal silicon dioxide (traditionally, talc was used)

- **Good bulk powder flowability is especially important during high speed processing**
- **Glidants improve flow by adhering to particles and so reducing inter-particulate friction**
  - Most common in dry powder formulations, e.g. direct compression tablets
  - Can also be added to granules to improve flow prior to compression
  - NB: can get undesirable “flooding” if flow is too good
- **Very low levels required (ca. <0.2%)**
  - Control can be challenging with blends sensitive to levels
- **Very low bulk density (0.03 – 0.04g/cm^3)**
  - Difficult to work with (very voluminous) – not a standard excipient, only added if needed
  - Issues with dust exposure

Other excipients

- **Polymers for Modified Release of formulated API**

  Extended release dosage forms, e.g. HPMC, Xanthan Gum

- **Polymers for Protection of API**

  Enteric resistance dosage forms, e.g. Eudragits® poly(meth)acrylates

  – **Functional coating on or formulated in:**
    - Tablets and Capsules
    - Granules
    - Microspheres

Excipient challenges (FDCs)

Anti-retroviral (ARV) and anti-tuberculosis drugs have a common challenge in being high dose. There is also a patient preference for the drug cocktails associated with these diseases to be presented as a fixed dose combination (FDC) tablet rather than multiple single-API tablets. FDC's also simplify the treatment and management of drug supply, which may help impede the emergence of drug resistance.

This poses certain technical challenges, specifically for the paediatric market, because the tablets must be swallowable.

Formulation design approach:

- Understand variability in API(s) characteristics and minimize if possible, through processing (granulation/slugging) if necessary
- Choose excipients and appropriate grades that will, with minimal extra weight additional to the API loading:
  - Enable development of a robust formulation and manufacturing process
  - Provide tablets with desired and consistent physical characteristics, stability profile and bioavailability
- Consider a breakline (on top and bottom of tablet) to enable splitting of tablet to ease swallowing and/or provide flexibility of dosing; each fragmented half will need to incorporate the appropriate half-dose within specified limits

Oro-dispersible tablets (ODT)

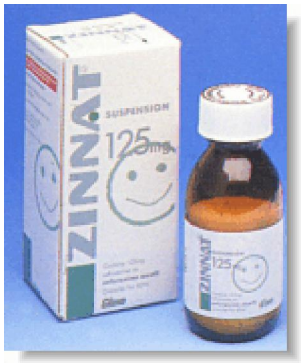
Tablets that rapidly disintegrate without chewing, when placed on top of tongue. No water required for administration. Two main types of ODT:

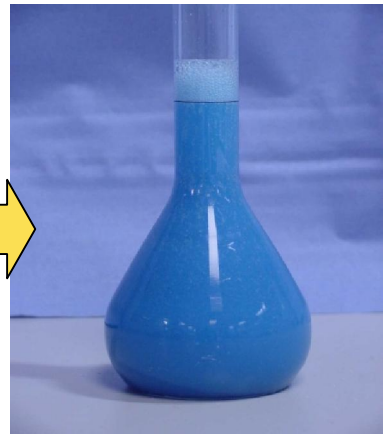
- **Lyophilised units**
  - Carrier excipient – predominantly sucrose
  - Disintegrate in <5 seconds
  - Only low drug loading possible (~5-10mg)
  - Prone to friability – packed into blisters
- **Conventional tablets**
  - Standard tableting processes; can involve novel/modified conventional and/or combination excipients
  - Disintegrate in 20-60 seconds
  - Larger drug loading possible (up to ~500mg)
  - More robust – can be packed into bottles as well as blisters

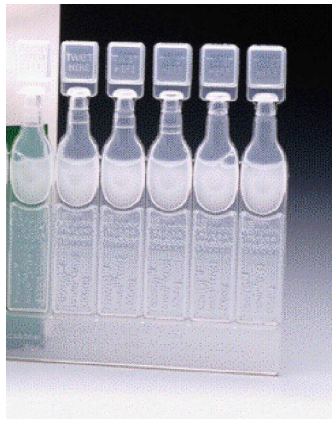
Issues:

- Novelty of some excipients
- Taste masking is a challenge and it can be an expensive technical hurdle using excipients with little or no paediatric safety information

Liquid dosage forms for paediatrics







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Excipients For Solution/Suspension Products

Again, excipients are sub-divided into various functional classifications, depending on the role that they play in the resultant formulation….

