

**Review Article****Dry syrup: An overview****M. Ola and R. Bhaskar and Priya Patil***Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Maharashtra, India***ARTICLE INFO:****Article history:**

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Abstract

The advantages of oral dosage form that are responsible for its popularity are its ease of administration, patient compliance and stability of formulation. The most popular oral dosage forms being tablets and capsules, but one important drawback of the dosage forms however is the difficulty to swallow especially when a dosage form is developed for pediatric and geriatric patient. The modern scientific and technological advancement in the pharmaceutical field had created bank of interest in reconstitutable oral suspension dosage form in the recent year. The reconstituted system is the formulation of choice when the drug stability is a major concern. Reconstitutable oral systems show the adequate chemical stability of the drug during shelf life and also reduce the weight of the final product. Dry syrup form of the drug is also useful in case of bioavailability as it has high bioavailability rather than tablets and capsules as it disintegrates in water outside of the oral cavity and directly the suspension is gone through the gastrointestinal tract. So the suspension easily absorbs in the GIT. The present review gives an account of the excipients used, methods of preparation of dry syrups along with their evaluations, their packaging, ICH guidelines.

Introduction

Pharmaceutical dosage form can be divided into various classes. Classification of dosage form shown in table no. 1.

Table no. 1: Classification of dosage form

Dosage Form	Advantages	Disadvantages
Solid dosage form Eg. Tablet, Capsule, Suppository, Powder	Most stable dosage form Cost effective Less microbial Contamination	Pediatric and geriatric as well as seriously ill patient cannot swallow. Some drugs resist to compress into dense compacts
Semi-solid dosage form Eg. Paste, Cream, Gel, Ointment	Generally used externally Reduced side effects Local action	No dosage accuracy The base which is used can be easily oxidised
Liquid dosage form Eg. Solution, Suspension, Syrup	More rapid action Useful for the patient who have difficulty in swallowing solid dosage form	Less stable dosage form Difficult for transportation Less dosage accuracy
Vapor dosage form Eg. Inhalation therapy, Aerosol	Local action Some drugs are only administered by this type of dosage form	For preparing this type of dosage form more excipients and equipment required.

An oral route is the most preferred route of administration^[1]. Tablets and capsules are unsuitable for administering high doses of Active Pharmaceutical Ingredient (API) since individual large dose is difficult to swallow, or require the administration of several tablets or capsules at a time, making it less patient compliant. Due to need of chewing, poor taste masking and lack of controlled release possibility chewable tablets are not ideal with pediatric and geriatric patients. Oral liquid suspensions are mainly formulated for the patients with difficulty in swallowing. But controlled release form of liquid suspension is difficult due to the chances of early release of the API in the suspending media during storage. Hence it is essential to develop a reconstitutable suspension dosage form^[2].

Dry Syrups: "Dry pharmaceutical syrup may be defined as a finely divided insoluble particle ranging from 0.5-5 μ , which is to be distributed in a suitable vehicle".

Dry syrups are the solid dosage form that can be reconstituted by the addition of water to administer by the oral route. Mostly antibiotics, some moisture sensitive and pediatric drugs are available in the form of dry syrup [3].

Many preparations like Amoxicillin trihydrate, Erythromycin ethyl succinate, Dicloxacillin sodium etc. are available as dry powder mixtures or granules that are intended to be suspended in water or some other vehicle before oral administration. The

reconstituted system is the formulation of choice when the drug stability is a major concern. The dry mix for oral suspension contains the drug, colorants, flavors, sweeteners, stabilizing agents, suspending agents and preserving agents that may be needed to enhance the stability of the formulation. Dry syrup form of drug shows improved bioavailability as compared to tablets and capsules as it is in the dispersed state at the time of administration. A reconstitutable suspension can offer several advantages such as maintenance of the chemical stability of the active compounds until reconstitution at the start of treatment. The same suspension can be easily administered to children of different ages by adjusting the volume to swallow [3, 4].

