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Review Article

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Dry Syrup: A Comprehensive Review

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Abstract: The oral dosage forms are most popular because of their ease of administration, patient compliance, and formulation stability. Tablets and capsules, the most popular oral dosage form, have the drawback of difficulty swallowing the dosage form specially developed for pediatric and geriatric patients. In recent times the, modern scientific and technological advancement in pharmaceutical field has created a bank of interest in the reconstitutable oral suspension (Dry syrup). Dry syrups are the dry mixtures that require adding water at the dispensing time. Dry syrups show adequate chemical stability of drug during shelf life and reduce the final product's weight. Moreover, dry syrups show higher bioavailability than tablets and capsules as they disintegrate in water outside the oral cavity and directly enter the gastrointestinal tract. Most of the drugs prepared as dry powders for oral suspensions are antibiotics. The present review gives an account of the excipients used, methods of preparation of dry syrup, their evaluation, and their packaging. When manufacturing dry syrup medicine, the dry mixture should have a uniform concentration of the required ingredients. This ensures that the drug does not break up into a non-homogeneous mixture when reconstituted, which may lead to errors in dosage. The items used in the manufacturing of dry syrup include excipients, granule disintegrating, granule binder and powder blends. Excipients are used to stabilize active ingredients for a long period. The type of excipient used is based on the suitability for reconstitution and the type of the powder the granule disintegrate helps ensure the dry syrup particles do not aggregate during reconstitution. The granule binder helps ensure that the dry syrup's particles settle in the suspension.

Keywords: Dry Syrup, Paediatrics, Mixing, Oral Administration, and Blending.

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1. INTRODUCTION

An oral route is the most preferred route of administration. Tablets and capsules are not suitable for administering high doses of active pharmaceutical ingredients and require administration of tablets and capsules several times, making it less patient compliance. Oral liquid suspensions are mainly formulated for pediatric and geriatric patients with difficulty swallowing. The reconstituted system is the choice of formulation when the drug stability is a significant concern [1].

2. DRY SYRUPS

Dry syrup may be defined as finely divided insoluble particles ranging from 0.5-5 µ, which is to be distributed in a suitable vehicle. Dry syrups are dry mixtures that require adding water while dispensing. Mostly antibiotics, pediatric and some moisture-sensitive drugs are available in the form of dry syrup. 2 Many preparations like Dicloxacillin sodium, Erythromycin ethyl succinate, and amoxicillin trihydrate etc are available as dry powder mixtures or granules that are suspended in water or some other vehicles before oral administration. The dry mix contains drug, sweeteners, suspending agents, colorants, flavours, stabilizing agents and preservatives that enhance the stability of the formulation. Dry syrup shows improved bioavailability compared to tablets and capsules as it is in a dispersed state at the time of administration. Although studies have shown that a dry mixture after the constitution in liquid is stable for 24 hours after preparation, it is recommended that suspension be consumed immediately after the preparation.[3]

2.1. Advantages of Dry Syrup[4]

- Easy to carry and more stable than other conventional dosage forms
- Appropriate unit dosage form
- Convenient to administer
- Suitable dosage form to pediatrics

2.2. Disadvantages of Dry Syrup[5]

- After reconstituting the dry syrup, upon storage caking may occurs.
- Chances of inaccuracy in single dosing.
- There is a possibility for deterioration of the dry syrup due to the effect of biphasic properties such as viscosity, redispersion, sedimentation rate etc

3. SUSPENSION

A pharmaceutical suspension is defined as a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase.