Solvents/Co-Solvents

- **Water is the solvent most widely used as a vehicle due to:**
  - Lack of toxicity, physiological compatibility, and good solubilising power (high dielectric constant), *but*
    - Likely to cause instability of hydrolytically unstable drugs
    - Good vehicle for microbial growth
- **Sorbitol, dextrose, *etc.* are often added as solubilisers, as well as base sweeteners**
  - Similar pros and cons to water alone
- **Water-miscible co-solvents are used to:**
  - Enhance solubility, taste, anti-microbial effectiveness or stability
  - Reduce dose volume (e.g. oral, injections)
  - Or, conversely, optimise insolubility (if taste of API is an issue)
  - Examples: propylene glycol, glycerol, ethanol, low molecular weight PEGs
- **Water-immiscible co-solvents, e.g.**
  - Emulsions / microemulsions using fractionated coconut oils

Buffering Agents

- **Can be necessary to maintain pH of the formulation in order to:**
  - Ensure physiological compatibility
  - Maintaining/optimising chemical stability
  - Maintaining/optimising anti-microbial effectiveness
  - Optimise solubility (or insolubility if taste is an issue)
    - *But*, optimum pH for chemical stability, preservative effectiveness and solubility (or insolubility) may not be the same

⇒ Compromises need to be made

Anti-microbial Preservatives

- **Preservatives are used in multi-use cosmetic/pharmaceutical products (including paediatric formulations)**
  - Prevents an increased risk of contamination and proliferation by opportunistic microbes (from excipients or introduced externally), that would result in potential health issues
  - Avoid use wherever possible, especially in products aimed at younger paediatric patients
    e.g. not required for sterile, single-dose products (as recommended for neonates)
- **Ideally targeted for microbial cells - showing no toxicity/irritancy towards mammalian cells**
  - Challenge is that the active groups involved are usually harmful to all living tissue
- **There are a limited number of approved preservatives available for multi-use oral products, and options are even more limited for other routes of administration**
  - Should not use in parenteral infusions
  - Must avoid access to cerebrospinal fluid and retro-ocular administration
- **This restricted number can be further reduced by consideration of factors such as levels required (dose), pH-solubility profiles, API & excipient incompatibilities, adsorption, irritancy and toxicity.**

Anti-Oxidants

- **Used to control oxidation of:**
  - API
  - Preservative, *e.g.* potassium sorbate
  - Vehicle, *e.g.* oils or fats susceptible to β-oxidation (rancidification)
  - Colourants (ageing discolouration)
- **They are sacrificial (more oxidisable than API, preservative, etc). Levels will reduce with time…. need to be monitored by specific assay**
  - Light exposure and metal ion impurities can accelerate oxidative degradation and hence depletion of anti-oxidant
- **Need to assess regulatory acceptability (varies in different countries)**
- **Efficacy can be affected by:**
  - Incompatibility with other excipients
  - Partitioning into micelles (from surfactants)
  - Adsorption onto surfaces (container, thickening agent and suspended particles)
  - Interaction with metal ions

Wetting Agents

- **To aid 'wetting' and dispersion of a hydrophobic API, preservative or antioxidant**
  - Reduce interfacial tension between solid and liquid during manufacture or reconstitution of a suspension
  - Not all are suitable for oral administration
- **Examples include:**
  - Surface active agents, e.g.
    - Oral: polysorbates (Tweens), sorbitan esters (Spans)
    - Parenteral: polysorbates, poloxamers, lecithin
    - External: sodium lauryl sulphate

    … but these can cause excessive foaming (see anti-foaming agents) and can lead to deflocculation and undesirable physical instability (sedimentation) if levels too high
  - Hydrophilic colloids that coat hydrophobic particles, e.g. bentonite, tragacanth, alginates, cellulose derivatives. Also used as suspending agents, these can encourage deflocculation if levels are too low.

Anti-Foaming Agents

- The formation of foams during manufacturing processes or when reconstituting liquid dosage forms can be undesirable and disruptive.
- Anti-foaming agents are effective at discouraging the formation of stable foams by lowering surface tension and cohesive binding of the liquid phase.
- A typical example is Simethicone (polydimethylsiloxane-silicon dioxide), which is used at levels of 1-50ppm.

