“How Sweet is the Medication?”
“A Robust Encapsulation Solution with Focus on Pediatric Dosage Delivery”

Pediatric Formulations
Major US & EU Regulatory Milestones

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Labeling Rule</td>
<td>Pediatric Rule FDAMA: Food and Drug Administration Modernization Act</td>
<td>BPCA: Best Pharmaceuticals For Children Act</td>
<td>PREA: Pediatric Research Equity Act</td>
<td>FDAAA: Food and Drug Administration Amendments Act</td>
</tr>
<tr>
<td>Supplemental NDA required to label drugs for pediatric use</td>
<td>Specific drugs required additional Label information for pediatric use</td>
<td>Exclusivity incentives, public disclosure of study results</td>
<td>Requires Pediatric formulation development assessment unless waived</td>
<td>Pediatric Review Committee (PeRC) established to provide framework for Pediatric development plans</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EMEA Round Table</td>
<td>ICH Discussion</td>
<td>Guideline ICH E11</td>
<td>Consultation Paper</td>
<td>Pediatric Regulation Agreed</td>
<td>Pediatric Regulation Enforced</td>
</tr>
<tr>
<td>Incentives for pediatric development</td>
<td>Guidelines for pediatric clinical investigations</td>
<td>Better Medicines for Children via pediatric regulatory actions</td>
<td>Remedy unauthorized pediatric med use</td>
<td>New legislation implemented governing development &amp; authorization of pediatric drugs</td>
<td></td>
</tr>
</tbody>
</table>

Drug Development for Pediatric Populations: Regulatory Aspects; J. Zisowsky, A. Krause & J. Dingemanse; Pharmaceutics 2010, 2, 364-388
Pediatric Formulations are Challenging

- Diversity of Dosing
  - Infants to Adolescents
  - Accurate measurement

- Excipient Selection
  - Regulatory acceptance
  - Safety in children

- Patient Compliance
  - ODTs / Minitabs
  - Syrups / Suspensions
  - Thin film delivery systems

- Sugar-Free vehicles
  - Diabetics
  - Tooth caries prevention

- Stability
  - Chemical
  - Physical
  - Microbial

- Palatability
  - Taste / Odor masking
  - Flavors
  - Sweeteners

- Administration
  - Need for Refrigeration
  - Clean water for reconstitution

POLYOLS: Versatile Excipients for Pediatric Delivery

- Solid Dosage
  - ODT, Chewables, Gummies, Soft-gels

- Liquid Orals
  - Syrups
  - Dry & Ready to Use Suspensions

- Regulatory Safety
- Enhance Flavors
  - Cooling Effect
- Sugar-free Sweetness
  - Noncariogenic
  - Diabetic friendly

- Physical & Chemical Stability
Acceptability of Solid & Liquid Dosage Forms vs. Age

Survey of 873 children showed that 89% (n=870) preferred Orapred ODT® over liquid versions.

How are ODTs Formulated?

**Wet Granulation**

- **Powdered Mannitol** → Wet granulation w/ API + Excipients → Add Superdisintegrant (Crosspovidone)

**Direct Compression**

- **Spray Dried Mannitol** → Dry Blend API + Other Excipients → Add Superdisintegrant (Crosspovidone) → Compressed ODT

**ODT Platforms**

- **All-In-One Mannitol (Binder + Disintegrant)** → Dry Blend API + Other Excipients
ODTs By Direct Compression

ANTI-OXIDANT ORAL DISINTEGRATING TABLETS WITH RESVERATROL, VIT B2, B6 & B12

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% (by weight)</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEARLITOL™ 200SD</td>
<td>82.75</td>
<td>331.0</td>
</tr>
<tr>
<td>Kelledon® CL-SF (BASF)</td>
<td>8.00</td>
<td>32.0</td>
</tr>
<tr>
<td>Resvida® Resveratrol 99% pure (DSM)</td>
<td>5.00</td>
<td>20.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.50</td>
<td>6.0</td>
</tr>
<tr>
<td>FD&amp;C Red # 40 lake</td>
<td>1.00</td>
<td>4.0</td>
</tr>
<tr>
<td>Vit B2</td>
<td>0.748</td>
<td>3.0</td>
</tr>
<tr>
<td>Vit B6</td>
<td>0.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Sucrose</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Cherry Berry Flavor (FONA)</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Vit B12</td>
<td>0.002</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>400</strong></td>
</tr>
</tbody>
</table>