4. CLASSIFICATION OF SUSPENSION[6]

4.1. Based On Route of Administration

- Oral suspension
- Topical suspension
- Parenteral suspension

4.2. Based On Proportion of Solid Content

- Dilute suspension (2 to10%w/v solid)
- Concentrated suspension (10 to 50% w/v solid)

4.3. Based On the Electro Kinetic Nature of Solid Particles

- Flocculated suspension
- Deflocculated suspension

4.4. Based On Size of Solid Particles

- Colloidal suspension (< 1 micron)
- Coarse suspension (>1 micron)
- Nano suspension (10 ng)

4.5. Based On Method of Administration

- Dry powder for reconstitution
- Ready to use suspension

4.6. Based On Release

- Conventional suspension

5. DESIRED ATTRIBUTES FOR RECONSTITUTED SUSPENSION[7]

5.1. The Dry mixture must contain an appropriate concentration of each ingredient. If the mixture is non-uniform it results in an inappropriate dose.
5.2. The powder blend must be readily and rapidly dispersed in aqueous vehicle.
5.3. The reconstitution must be easy and readily pourable by the patient to provide an accurate dose.
5.4. The high viscosity caused by the refrigerated storage temperature after reconstitution should not disturb the dose administered by the patient.
5.5. Final product should have an acceptable taste, odour and appearance.

6. REASONS FOR FORMULATION OF RECONSTITUTED SUSPENSIONS[8]

6.1. Oral Reconstituted suspension shows more bioavailability than tablets and capsules as they enter the gastrointestinal tract.
6.2. These reconstituted suspensions avoid physical stability problems like incompatibility of ingredients, and increased drug solubility due to changes in PH, caking and crystal growth.
6.3. The final product of this suspension has reduced weight because the aqueous vehicle is absent, which makes transportation expenses cheaper.
6.4. Safe and convenient for pediatric and geriatric patients.
6.5. This suspension is suitable for insoluble or poorly soluble active pharmaceutical ingredients.

7. EXCIPIENTS USED[9]

Excipients should be selected based on the suitability for reconstitution and physical type of the powder mixture.

- The number of excipients used should be minimum as there may be the possibility of problems like compatibility problems due to the more significant number of excipients used.

- A simple method to reduce the number of excipients is to use the excipients which perform more than one function. E.g., Sucrose is used as a sweetener, suspending agent, and diluent.
- All the excipients should disperse rapidly on reconstitution.

7.1. Granule Disintegrant

It prevents particle aggregation.

7.2. Granule Binder

It reduces the settling down of particles in suspension. Example-povidone (high molecular weight).

7.3. Suspending Agents

During reconstitution suspending, agents should be easily dispersed, which rules out several common suspending agents because they require hydration, elevated temperature or high shear mixing for adequate dispersion. Some suspending agents are acacia, microcrystalline cellulose, carboxy methyl cellulose, tragacanth and xanthan gum. Xanthan gum is the most commonly used suspending agent in this type of suspension.

7.4. Sweeteners

Sweeteners are generally used to mask the unpleasant taste and enhance the patient acceptance. Some drugs have bitter and bland taste. Inorder to mask this taste sweetener are used. Example-Sucrose, mannitol, dextrose

7.5. Wetting Agents

Many drugs in suspensions are not easily wetted as they are hydrophobic. An appropriate wetting agent must be selected to obtain optimum drug dispersion at the lowest effective concentration. Excess wetting agent results in foaming and impart an unpleasant taste. Example- Sodium lauryl sulphate, polysorbate 80.

7.6. Other Excipients

Other excipients are

7.7. Buffers

These are used to maintain the optimal PH for all the excipients.

Example - sodium citrate is the most commonly used buffer.

7.8. Preservatives

These are most commonly used because sweetener and suspending agent act as good growth media for micro-organisms. However, the choice of preservatives should be limited because most of the ingredients require an extended time period for dissolution at room temperature. Example - Sorbic acid. Common preservatives used are sodium benzoate and sodium propionate.

7.9. Flavours

It enhances the patient acceptability of the product. Available in both natural and artificial flavours.

7.10. Colourants

Used to provide aesthetic appearance to final suspension. Example- FD and C

7.11. Anticaking Agents

The most common problem in dry mixture is caking and poor powder flow. This is due to moisture uptake and powder agglomeration. So, these agents remove moisture from the powder blend, improve flow property, and prevent caking.