➢ Of course, a foam is also a very valid dosage form option for certain situations, e.g. for topical administration and in wound dressings.

In addition, wet granulation using a foam rather than aqueous granulation fluid is gaining popularity.

Thickening Agents

- **Suspension stabilisers: prevent settling/sedimentation (particularly if a wetting agent present)**
- **They usually modify viscosity and are often thixotropic (where viscosity is dependent on applied shear and exhibits 'shear thinning')**
  - Easily poured when shaken
  - Must permit accurate dosing with chosen method (e.g. graduated syringe, spoon)
  - Quickly reforms 'gel-like' structure
  - They can impact on flocculation at low levels
- **Work by entrapment of solid particles, e.g. API, in a viscous or even 'gel-like' structure**
  - Can be either water-soluble, e.g. methylcellulose or hydroxyethylcellulose
  - Or water-insoluble, e.g. microcrystalline cellulose

Sweetening Agents

- **Natural sweeteners**
  - Sucrose; soluble in water (vehicle), colourless, stable (pH 4-8), increases viscosity; Arguably the best taste/mouthfeel overall but cariogenic (long term) & calorific → avoid in paediatrics?
  - Sorbitol (non-cariogenic, non-calorific - appropriate for paediatric formulations), but lower sweetness intensity than sucrose (so you need more) & can cause diarrhoea

- **Artificial sweeteners**
  - Regulatory review required – often restricted territories
  - Much more intense sweeteners compared with sucrose
  - As a consequence the levels are much lower (<0.2%) but still need to refer to WHO Acceptable Daily Intakes (ADIs)
  - Can impart a bitter or metallic after-taste (hence used in combination with natural sweeteners)
  - Examples:
    - Saccharin and it's salts
    - Aspartame
    - Acesulfame –K
    - **Sucralose – excellent sweetness, non-cariogenic, low calorie, wide & growing regulatory acceptability but relatively expensive**

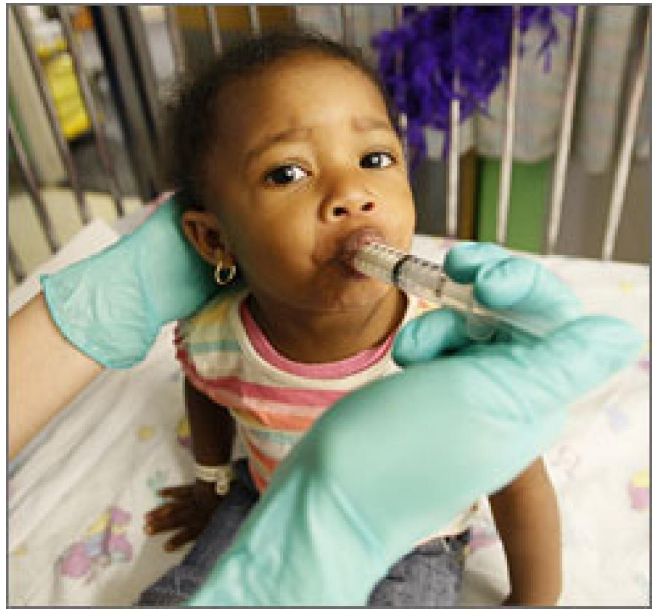
Flavouring Agents

- **Supplement and complement a sweetening agent**
  - Ensures patient compliance (especially in paediatric formulations – a big issue)
  - Can be natural, e.g. peppermint, lemon oils,
  - Or artificial e.g. butterscotch, 'tutti-frutti' flavour
  - Instability can be an issue – combinations can be used to cover intended product shelf-life
- **Taste appreciation is not globally consistent…**
  - Genetic element: one person's acceptable taste is another's unacceptable taste
  - Territorial (cultural) differences in preference
  - Affected by age (paediatric perception and preferences are different from adult)
  - Can be affected by certain disease states, e.g. during cancer chemotherapy
- **Regulatory acceptability of flavours needs to be checked**
  - Different sources, different compositions, different flavour, e.g. there are >30 different "strawberry flavours"!
  - Usually complex of composition (so refer to internationally recognised standards)