Tablet weight: 400mg
Tablet hardness: 120N
Friability: 0.02%
Oral disintegration time: 28sec

CLAIMS:
Anti-oxidant and Vitamin supplement

Pediatric Minitabs: Acceptability

### IMPURITIES !!

<table>
<thead>
<tr>
<th>Impurity</th>
<th>Excipient</th>
<th>Level (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroxides</td>
<td>Povidone</td>
<td>30-70</td>
</tr>
<tr>
<td></td>
<td>Crospovidone</td>
<td>100-400</td>
</tr>
<tr>
<td></td>
<td>Hydroxypropyl cellulose</td>
<td>20-60</td>
</tr>
<tr>
<td></td>
<td>Polysorbates</td>
<td>10-250</td>
</tr>
<tr>
<td></td>
<td>MW PEGs</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>MCC</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Lactose</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pre-gelatinized starch</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Sodium starch glycolate</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Croscarmellose sodium</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Magnesium stearate</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Stearic acid</td>
<td>3</td>
</tr>
<tr>
<td>Formic acid</td>
<td>HPC</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>MCC</td>
<td>10-20</td>
</tr>
<tr>
<td></td>
<td>Tracelitin</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Polyvinyl alcohol</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Croscarmellose sodium</td>
<td>25</td>
</tr>
<tr>
<td>PEGs</td>
<td>Povidone</td>
<td>10-86</td>
</tr>
<tr>
<td></td>
<td>HPC</td>
<td>10-15</td>
</tr>
<tr>
<td></td>
<td>MCC</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Tracelitin</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Polyvinyl alcohol</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Pre-gelatinized starch</td>
<td>10-100</td>
</tr>
</tbody>
</table>

### All-in-One ODT Platform

- **DC Co-processed Excipient**
  - Mannitol + Starch

- **Regulatory Acceptance**
  - Mix of Compendial Excipients

- **Creamy Mouth feel**
- **Fast Disintegration**
  - NO Superdisintegrants

- **Mannitol + Starch**

- **Superior Stability**
  - No Peroxides
  - Low Hygroscopicity

- **Licensing Fees**
- **Patent Restrictions**
What is PEARLITOL® Flash?

Co-spray dried Combination (NO Superdisintegrants)!!

80% Mannitol + 20% Corn Starch

Excellent Stability
- Chemical Inertness
- Low Hygroscopicity

Added Functionality
- Fast Disintegration
- Creamy Mouthfeel
- Self Lubricant

PEARLITOL® Flash Disintegration
No Significant Effect of Tablet Hardness

Pearlitol® Flash:
Quick disintegration (20-30 sec) with low friability
DT is independent of compression force and hardness

Competitive ODT Platform:
Disintegration dependent on tablet hardness
Acceptable hardness and friability
Polyols: "Sugar-free" Sweetness & Cooling Effect

**Sweetness Index**

- Sugar-free Nature
  - Allows use in "diabetic" patients
  - Prevents tooth caries in children

**Temperature Drop (°C)**

- Cooling effect of polyols enhances flavor & freshness

---

Polyols: Excellent Chemical Stability in Solid & Liquid Forms

**SUGARS (-ose)**
- Glucose, Maltose, Mannose, Xylose

**POLYOLS (-ol)**
- Sorbitol, Maltitol, Mannitol, Xylitol

Polyols are chemically INERT excipients & provide high chemical stability to formulations
Stability of low concentrations of guanine-based antivirals in sucrose or maltitol solutions.

Ashish A. Joshi, Ph.D. – Pediatric Formulations

Abstract

Three guanine-based antiviral drugs, entecavir, lovirab, and ayoclovir showed degradation in the presence of sucrose in ready-to-use solutions held at 50 degrees C. with more degradation at pH 4 than at pH 6 or 7. LC-MS analysis of the solutions showed isomeric adducts of the drugs and reducing sugars. Maltose, a disaccharide and a non-reducing sugar, was the source of monosaccharides, the reducing sugars. Sucrose showed pH-dependent hydrolysis at 50 degrees C. into two monosaccharides, fructose and glucose, with more sucrose hydrolyzing at pH 4 than pH 6 or 7. Additionally, the tests showed pH-dependent degradation at 50 degrees C in fructose and glucose solutions with the following rank order: pH 4 > pH 6 > pH 7. This indicated that the increased degradation of the drug in sucrose solutions at pH 4 was mainly due to more hydrolysis of sucrose into fructose and glucose compared to pH 6 or 7, and subsequent reactions of the fructose and glucose with the drugs. Based on the structures of the major degradation products, it was proposed that the main cause of the degradation was nucleophilic addition of the primary amine group of the drugs to the carbonyl group of the fructose and glucose. This reaction was facilitated as the solution pH increased from 4 to 7. All the drugs showed satisfactory stability regardless of the storage temperature or solution pH in maltose, an alternate sweetener. The free amine or keto group in alcohol or ketone precursors is reduced to a hydroxyl group after the hydrolysis process making maltose less susceptible to nucleophilic addition.