8. PREPARATION OF DRY MIXTURE[10-12]

1. Powder blends
2. Granulated products
3. Combination product

8.1. Powder Blends

These are called powder mixtures, prepared simply by mixing the Excipients of dry mixture in powder form. The excipients which are present in small quantities require a two-stage mixing operation. The first stage is small quantities of excipients mixed with a portion of significant excipients to aid in their dispersion. The second stage comprises of mixing the remaining excipients. The equipment mixer selected should produce a homogenous mixture.

Types of mixers used are:

1. Dry mixer
2. Paddle mixer
3. Vertical screw mixer
4. Double cone mixer
5. Tumbling mixer
6. V-blender

8.1.1. Dry Mixer

The dry mixer is commonly used for batch work. It consists of a semi-cylindrical trough, and is provided with two or more ribbon spirals. One spiral is right-handed and other is left-handed so the material moves back and forth in the trough. A broad ribbon lifts and moves the material, while the narrow one will cut materials while conveying. Ribbon blenders are adapted for continuous mixing. The mixer is shown in fig no.1.

Fig 1: Dry mixer

Processing the dry mixture [4, 5]Proper mixing and sufficient mixing duration of time was maintained. Overlapping of heat and moisture should be avoided during mixing. Temperature and humidity variations should be controlled. The uniformity and consistency of the formulation batches are monitored regularly.

8.1.2. Paddle Mixer

This mixer has a stationary outer vessel, and powders are agitated by paddles rotating within. This equipment is suitable for heating, by jacketing the vessel and it also permits the kneading effect by use of appropriately shaped beaters or paddles. The mixer is shown in fig no. 2

Fig 2 : Paddle mixer

8.1.3. V- Blenders

These blenders are used for dry mixing. They prevent the foreign particles from entering the chamber as it is totally enclosed. V-blender is shown in fig no. 3.

Fig 3: V- blender

8.1.3.1. Features

- Has minimal attrition while blending fragile granules.
- Easy to clean and unload blend.
- It requires minimal maintenance.

8.1.4. Granulated Products

Granulated products are prepared by the granulation process. Wet granulation is most common process and granulating fluid used is water or an aqueous binder solution. Wet granulation consists of the following steps. First, the solid excipients are blended in a suitable mixer and granulating fluid is added to form a wet mass. The wet mass is formed into granules by screening. The formed granules are dried in a tray oven or fluid bed dryer. The dried granules are again screened through a sieve to break up or remove aggregates of granules. The Equipment Planetary mixer is used.

8.1.5. Planetary Mixer

This mixer is used to mix wet and dry powders, light gels, pastes and doughs. As the mixing blade rotates in planetary motion inside mixing bowl it is named as the planetary mixer. The bowl of single planetary mixer consists of an upper cylindrical section and lower hemispherical section. The mixing bowl is secured with semi-circular frame at the time of mixing. The beater profiles are shaped to match the bowl's

lower curved surface. Beater has two types of movements. That is, it revolves on its own vertical axis at high speed and at the same time this vertical axis rotates around the center of bowl at low speed. (13,14) Planetary mixer is shown in the fig no. 4.

Fig 4: Planetary mixer

8.1.6. Granulated Products[13]

The granulation process prepares granulated products. Wet granulation is the most common process and granulating fluid used is water or an aqueous binder solution. Wet granulation consists of the following steps. First, the solid excipients are blended in a suitable mixer and granulating fluid is added to form a wet mass. The wet mass is formed into granules by screening. The formed granules are dried in a tray oven or fluid bed dryer. The dried granules are again screened through sieve to break up or remove aggregates of granules. The Equipment Planetary mixer is used.

8.1.6.1 Advantages

- Enhanced powder mixture appearance
- Increased micromeritic properties of the powder therefore less aggregation property.
- Minimized dust during powder filling

8.1.6.2 Disadvantages

- More expensive to setup
- It is complicated to remove the minute traces of granules; hence stability problems may arise.

8.1.7. Combination Product[14]

Granulated and powdered excipients can be combined to overcome some disadvantages of the granulated products.
The method is first to granulate some of the excipients and then blend the remaining excipients with dried granules before filling the container.