Suspension: A Pharmaceutical suspension is a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase. The internal phase consisting of insoluble solid particles having a specific range of size which is maintained uniformly throughout the suspending vehicle with the help of single or combination of suspending agent. The external phase (suspending medium) is usually aqueous in some case, may be an organic or oily liquid for non-oral use [5].

Classification of Suspension^[5, 6]

Suspension is classified based on various parameters. Suspension is classified as below:

Based on Route of administration

- Oral suspension
- Topical suspension
- Parenteral suspension

Based on Proportion of Solid content

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

Based on Electro kinetic Nature of Solid Particles

- Flocculated suspension
- Deflocculated suspension

Based on Size of Solid Particles

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

Based on Method of Administration

- Dry powder for reconstitution
- Ready to use suspension

Based on Release

- Conventional suspension
- Sustained release suspension

Advantages of Sustained/Controlled release drug delivery system over the conventional dosage form^[1, 7-11]

Sustained release drug delivery is novel drug delivery system which has many advantages over conventional dosage form.

1. Dosing frequency reduced due slow release
2. Dose reduction
3. Better patient compliance
4. Reduction in gastrointestinal irritation due to decrease in local and systemic side effects.
5. Constant level of drug concentration in blood plasma
6. Reduces chances of toxicity due to overdose

7. Reduced healthcare costs through improved therapy
8. Reduces the fluctuation of peak valley concentration
9. Night time dosing can be avoided

Drug selection criteria for sustained release dosage forms^[1, 3, 12]

For preparation of sustained release dosage form drug should follow below criteria.

1. **Desirable half-life:** The half-life of a drug is residence time of drug in the body. Preferably, the drug should have half-life of three to four hours. If half-life of drug is more than no need to prepare sustained release dosage form.
2. **High therapeutic index:** Drugs with low therapeutic index are unsuitable for incorporation in sustained release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities. eg. Digitoxin.
3. **Small dose:** Minimum dose is preferred for sustained release formulation because the size of a unit dose sustained release formulation would become too big, to administer without difficulty.
4. **Desirable absorption and solubility characteristics:** Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into sustained release formulations is therefore impractical and may decrease overall absorption efficiency.
5. **Desirable absorption window:** Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is called as the 'absorption window'. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as sustained release dosage form are unsuitable.
6. **First pass clearance:** Delivery of the drug to the body in desired concentrations is really hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in sustained release forms.

Qualities of ideal oral suspension^[2, 5, 12, 13]

1. The dispersed particle should not settle readily and the settle particles should redispersesuddenly.
2. On settling cake should not form by the particle.
3. Preparation can be easily poured.
4. It should be chemically and physically stable.
5. It should be palatable.
6. It should be free from gritting particle.

Disadvantages of liquid oral suspensions [12, 14]

Liquid oral suspension has certain disadvantages. To overcome these disadvantages reconstitutable suspension prepared.

- (1) There are chances of inaccuracy in single dosing because it is a bulk formulation
- (2) Drug dose depends on various physical factors of the dosage form such as temperature of storage, sedimentation rate of the formulation, liquid flow properties like viscosity, pourability, redispersion, flocculation and content uniformity.

- (3) The drug may be less stable in a liquid formulation rather than in tablets or capsules.
- (4) Stability of the liquid suspension largely depends on the temperature of storage.
- (5) Caking occurs upon storage.

Advantages of dry granules for oral suspension[3, 14]

- (1) There is accurate single dosing as the dose is packed in single dose sachets.
- (2) Drug dose is relatively independent of any physical factors like temperature, sedimentation rate and liquid flow properties.
- (3) Packaging of the powder mixture is done in sachets (single dose) making the formulation easy to carry.
- (4) Enhanced convenience of single dosage regimen.
- (5) Colored, flavored, sweetened formulation is advantageous for administration to the pediatric population.
- (6) Stable on storage and when reconstituted with an ingestible liquid for administration, the corresponding liquid suspension is stable for the duration for which the therapy is required.

