DRY SYRUPS

SEMINAR BY
SWAPNA.M
M.PHARMACY
1st semester

DEPARTMENT OF PHARMACEUTICS
UNIVERSITY COLLEGE OF PHARMACEUTICAL SCIENCES
KAKATIYA UNIVERSITY, WARANGAL
• DEFINITION
• CHARACTERISTICS OF SUSPENSIONS FOR RECONSTITUTION
• COMMONLY USED INGREDIENTS
• PREPARATION OF DRY MIXTURE
• STABILITY CONSIDERATIONS
• GUIDELINES FOR STABILITY TESTING
• CONCLUSION
• REFERENCES
Dry Syrups

Definition

Dry powders for oral suspension are powder mixtures that require the addition of water (reconstitution) at the time of dispensing and are mostly for paediatric use. These are called dry syrups or reconstitutiable oral suspensions.

Rationale

• Inadequate chemical stability of the drug in the aqueous vehicle.
• Avoid the physical stability problems like viscosity changes, conversion of polymorphic form, incompatibility, crystal growth, caking.
• Reduces the weight of final product because the aqueous vehicle is absent

• Shipped without regard to seasonal temperatures
Required characteristics of Suspensions for reconstitution

- Powder blend must be a uniform mixture of the appropriate concentration of each ingredient.
- During reconstitution the powder blend must disperse quickly and completely in the aqueous vehicle.
- Reconstituted suspension must be easily redispersed and poured by the patient to provide accurate and uniform dose.
- Final product must have an acceptable appearance, odor, and taste.
### Commonly used Ingredients

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Infrequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspending agent</td>
<td>Anticaking Agent</td>
</tr>
<tr>
<td>Wetting agent</td>
<td>Flocculating agent</td>
</tr>
<tr>
<td>Sweetener</td>
<td>Solid diluent</td>
</tr>
<tr>
<td>Preservative</td>
<td>Antifoaming agent</td>
</tr>
<tr>
<td>Flavor</td>
<td>Granule binder</td>
</tr>
<tr>
<td>Buffer</td>
<td>Granule disintegrant</td>
</tr>
<tr>
<td>Color</td>
<td>Antioxidant</td>
</tr>
<tr>
<td></td>
<td>Lubricant</td>
</tr>
</tbody>
</table>

- Number of ingredients should be kept minimum.
- An ingredient that performs more than one function – Sucrose
- All ingredients should disperse rapidly on reconstitution.
# Typical Reconstitutable Oral Suspensions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin trihydrate</td>
<td>SmithKline</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Beecham</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Biocraft</td>
</tr>
<tr>
<td>Dicloxacillin sodium</td>
<td>Dista</td>
</tr>
<tr>
<td>Erythromycin ethylsuccinate</td>
<td>Apothecan</td>
</tr>
<tr>
<td>Pencillin V potassium</td>
<td>Abbott</td>
</tr>
<tr>
<td>Ampicillin and Probenecid</td>
<td>Lilly</td>
</tr>
<tr>
<td></td>
<td>Biocraft</td>
</tr>
</tbody>
</table>

- Nearly all drugs formulated as reconstitutable oral suspensions are antibiotics
- Sodium dicloxacillin is water soluble, it is formulated as an insoluble form in suspension to help mask the odor and taste
Suspending agents suitable for use in Suspensions for Reconstitution

- Acacia
- Carboxy methylcellulose sodium
- Iota carrageenan
- Microcrystalline cellulose with sodium CMC
- Povidone
- Propylene glycol alginate
- Silicon dioxide, colloidal
- Tragacanth
- Xanthan gum

• Suspending agents should be easily dispersed by vigorous hand shaking during reconstitution.

• Combination of microcrystalline cellulose and sodium CMC is a common suspending agent.
Natural gums

• Anionic and include exudates of tree and extracts from seaweed e.g. Carrageenan and alginates.

• Alginates produce highly viscous solutions and the iota carrageenanans produce thixotropic dispersions.