8.1.7.1 Disadvantages

- Obtained powder particles may not be uniform.
- Different sizes of particles should be carefully monitored.

8.2. ICH Guidelines (Q6a) For Re-Considerable Oral Suspensions[15]

Oral liquids: generally, Oral liquids/suspensions may follow the specific tests such as

8.2.1. Uniformity of Dosage Units

As per the pharmacopoeial pattern when weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate. If appropriate, tests may be performed in-process; however, the acceptance criteria should be included in the specification. This concept may be applied to both single dose and multiple-dose packages. b) pH Acceptance criteria for pH should be provided where applicable, and the proposed range should be justified.

8.2.2. Microbial Limits

Microbial limit testing is seen as an attribute of Good Manufacturing Practice and quality assurance. Therefore, it is generally advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation.

8.2.3. Antimicrobial Preservative Content

For oral liquids needing an antimicrobial preservative, acceptance criteria for preservative content should be established. Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf-life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

8.2.4. Antioxidant Preservative Content Release

Testing for antioxidant content should normally be performed. However, under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary, and in-process testing may suffice instead of release testing where permitted.

8.2.5. Extractables

Where data demonstrate the need, tests and acceptance criteria for extractable from the container/closure system components (e. g., rubber stopper, cap liner, plastic bottle, etc.) are considered appropriate for oral solutions packaged in non-glass systems or in glass containers with non-glass closures. The container/closure components should be listed,

and data collected for these components as early in the development process as possible. g) Alcohol content Where it is declared quantitatively on the label in accordance

8.2.6. Dissolution

In addition to the attributes recommended immediately above, it may be appropriate (e. g., insoluble drug substance) to include dissolution testing and acceptance criteria for oral suspensions and dry powder products for resuspension. Dissolution testing should be performed at release.

8.2.7. Particle Size Distribution

Quantitative acceptance criteria and a procedure for determining particle size distribution may be appropriate for oral suspensions. Acceptance criteria should be set based on the observed range of variation. They should take into account the dissolution profiles of the batches that showed acceptable performance in vivo, as well as the intended use of the product.

8.2.8. Redispersibility

For oral suspensions acceptance criteria for re-dispersibility may be appropriate. Shaking may be an appropriate procedure. The time required to achieve resuspension by the indicated procedure should be clearly defined

8.2.9. Rheological Properties

For relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity/specific gravity) in the specification.

8.2.10. Reconstitution Time

Acceptance criteria for reconstitution time should be provided for dry powder products which require reconstitution. The choice of diluent should be justified.

8.2.11. Water Content

For oral products requiring reconstitution, a test and acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally considered sufficient if the effect of absorbed moisture vs. water of hydration has been adequately characterized during the development of the product. In some instances, a more specific procedure (e. g., Karl Fischer titration) may be preferable

9. CONDITIONS FOR MANUFACTURING OF DRY SYRUP:[16]

The following conditions should be maintained for the manufacturing of dry syrup.

- Relative humidity should not be more than 60%.
- Temperature should be below 25°C.
- Equipment should be clean.
- Balance should be calibrated.

10. LABELLING[17]

- The label should contain API with contents meant for preparing an oral liquid.
- The directions for preparing the oral liquid including nature and quantity of liquid to be used.
- Before usage reconstitute with water.
- The directions are mentioned as directed by physician

10.1. Directions for reconstitution

- When called on to reconstitute and dispense one of these products, the pharmacist loosens the powder at the bottom of the container by lightly tapping it against a hard surface and then add the label-designated amount of purified water, usually in portions and shake until all the dry powder has been suspended.
- It is essential to add precisely the prescribed amount of purified water to the dry mixture if the proper drug concentration per dosage unit is to be achieved.
- Also, purified water rather than tap water is needed to avoid the possibility of adding impurities that could adversely affect the stability of the resulting preparation.
- Generally, manufacturers provide the dry powder or granule mixture in slightly oversized containers to permit adequate shaking of the contents after the entire amount of purified water has been added.
- The pharmacist should not "eyeball" the amount of water to be added or fill up the bottle with purified water.