Required Characteristics of Suspensions for Reconstitution^[14, 15]

1. Powder blend must be a uniform mixture of the suitable concentration of each ingredient. During reconstitution, the powder blend must disperse rapidly and completely in the aqueous vehicle.
2. Reconstituted suspension must be easily re-dispersed and poured by the patient to provide exact and uniform dose.
3. After reconstitution the high viscosity caused by the refrigerated storage temperatures should not obstruct dose administration by the patient.
4. Final product must have an acceptable appearance, odor and taste.

Reasons for formulation of such suspensions^[16]

Reconstituted suspension is formulated due many reasons such as for patient which have difficulty in swallowing, drug stability etc. Some reasons are discussed below.

1. The main reason for the formulation of suspensions for reconstitution is inadequate chemical stability of the drug in an aqueous vehicle.
2. Another reason for the formulating suspensions for reconstitution is to avoid the physical stability problems. These problems include possible increased drug solubility due to pH changes from chemical degradation, incompatibility of ingredients, viscosity changes, conversion of polymorphic form and crystal growth and caking.
3. Formulation for reconstitution reduces the weight of the final product because the aqueous vehicle is absent and consequently, transportation expenses may be reduced.
4. Suspension for reconstitution is convenient dosage form for large doses [2].
5. Safe and compliant for pediatric and geriatric patient.
6. Suitable for insoluble or poorly soluble API.

Excipients used^[3, 16]

Number of excipients should be minimum as more the number of excipients in the formulation, the greater is the possibility of problems, for example, the chances of compatibility problems are increased as more excipients are used. More processing is required to incorporate more excipients. For reducing the number of excipients use an excipient that performs more than one function. Eg. Sucrose can be used as a diluents, sweetener and suspending agent.

All excipients should disperse rapidly on reconstitution. This criterion eliminates several suspending agents.

Granule disintegrant: It results in prevention of the particle aggregation.

Granule binder: It helps to reduce the settling of particles in suspensions. It is also used as a stabilizer for suspensions. Eg. High molecular weight povidone.

Suspending agents

Suspending agents should be easily dispersed during reconstitution. These rules out several common suspending agents because many require hydration, elevated temperatures or high shear mixing for adequate dispersion. Some of the suspending agents that are recommended for use are Acacia, Carboxymethylcellulose sodium, Iota carrageenan, Microcrystalline cellulose with carboxymethylcellulose sodium, Silicon dioxide, Sodium starch glycolate, Tragacanth, Xanthan gum.

Xanthan gum is a common suspending agent in suspensions for reconstitution. Its solution viscosity is practically independent of pH and temperature.

Sweeteners

Sweeteners can mask the unfavorable taste and enhance patient acceptance in the pediatric population that uses this product. The sweetener is a significant component of suspensions for reconstitution. Drugs frequently have a bitter taste and suspending agents, particularly clays, may have a bland taste.

Eg. Sucrose can perform both functions of sweetener and suspending agent, and serve as a diluent in the dry mixture. Saccharin may become restricted by the Food and Drug Administration because of its carcinogenic potential. Others include Mannitol, Dextrose, Aspartame, Saccharin Sod.

Wetting agents

Many drugs in suspension are hydrophobic; they repel water and are not easily wetted. Must select the appropriate wetting agent for optimum dispersion of the drug at the lowest effective concentrations excess wetting agent can produce foaming and impart an unpleasant taste. Eg. Polysorbate 80, Sodium lauryl sulfate.

Other excipients^[16]

The other excipients include buffers, preservatives, flavors and colors.

Buffers are used to maintain the optimal pH for all excipients. Suspension pH is often adjusted to ensure that the drug remains insoluble. Eg. Sodium citrate

Preservatives are required in most suspensions because the suspending agents and sweetener are good media for growth of microorganisms. Eg. Sorbic acid. Sucrose in sufficient concentrations (60% w/w) can aid in the prevention of

microbial growth. Other common preservatives used are Sodium benzoate and Sodium propionate.

Flavors enhance patient acceptability of product. Both natural and artificial flavors are used. Additional flavors used include raspberry, pineapple etc. In some cases refrigeration after reconstitution is required for the stability of the flavoring agent rather than for the stability of the drug.