Drug-excipient compatibility testing-identification and characterization of degradation products of phenylephrine in several pharmaceutical formulations against the common cold.


Zentiva, a.s. Praha, U Kabelovych 130, 102 37 Praha 10, Czech Republic, hplc@hplc.cz

Abstract

Different pharmaceutical preparations against the common cold containing phenylephrine (PHE) and saccharose were studied. New impurities were discovered in these preparations after exposure using isocratic ion-pair chromatography separation on a C18 column. LC-MS and NMR techniques were employed to identify these new compounds. The products were identified as 1-[5-(hydroxymethyl)-2-furyl]-2-methyl-1,2,3,4-tetrahydrosoconorin-4,6-diol and 1-[5-(hydroxymethyl)-2-furyl]-2-methyl-1,2,3,4-tetrahydrosoconorin-4,6-diol. Identification of these degradation products allowed to understand and to confirm their formation mechanism. The developed HPLC method separates all known impurities and impurities originated from PHE as well.


Polyols: No Toxicological Risk in Neonates and Infants <6 months age

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Administration</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzy alcohol</td>
<td>Oral, parenteral</td>
<td>Neurotoxicity, metabolic acidosis</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Oral, parenteral</td>
<td>Neurotoxicity</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>Parenteral</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Polysorbate 20 &amp; 80</td>
<td>Parenteral</td>
<td>Liver &amp; kidney failure</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Oral, parenteral</td>
<td>Seizures, neurotoxicity, hyperosmolarity</td>
</tr>
</tbody>
</table>

Important Info

May 2000

GiaxolWelcome

HIV: Potential safety concerns with the label amount of propylene glycol in AGINARIDE®

- BOXED WARNING (new statements to the box are underlined)

*AGINARIDE* contains propylene glycol. 

- BOXED WARNING (new statements to the box are underlined)

AGINARIDE (zidovudine) is a potent antiviral agent that is indicated for the treatment of HIV-1 infection. This information is based on analyses of plasma HIV-1 RNA, CD4+ cells in treated subjects up to 12 weeks in duration. At present, there are no studies from controlled trials using long-term suppressive therapy (HIV-1 RNA, in disease progression or AGINARIDE. Duration of the prophylactic effect: Sire for the label amount of the antigen propylene glycol. AGINARIDE (zidovudine) is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients with dialysis therapy (see CONTRAINDICATIONS AND WARNING).

AGINARIDE should be used only when AGINARIDE (zidovudine) capsules are not therapeutic options.

GiaxolWelcome Inc.


Ashish A. Joshi, Ph.D. – Pediatric Formulations
**Taste-Masking in Pediatric Liquid Oral Formulations**

**The Layer Cake Approach**

- **Primary Taste-masking Agent + API**
- **Sweetening Vehicle**
- **Flavors, Solubilizers**

**Grape, Bubble Gum Or Fruit Flavors**

**Propylene Glycol**

**Sugars**
- Maltitol, Sorbitol
- Xylitol
- Glycerin

**Cyclodextrins**
- Maltodextrins
- Resins

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Adapted from: Woertz K., et al. J. Pharm. Sci. 100(10), 2011

---

**Cyclodextrin Water Solubility Determines End Use**

<table>
<thead>
<tr>
<th>Cyclodextrin</th>
<th>Aqueous Solubility</th>
<th>Major End Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native BCD KLEPTOSE®</td>
<td>1.85 g/100mL</td>
<td>Taste-masking, Convert Oily drugs to Powder</td>
</tr>
<tr>
<td>HPBCD KLEPTOSE® HPB</td>
<td>&gt; 65.0 g/100mL</td>
<td>Solubility &amp; Bioavailability Enhancement</td>
</tr>
</tbody>
</table>