Humectants

- **Hygroscopic excipients used at ~5% in aqueous suspensions and emulsions for external application.**
- **Their function is to retard evaporation of aqueous vehicle of dosage form:**
  - To prevent drying of the product after application to the skin
  - To prevent drying of product from the container after first opening
  - To prevent cap-locking caused by condensation onto neck of container-closure of a container after first opening
- **Examples include:**
  - propylene glycol
  - glycerol
  - PEG

Paediatric Issues with Common Excipients



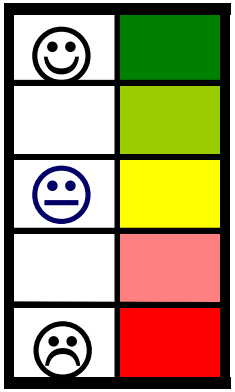
Overview thoughts for paediatric dosage forms

- **Technical Challenges:**
  - Good taste and mouth feel (oral liquids, chewable/dispersible/"melt-in-mouth" units, inhaled, intranasal)
  - Inability to swallow solid dosage forms; needing an alternative option
  - Constraints of dosage form size and volume related to dose required, e.g. drug solubility in small injection volumes
  - Dosing flexibility
  - Physical, chemical and, where appropriate, anti-microbial stability
  - Accuracy of dosing – potentially more of a challenge with lower doses & dose volumes
  - Parenterals: needlephobia, small veins needing small needles & injection volumes
  - Important routes: oral, topical, inhaled, rectal, eye drops & nose drops/spray, injectables

Influence of target age population…….

Paediatric Dosage Forms of Choice (1)

Route	Dosage Form	*Preterm newborn infants*	*Term newborn infants*	*Infants and Toddlers*	*Children (pre-school)*	*Children (School)*	*Adolescents*
			(0d-28d)	*(1m-2y)*	*(2-5y)*	*(6-11y)*	*(12-16/18y)*
Peroral							
	Solution/Drops						
	Emulsion/Suspension						
	Effervescent DF						
	Powders/Multiparticulates						
	Tablets						
	Capsules						
	Orodispersible DF						
	Chewable Tablets						
Nasal							
	Solution						
	Semisolid DF						
Rectal							
	Suppositories						
	Rectal Enema						
	Rectal Capsules						



Suitability and Preference

EMA Reflection Paper, Formulations of Choice for the Paediatric Population (2005)

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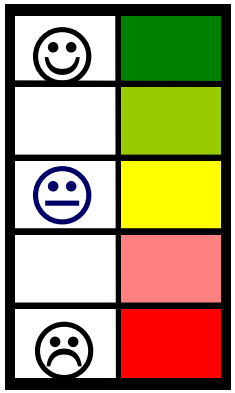
Paediatric Dosage Forms of Choice (2)

Route	Dosage Form	*Preterm newborn infants*	*Term newborn infants*	*Infants and Toddlers*	*Children (pre-school)*	*Children (School)*	*Adolescents*
			(0d-28d)	*(1m-2y)*	*(2-5y)*	*(6-11y)*	*(12-16/18y)*
Topical/Transdermal							
	Ointment, Cream, Gel						
	Liquid DF						
	Transdermal Patch						
Parenteral							
	I.V. Solution						
	I.M.						
	S.C.						
	Pump System						
Pulmonary							
	Nebuliser						
	MDI/Spacer						
	DPI						
Ocular							
	Eye Drops						
	Semisolid DF						



Suitability and Preference

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Overview thoughts for paediatric dosage forms

So…..

⇒ A quite wide range of dosage forms and hence excipients needs to be considered

Key considerations for paediatric formulations are to minimize the use of excipients, understand the limitations of those types of excipient that can and are used and be able to justify their use at the dose levels involved.

