DRY SYRUPS

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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 reconstitutable 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

Frequent

Suspending agent
Wetting agent
Sweetener
Preservative
Flavor
Buffer
Color

Infrequent

Anticaking Agent
Flocculating agent
Solid diluent
Antifoaming agent
Granule binder
Granule disintegrant
Antioxidant
Lubricant

- 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

Drug	Manufacturers
Amoxicillin trihydrate	SmithKline Beecham
Ampicillin	Biocraft
Cephalexin	Dista
Dicloxacillin sodium	Apothecan
Erythromycin ethylsuccinate	Abbott
Pencillin V potassium	Lilly
Ampicillin and Probenecid	Biocraft

- 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 carrageenans 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 concenrations $\leq$ 0.1 %.
- Another common wetting agent is sodium lauryl sulfate. Anionic and may be incompatible with cationic drugs.

Other ingredients

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 sufficent 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**

Powder Blends

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

Type	Advantage	Disadvantage
Powder blend	Economy Low incidence of instability	Mixing&Segregation problems Losses of drugs
Granulated Products	Appearance Flow characteristics Less segregation Less dust	Cost; Effects of heat & granulating fluid on drug and excipients
Combination product	Reduced cost Use of heat sensitive ingredients	Ensuring nonsegregating mix of granular and nongranular ingredients

Processing the Dry Mixture

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.**

Stability of Dry Mixtures

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).

Guidelines for Stability Testing

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.

Comparison of Ingredients in Two Commercial Amoxicillin Suspensions for Reconstitution

Ingrdient function	Product1	Product2
Active Ingredient	Amoxicillin trihydrate	Amoxicillin trihydrate
Sweetener	Sucrose	Sucrose, Mannitol
Suspending agent	Xanthan gum	Cellulose, Na CMC
Desiccant	Silica gel	
Buffer	Sodium Citrate	Sodium Citrate
Preservative	Sodium benzoate	
Colorant	FD&C Red N0.3	FD&C Red N0.40
Flavor	Flavors	Artificial flavors

conclusion

- **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

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