**Anything that native BCD does, HPBCD can do it better!**
Taste-masking with Native β-cyclodextrin

**Wet Granulation**

- KLEPTOSE® β-CD (12% H2O) 58.6%
- Acetaminophen 19.2%
- LYCATAB® DSH (5.4% H2O) 5.0%

Dry mix Kleptose, Acetaminophen, add water and Lycatab DSH – Granulate (color may be added)

Dry granules in a fluid bed dryer

**Compression**

- Aspartame 2.4%
- Anhydrous citric acid 0.8%
- Vanilla flavor 4.8%
- Mg stearate 1.0%
- Water 8.2%

**Direct Compression with DC Kleptose**

- Dextromethorphan hydrobromide 1.67 20.0
- KLEPTOSE® DC β cyclodextrin 48.0 576.0
- PEARLITOL® SD 200 mannitol 47.13 565.6
- Blackberry flavor 0.70 8.4
- Aspartame 0.50 6.0
- Magnesium stearate 2.00 24.0

-----

1200 Tablets prepared by direct compression

- Weight 1.243 g
- Thickness 4.01 mm
- Density 1.218
- Hardness 173N

**Dextromethorphan chewable tablets**

**API-Cyclodextrin Complexation by Kneading**

**Acetaminophen chewable tablets**
Cyclodextrin Complexation End Point: By Torque measurement

Inactive Ingredients: acesulfame potassium; artificial grape flavor; betadex, NF; blue dye; colloidal silicon dioxide; lactose monohydrate; magnesium stearate; mannitol; microcrystalline cellulose; natural flavor; red dye (carmine).

Taste masked, sugar-free Dextromethorphan syrup

- Dextromethorphan hydrobromide: 1.33 g
- KLEPTOSE® β-CD (dry): 5.56 g
- LYCASIN® 80/55 maltitol solution: 840.00 g
- Sodium benzoate: 1.00 g
- Caramel flavor: 6.00
- Purified water: qs1000mL
Sodium Starch Glycolate
Immediate Dispersing Dry Suspension Viscosifier?

GLYCOLYS®
- Disperses immediately in water
- Swells ~300 times to a translucent gel

Immediate Dispersing Viscosifier in a Dry Suspension for reconstitution?
Vs.
Difficult to disperse Gums & Cellulosics

Pediatric Orodispersible Films (ODF)
Pea Starch: Easy to Use Alternative Polymer

- Each marketed ODF could contain upto 6 film forming polymers in combination
  e.g. Pullulan, HPC, HPMC, CMC, Pregel starch, Pectin, Carrageenan, Sodium alginate, Locust bean gum, Xanthan gum, Gum Arabic, Tapioca dextrin
- Complex and expensive formulation
- Many formulations are patented

EP/USP compliant Pea Starches allow formulating ODFs using only ONE polymer
PEA STARCH Has Excellent Film Forming Ability
Optimal Amylose : Amylopectin Ratio

Confers film forming properties
Causes starch retrogradation/gelation
Amylose rich starches difficult to pregelatinize

% Amylose | % Amylopectin
---|---
Standard maize | 24.0 | 76.0
Waxy maize | 0.8 | 99.2
High amylose maize | 70.0 | 30.0
Potato | 20.0 | 80.0
Rice | 18.5 | 81.5
Tapioca | 16.7 | 83.3
Yellow Peas | 35.0 | 65.0
Wheat | 25.0 | 75.0

Reduces Retrogradation/gelation

Pea Starch in Orodispersible Films (ODF)
Lab Scale Development

Vacuum Mixing
Apply solution to film casting equipment
Film Spreading
Drying @ 20°C
80% to 50%RH, 12hrs

LYCOAT®RS720 - 24.93 %
Lecithin - 4.99 %
Glycerin - 4.22 %
Ethanol - 1.44 %
Water - 64.43 %

Simple Formulation with LYCOAT® as the sole polymer
Pea Starch in Orodispensible Films (ODF)
Proven Performance on Commercial Scale Film Equipment

Coating width: 120 mm
Coating speed: 0.7 meter/min
Drying: Four drying zones: 55°, 65°, 65°, 55°C
Siliconized foil