General philosophy regarding excipients for paediatric dosage forms (1)

- **Ensure proper excipient pedigree and a secure supply chain**
  - Several historical examples of uncontrolled supply chains leading to dangerous and life-threatening changes to an excipient , sometimes fatalities
  - Need to track "chain of custody" from manufacture through to use, e.g. a "verified paper trail"
  - IPEC (International Pharmaceutical Excipients Council) Dec-2008 position paper is a relevant current reference: (www.ipecamericas.org)
- **Emphasis on safety – apply a benefit vs. risk balance assessment:**
  - Minimum age of target population
  - Maximum duration of therapy (e.g. acute or chronic?)
  - Double-check age-related safety of "established" (adult dosage form?) excipients
  - Novel excipients need comprehensive safety testing
  - Regulatory acceptability; global by first intent

General philosophy regarding excipients for paediatric dosage forms (2)

- **Justify inclusion and minimise number of excipients and quantity to be used:**
  - Especially younger age groups
  - Choose dosage forms that achieve this
  - Not appropriate for purely aesthetic or cosmetic purposes
  - Avoid sucrose for long-term use
  - Can any taste issue be reduced without resorting to the use of additives? e.g. through dilution, pH control, API version selection (does reduced API solubility resolve the issue?)
  - Avoid biologically active excipients, e.g. preservatives, anti-oxidants, unless required dosage flexibility warrants inclusion. Use lowest feasible levels
  - Compliance with relevant regulations and be alert to the latest guidance

Solvents/Solvent sweeteners

- **Need for oral liquid preparations (that children typically find easier to swallow) often necessitates:**
  - Taste-masking; which often relies on sweeteners
  - Addition of co-solvents to improve drug solubility …if a solution is wanted (elegance/mouth feel vs. taste challenge)
- **Most commonly used solvent sweeteners are**
  - Propylene glycol
  - Glycerine (Glycerol)
- **However, note that it was historical adulteration of oral medicine with the orally toxic diethylene glycol (used in anti-freeze, brake and transmission fluids) that led to tragic consequences:**
  - Impetus for formation of US Food & Drugs Administration
  - Genesis of cGMP's
  - An issue that requires continuing vigilance

Solvents/Preservatives

- **Propylene Glycol Toxicity**
  - Propylene glycol (PG) is a general solvent with anti-microbial properties used in a wide range of pharmaceutical preparations including oral liquids, topicals and parenteral preparations
  - However, it's use in large volumes in children is very much discouraged:
    - PG has been associated with cardiovascular, hepatic, respiratory and CNS adverse events, especially in neonates where the biological half-life is prolonged (~17h) compared with adults (5h).
    - I.V. parenterals containing PG must be infused slowly
    - PG also has a laxative action at high oral doses through high osmotic pressure effects.

Solvents

- **Ethanol Toxicity**
  - Widely used as a co-solvent to aid solubility
  - In US, maximum permitted quantities in OTC products:
    - <0.5% for children under 6-years
    - <5% for children 6-12-years
    - <10% for children over 12-years
  - Acute (overdose) or chronic (long-term use) toxicity is possible
  - May cause adverse symptoms of intoxication, lethargy, stupor, coma, respiratory depression and cardiovascular collapse

- **Peanut Oil Toxicity**
  - Peanut oil is used as a food additive and as a solvent in intra-muscular injections
  - It has been suggested that the use of peanut oil in childhood (infant formula and topical preparations) can lead to later episodes of hypersensitivity, and therefore should be discontinued

Sweeteners

- **Saccharin**
  - Restricted regulatory acceptability
  - Poor aftertaste
  - Hypersensitivity reactions; mainly dermatologic
  - Paediatrics with allergy to sulphonamides should avoid saccharin
- **Aspartame Toxicity**
  - Source of phenylalanine – possibly an issue for phenylketoneurics
  - Aspartame has been blamed for hyperactivity in children but as yet unproven
- **Sorbitol**
  - Can induce diarrhoea

Anti-microbial Preservatives (1)

- **Benzyl Alcohol toxicity in neonates**
  - Widely used as a preservative in cosmetics, foods and pharmaceuticals (including injectables and oral liquids)
  - Toxic syndrome observed in neonates – it was attributed to the practice of "flushing out" umbilical catheters with solutions containing benzyl alcohol (BA), because of trace levels of benzaldehyde that were present
  - Dilution of nebulisation solutions with BA-preserved saline led to severe respiratory complications and even death in neonates. Attributed to accumulation of BA due to an immature metabolic capability.