• Acacia and tragacanth have been used as suspending agents for many years.

Disadvantage: Variation in color, viscosity, gel strength and hydration rate.

Xanthan gum

• Common suspending agent in suspensions for reconstitution.

• Produced by microbial fermentation, good batch-to-batch uniformity and few microbial problems.

Required concentrations for rapid dispersion during reconstitution must be determined for each suspending agent.
Sweeteners

- Sweeteners can mask the unfavorable taste and enhance patient acceptance in the pediatric population that uses this product.
- Any increased viscosity as a result of the sweetener aids suspension of the drug particles.
- Sucrose can perform both above functions of sweetener and suspending agent, and serve as a diluent in the dry mixture.
- Others include Mannitol, Dextrose, Aspartame, Sodium saccharin
Wetting Agents

- Drugs in suspension are hydrophobic, repel water and are not easily wetted.

- Surfactants are commonly used to aid in the dispersion of hydrophobic drugs.

- Excess wetting agent can produce foaming and impart an unpleasant taste.

- Polysorbate 80 is a common wetting agent. Nonionic and is chemically compatible with both cationic and anionic excipients and drugs. Used in concentrations $\leq 0.1\%$.

- Another common wetting agent is sodium lauryl sulfate. Anionic and may be incompatible with cationic drugs.
Buffers, Preservatives, Flavors & Colors

- Buffers are used to maintain the optimum pH for all ingredients.
  - Sodium citrate buffer.

- Preservatives are required in most suspensions because the suspending agents and sweetener are often good growth media for microorganisms.
  - Sucrose in sufficient concentrations (60% w/w)
  - Sodium benzoate

- Natural and Artificial flavors – Raspberry, Pineapple

- FD&C Red No 40 and Yellow No 6.

Common problem in dry mixtures is poor powder flow and caking
  - Anticaking agents, Amorphous silica gel
Preparation of Dry Mixture

- Powder Blends
- Granulated Products
- Combination Products
Mixing the ingredients of the dry mixture in powder form.

Ingredients present in small quantities may require a two stage mixing operation.

Mixer should rapidly and reliably produce a homogeneous mixture.

Advantages
• Least capital equipment and energy
• Least likely to have chemical and stability problems because no heat or solvents are used.
• Low moisture content can be achieved in dry mixture.

Disadvantages
• Prone to homogeneity problems – Particle size and Powder flow
• Loss of the active ingredient during mixing
• Potent drug used in very low concentrations
Granulated Products

• Wet granulation is the usual process and granulating fluid is water or an aqueous/nonaqueous binder solution.

• Drug can be dry blended with other ingredients or it can be dissolved or suspended in the granulating fluid.

• Solid ingredients are blended and massed with granulating fluid in a planetary mixer.

• Wet mass is formed into granules: Vibratory sieve, Oscillating granulator or mill.

• Granules dried in a tray oven or Fluid bed drier.

• Dried granules screened in a vibratory seive or oscillating granulator to break up or remove aggregates or granules.
Granulated Products

**Advantages**
- Improved appearance
- Improved flow characteristics
- Less segregation problems
- Less generation of dust during filling operations

**Disadvantages**
- More capital equipment and energy
- Difficult to remove the last traces of granulating fluid, reduce the stability
- Uniform granulation is necessary, excess of very small particles, or fines, will result in rapid segregation.
Combination Product

- Less energy and equipment for granulation may be required if majority of the diluent can be added after granulation.
- Heat sensitive ingredients, such as flavors can be added after drying of granules.
- First to granulate some of the ingredients and blend the remaining ingredients with the dried granules before filling into container.