11. EVALUATION OF ORAL RECONSTITUTABLE SUSPENSION:[18-19]

11.1. Flow Properties

The flow properties such as bulk density, tap density, angle of repose and porosity of the powder mixture,granulation and combination product should be carried out.

11.2. Rheological Behaviour

Using Brookfield viscometer, the rheological behaviour of the oral reconstituted suspensions is determined.

11.3. Sedimentation Behaviour

a) Redispersibility: It is determined by studying the number of strokes required to redisperse the formed at the end of seven days of storage. Redispersibility should be at most 100 strokes.

b) Sedimentation Volume Ratio(SVR): It is expressed by the ratio of the equilibrium volume of the sediment (Vu) to the total volume (Vo) of the suspension.
F=Vu/Vo
F values lies between 0 to 1 for any pharmaceutical suspension.

11.4. Drug Content

The required weight of the drug mixture is taken and is extracted with 100 ml of solvent. The solution formed is filtered through nylon filter membrane. 0.1 ml solution taken and further diluted to 10 ml with solvent and absorbance is read on UV spectroscopy.

11.5. Invitro Drug Release

In vitro dissolution studies were carried out by using USP type-2 apparatus at 100 rpm. The dissolution medium consists of

900 ml of buffer maintained at 37 +/- 0.5 °C. The drug release at different time intervals was measured by using a UV spectrophotometer.

11.6. Particle Size

The formulation's average particle size is examined using standard microscopy method average and the standard deviation of 100 particles were estimated.

11.7. Zeta Potential Measurement

The suspension is diluted with distilled water and measurements are taken triplicately.

11.8. Stability Study

The oral reconstituted suspension is stored in airtight amber colour glass container for 36 days at 45°C, and it is reconstituted with distilled water to make up the volume to 60 ml. The reconstituted suspension is also stored at different temperatures.

11.9. PH Values

The PH of the suspensions is measured with the help of PH meter.

12. PACKAGING AND STORAGE[20]

1) Dry powders should be packed in wide-mouth container having sufficient free space above the liquid.
2) Stored in air tight amber colour glass container to protect it from excessive heat and light.
3) The label should contain the direction stating "shake well before use" to ensure the uniform distribution of the particles.
4) The dry powders for oral reconstitution should be stored at room temperature.
5) Sachets made of 4 layers of aluminum foil are used for single-dosage packing.

13. MARKETED PREPARATIONS

Name	Drugs
MoximaxCV dry syrup	Clavulanic acid, amoxicillin
Kefloxin DS	Cefadroxil
Azimax 200 dry syrup	Azithromycin
Flucamed powder for oral suspension	Fluconazole
Betaclox 125 dry syrup	Dicloxacillin

The main acceptable benefits of dry syrup are useful in case of bioavailability as it shows maximum bioavailability than solid dosage forms (tablets and capsules as it disintegrates in water outside of the oral cavity) and in dry syrup, suspension directly pass through the gastrointestinal tract (GIT). Hence, it gets easily absorbed from GIT. It has a highly accepted dosage form due to its ease of self administration and convenient dosage form.

14. CONCLUSION

The reconstituted oral suspension shows a high level of acceptance in administration, patient compliance, and physical and chemical stability compared to other dosage forms. This system shows more bioavailability than tablets and capsules. The dry mixture of this oral reconstituted suspension has reduced weight because the aqueous vehicle is absent, making transportation charges cheaper. Therefore, dry syrup is an ideal formulation for paediatrics for the administration of mainly antibiotic drugs.

15. AUTHORS CONTRIBUTION STATEMENT

Mary swarnalatha has designed the current review. Hasika has collected the literature which supports the work. Iswariya and Madhavi has framed the manuscript.

16. CONFLICT OF INTEREST

Conflict of interest declared none.

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