  ⇒ Only dilute inhaled solutions with non-preserved, sterile diluents

Anti-microbial Preservatives (2)

- **Sodium Benzoate toxicity**
  - Widely used as a preservative in cosmetics, foods and pharmaceuticals (including injectables and oral liquids)
  - Injectable combinations of Na Benzoate and Caffeine should not be used in neonates; found to elicit non-immunological contact reactions, including urticaria and atopic dermatitis
  - Limitation on dosing of Na benzoate to neonates - ⩽10mg/kg/day – due to immature metabolic capability
- **Thimerosal toxicity**
  - Formerly widely used as a preservative in cosmetics, in soft contact lens solutions and pharmaceuticals (primarily vaccines)
  - Being phased out from most paediatric vaccines as better options emerge
  - Possible links with toxicity in paediatric vaccines, e.g. childhood autism, have been discounted after much debate

Diluents/Fillers

- **Lactose toxicity (immature metabolism)**
  - Lactose occurs widely in dairy products and is used in infant feed formulae.
  - In pharmaceutical preparations it is widely used as a diluent in tablets and capsules, in lyophilised powders, as a sweetener in liquid formulations and as a carrier in dry powder inhalation products.
  - Lactose intolerance occurs when there is a deficiency in the intestinal enzyme lactase, leading to GIT build-up of lactose. There is then the risk of abdominal bloating and cramps.
  - Lactase is normally present at high levels at birth, declining rapidly in early childhood (4-8 years) . Hypolactasia (malabsorption of lactose) can thus occur at an early age and, furthermore, this varies among different ethic groups.
  - Significant lactose intolerance can also occur in adults but this is rare.

“E number” Additives

(Colourants, preservatives, stabilisers, anti-oxidants, etc.)

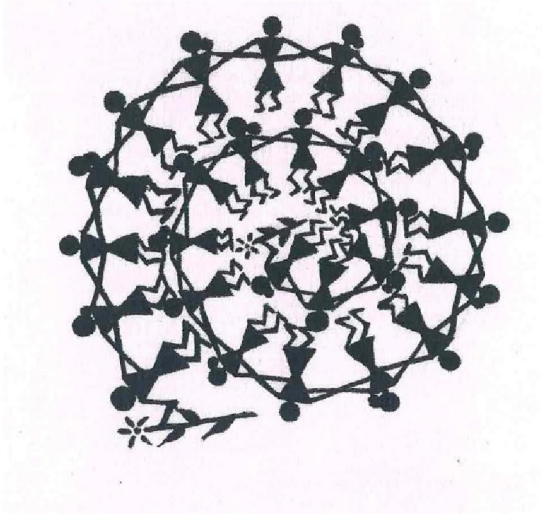
- **Current high profile concerns...**
  - Some opinion that additives in processed foods are linked to children's allergies.
  - Particular attention has been paid to infants and children's products because their immature organs are less efficient at removing such toxins from their systems.
  - Certain combinations of the following artificial food colours: sunset yellow (E110), quinoline yellow (E104), carmoisine (E122), allura red (E129), tartrazine (E102) and ponceau 4R (E124) have been linked to a negative effect on children’s behaviour.

Basic message: maintain good awareness of regulatory status of these materials in designing your paediatric drug formulation and don’t use them if you cannot justify it.

Summary of talk

- **Overview of excipients commonly used in medicines** (particularly in oral dosage forms)
  - **Role of Key Solid Dose Excipients**
  - **Role of Key Solution/Suspension Excipients**
- **Paediatric considerations with regard to excipients**

THANK YOU!



Glossary of Abbreviations (1)

ADI	-	Acceptable daily Intake
API	-	Active Pharmaceutical Ingredient
ARV	-	Anti-Retroviral
BA	-	Benzyl Alcohol
cGMP	-	Current Good Manufacturing Practice
CNS	-	Central Nervous System
d	-	Days
DF	-	Dosage Form
DPI	-	Dry Powder Inhaler
EMA	-	European Medicines Agency (was EMEA)
FDC	-	Fixed Dose Combination
GIT	-	Gastro-Intestinal Tract
HPMC	-	Hydroxypropyl Methylcellulose

Glossary of Abbreviations (2)

IM	-	Intramuscular
IV	-	Intravenous
Na	-	Sodium
ODT	-	Oro-Dispersible Tablet
OTC	-	Over the Counter
ppm	-	Parts per million
PEG	-	Polyethylene Glycol
PG	-	Propylene Glycol
PVP	-	Polyvinyl Pyrrolidone
SC	-	Subcutaneous
SiO_2	-	Silicon Dioxide
y	-	Years