Colorants are intended to provide a more aesthetic appearance to the final suspension.

Anticaking agents such as amorphous silica gel have many functions in suspensions for reconstitution. A common problem in dry mixtures is poor powder flow and caking. This is often caused by powder agglomeration due to moisture uptake.

Method of preparation of dry mixture^[17]

Mostly antibiotics are available in dry syrup form. Dry syrup is manufactured in three methods namely:

1. Direct Mixing,
2. Dry Granulation (Slugging) and
3. Wet Granulation (wet massing)

1. Flow Chart of Direct Mixing

Process of direct mixing is summarized in fig no. 1.

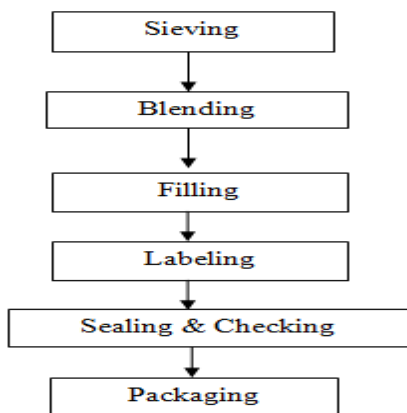


Fig no. 1: Direct mixing

2. Flow chart of dry granulation

Process of dry granulation is shown in fig no. 2.

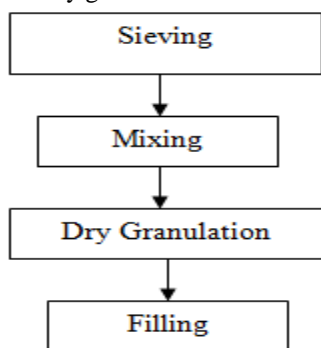


Fig no.2: Dry granulation process

3. Flow chart of wet granulation

Wetgranulation is one of the methods of preparation of dry syrup which is shown in fig no. 3.

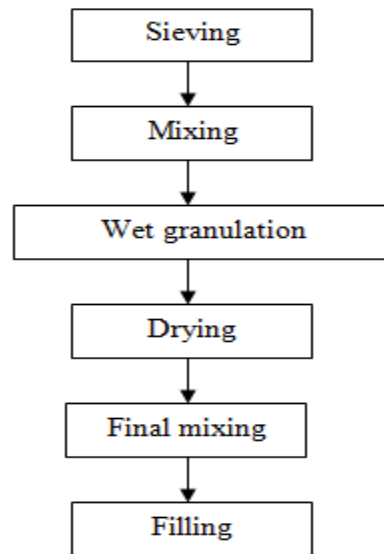


Fig no. 3: Wet granulation

Preparation of dry mixture^[13, 18]

- Direct mixing
- Granulated products
- Combination products

Direct mixing

Process of direct mixing with their advantages and disadvantages shown in table no. 2

Table no. 2: Direct mixing

Powder blend	Advantages	Disadvantages
Also called powder mixtures, are prepared by mixing the Excipients of dry mixture in powder form. Excipients Present in small quantities may require a two stage mixing operation.	Least capital equipment and energy Less chemical & physical stability problems because no heat or solvents are used	Loss of active ingredient during mixing. Prone to homogeneity problem.

The selection of the appropriate mixer involves several considerations, the most significant of which is that the mixer should rapidly and constantly produce a homogenous mixture.

The equipment used is mixers. Few types of mixers are discussed below.

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

Dry mixer: For batch work the dry mixer is commonly used. This consists of a semi-cylindrical trough, usually covered and provided with two or more ribbon spirals. One spiral is righthanded and the other left-handed so that the material is worked back and forth in the trough. A broad ribbon lifts and conveys the materials while a narrow one will cut through the materials while conveying. Ribbon blenders are often used on the large scale and may be adapted for continuous mixing. Dry mixer is shown in fig no. 4.



Fig no. 4: Dry mixer

Paddle mixer: It has a stationary outer vessel and the powders are agitated by paddles rotating within. The equipment is suitable to heating, by jacketing the vessel, and also permits a kneading effect by the use of appropriately shaped paddles or beaters. This mixer is shown in fig no. 5.