**Disadvantages**
- Risk of nonuniformity
- Particle sizes of various fractions should be carefully controlled.
## Advantages and Disadvantages of types of Dry mixtures

<table>
<thead>
<tr>
<th>Type</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Powder blend</strong></td>
<td>Economy, Low incidence of instability</td>
<td>Mixing &amp; Segregation problems, Losses of drugs</td>
</tr>
<tr>
<td>Granulated Products</td>
<td>Appearance, Flow characteristics, Less segregation, Less dust</td>
<td></td>
</tr>
<tr>
<td>Combination product</td>
<td>Reduced cost, Use of heat sensitive ingredients</td>
<td>Cost; Effects of heat &amp; granulating fluid on drug and excipients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ensuring nonsegregating mix of granular and nongranular ingredients</td>
</tr>
</tbody>
</table>
Recommended Guidelines for processing the Dry mixture

- Use efficient mixing.
- Determine an adequate duration of mixing time.
- Avoid accumulation of heat and moisture during mixing.
- Limit temperature/humidity variations (70°C at ≤ 40% RH)
- Finished batch should be protected from moisture.
- Sample for batch uniformity.
PHYSICAL STABILITY

• Physical stability should evaluate both the dry mixture and reconstituted suspension.

• Common evaluations on reconstituted suspensions include Sedimentation volume and ease of redispersion.

• exposure to a cycle of temperature changes (Freeze and Thaw).
Stability of Dry Mixtures

CHEMICAL STABILITY

- Chemical stability should be determined in both the dry mixture and reconstituted suspension.

- Both should be examined not only at controlled room temperature but also at temperatures of potential exposure such as during shipment or storage of the product.

- Stability evaluations of reconstituted oral suspensions should be conducted in a container of the same material and size in which the product is marketed.

- Effectiveness of the preservative is determined by challenge tests.

- Drug products are often exposed to elevated temperatures for the determination of a shelf-life (i.e., accelerated stability studies).
A screen based on temperature is a common test.

Samples of the reconstituted suspension are stored in containers at room temperature, 37°, and 45°C.

- Evaluated monthly for up to 4 months and should include:
  - Chemical analysis for drug and preservative
  - Preservative challenge test at the initiation and conclusion of the study
  - Appearance compared to that of sample stored at 2° to 5°C
  - Viscosity
  - Homogeneity
  - pH
  - Sedimentation volume
  - Ease of redispersion
• **Freeze-thaw test**

Conducted by placing the sample in a freezer for 18 hours followed by thawing at room temperature for 4 to 6 hours. Evaluate the appearance and conduct any other appropriate tests at this time.

Repeat the Freeze-Thaw cycle for up to 10 times

• **Full-Scale Stability**

Final formulation should be placed in the container for marketing and should be stored at 2° to 5°, RT, 37°, and 45°C.
<table>
<thead>
<tr>
<th>Ingredient function</th>
<th>Product 1</th>
<th>Product 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>Amoxicillin trihydrate</td>
<td>Amoxicillin trihydrate</td>
</tr>
<tr>
<td>Sweetener</td>
<td>Sucrose</td>
<td>Sucrose, Mannitol Cellulose, Na CMC</td>
</tr>
<tr>
<td>Suspending agent</td>
<td>Xanthan gum</td>
<td>Cellulose, Na CMC</td>
</tr>
<tr>
<td>Desiccant</td>
<td>Silica gel</td>
<td>Sodium Citrate</td>
</tr>
<tr>
<td>Buffer</td>
<td>Sodium Citrate</td>
<td>Sodium Citrate</td>
</tr>
<tr>
<td>Preservative</td>
<td>Sodium benzoate</td>
<td></td>
</tr>
<tr>
<td>Colorant</td>
<td>FD&amp;C Red N0.3 Flavors</td>
<td>FD&amp;C Red N0.40 Artificial flavors</td>
</tr>
<tr>
<td>Flavor</td>
<td>Flavors</td>
<td></td>
</tr>
</tbody>
</table>
The dry syrup preparation is suitable not only for children but also aged persons in view of easier administration.

Particularly dry syrup preparation is advantageous because it is easily weighed and packaged and further it is convenient for carrying.
References


Thank U