Molecular Encapsulation
Cyclodextrins vs. Linear Amylose

<table>
<thead>
<tr>
<th>Cyclodextrine</th>
<th>Amylose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion Compound Coenzyme Q10 + β Cyclodextrine</td>
<td>Complex Stearic acid + Amylose</td>
</tr>
<tr>
<td>Q10 Vital 15% (Valens, Slovenia)</td>
<td>6 AGU per turn to complex Stearic acid</td>
</tr>
<tr>
<td>Rigid Diameter</td>
<td>Flexible Chain Diameter</td>
</tr>
<tr>
<td>Defined molar ratio</td>
<td>6 – to 8 AGU possible</td>
</tr>
<tr>
<td></td>
<td>Flexible molar ratios</td>
</tr>
</tbody>
</table>
**Soluble Amylose Maltodextrin for Encapsulation**

Cold water soluble products with highest possible amylose content

- Pea starch, 40% Amylose
- Controlled Enzym. Hydrolysis
- Pea Maltodextrin
  - High Amylose Content
- Insoluble in cold water
  - Excessive Retrogradation
- Soluble in cold water
  - Limited Retrogradation

---

**Why Use Yellow Pea Maltodextrin?**

**KLEPTOSE® Linecaps**

Bypass limitations for use of cyclodextrins --

- Patent restrictions
- Regulatory restrictions (pediatric formulations)
- Low water solubility of Native cyclodextrins (syrup formulations)
- Label friendliness (food & nutraceutical use)

**KLEPTOSE® Linecaps (Pea Maltodextrin)**

- Taste/odor masking for Nutra/OTC/Pediatric (labeled as “maltodextrin”)
- Solubilization of nutraceutical actives
- Flavor encapsulation and protection
Yellow Pea Maltodextrins: Applications

Similar to applications of Cyclodextrins
- Solubility / bioavailability enhancement
- Taste/Odor masking
- Improve API stability

Method of use:
- Prepare a Dispersion of the “Amylose” in hot water
- Add the guest Molecule (e.g., 12% related on amyllose)
- Knead for 10 min
- Dry the paste

Yellow Pea Maltodextrins: Solubility Enhancement

Measured Drug solubilities [mg/ml] after autoclavage at 121°C

<table>
<thead>
<tr>
<th></th>
<th>Pure Water</th>
<th>Kleptose linecaps 17 [100mg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>0.32 ±0.05</td>
<td>0.70 ±0.06</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.09 ±0.01</td>
<td>0.60 ±0.04</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>0.22 ±0.04</td>
<td>0.39 ±0.02</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>15.94 ±1.14</td>
<td>19.13 ±0.55</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>4.45 ±0.23</td>
<td>4.51 ±0.51</td>
</tr>
</tbody>
</table>

Pea Maltodextrins provide good solubility improvement for steroidal molecules
Yellow Pea Maltodextrins: Taste/Odor Masking

Measured using Electronic Tongue: Taste sensing system equipped with 7 lipid membrane sensors
Umami, Saltines, Sourness, Astringency, Bitterness 1, (cat. subst.), Bitterness 2, (cat. subst.) and Bitterness 3 (anionic subst.)

Yellow Pea Maltodextrins: Taste Masking

Multivariate data analysis for all bitter sensors Simca-P V12.0.1

Drug free formulations
HPBCD
Pea Maltodextrin (Linecaps)
Regular Maltodextrin (Glucidex® 12)

Drug loaded formulations

Not much effect observed with regular maltodextrins
Strong masking observed with HPBCD and Pea Maltodextrin
Dimenhydrinate ODFs: Tastemasking with Pea Maltodextrins

- ODFs were prepared using Pregel Hydroxypropyl Pea Starch (Lycoat® RS720)
- Pea Maltodextrin & Cyclodextrins were used as Solubilizers/Tastemasking agents

Results:
Cyclodextrins & Pea maltodextrin improved solubility of API preventing recrystallization
Safe and cost-effective Pea maltodextrin not only ensured uniform drug distribution, but also improved the taste of dimenhydrinate ODFs
Maltodextrins are considered as safe food ingredients and also for use in infant formulas
Pea maltodextrin could thus be an interesting and safe tastemasking agent for pediatric use

Enabling Pediatric Formulations

- Diversity of Dosing
  - Infants to Adolescents
  - Accurate measurement

- Excipient Selection
  - Regulatory acceptance
  - Safety in children

- Patient Compliance
  - ODTs / Minitabs
  - Syrups / Suspensions
  - Thin film delivery systems

- Sugar-Free vehicles
  - Diabetics
  - Tooth caries prevention

- Stability
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  - Physical
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