Fig no. 5: Paddle mixer

Double cone mixer: A double cone mixer consists of a vessel with two cones base to base, with or without a cylindrical section in between. It is so mounted that it can be rotated about an axis at right angles to the line joining the points of the cones. Double cone mixer is an efficient mixer for mixing dry powder and granulates homogeneously. All the contact parts are made up of stainless steel. Two-third of the volume of the cone blender is filled to ensure proper mixing. This mixer shown in fig no. 6.



Fig no. 6: Double cone mixer

Features

1. The conical shape at both ends enables uniform mixing and easy discharge.
2. The cone is statically balanced to avoid any excessive load on the gear box and motor.
3. While the powder can be loaded into the cone through a wider opening, it can be discharged through a side valve.
4. Depending upon the product, paddle type baffles can be provided on the shaft for better mixing.

4. V- blenders: V blenders are used for dry mixing. They are totally enclosed to prevent any foreign particles to enter into the chamber. V blender shown in fig no. 7.



Fig no. 7: V blender

Features

- Minimal attrition when blending fragile granules.
- Large-capacity equipment available.
- It is easier to clean and unload the blender
- Minimal maintenance is required
- Available in various capacities from 25 litres to 1000 litres.

Granulated products^[18]

All the excipients in granulated products are processed by granulation. Wet granulation is the usual process and the granulating fluid is water or an aqueous binder solution. There are two methods of incorporating the drug. The drug can be dry blended with the other excipients or it can be dissolved or suspended in the granulating fluid.

Advantages

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

Disadvantages

- Requires more capital investment and energy.
- It is difficult to remove the last traces of granulating fluid from the interior of granules. Thus the residual fluid may reduce the stability of the product.
- The excipients and drug must be stable to the granulation process.
- Uniform granulation is necessary because an excess of very small particles, or fines, will result in rapid segregation

The equipment used in this process are

1. Planetary mixers
2. Rotating sieve
3. Fluid bed dryer

Planetary mixers: Planetary mixer shown in fig no. 8. The planetary mixer is used for mixing of dry and wet powders, light pastes, gels, and dough. The planetary mixer is so named because the mixing blade (commonly known as the beater) rotates in a planetary motion inside the mixer bowl. The bowl of the single planetary mixer consists of an upper cylindrical section and a lower hemispherical section. The mixer bowl is secured to a semi-circular frame (also termed as “fork”) at the time of mixing. The beater profiles are shaped to match the lower curved surface of the bowl. The beater has two types of movements: it revolves on its own vertical axis at high speed. At the same time, this vertical axis rotates around the centre of the bowl at a relatively lower speed. The direction of rotation of the beater on its own axis and that around the axis of the bowl is in opposite directions [13, 18].



Fig no. 8: Planetary mixer

Rotating sieve: The rotating sieve mill guarantees optimum sizing results plus excellent flow rates. The 360-degree rotor movement ensures constant, uniform speed and force effect for gentle sizing of the product. The advantage of this process resides in an exceptionally low fine particle fraction in the end product, as well, the low mechanical stress allows for the capability of processing heat sensitive products. This sieve shown in fig no. 9.



Fig no. 9: Rotating sieve

Performance and Characteristics

- Easy installation, maintenance and long service life
- All Stainless Steel in design
- Large non-marking castors
- Easy to clean Mirror polished side walls
- No cross contamination
- Low noise

Fluid bed dryer: Moist material is fed onto a shaking perforated steel bed through which the drying air flows. The air is of sufficient volume that it lifts, or fluidizes, the bed of material allowing intimate contact with each particle. The

shaking action of the bed assists in the transportation of the material over the length of the dryer. Moisture is carried away by the air into a dust recovery system, whereby the hot air can be recycled in a closed loop back to the process. The flow of air is controlled along the length of the dryer to maximize fluidization, enabling very wet and sticky materials to be handled. As the material passes along the dryer it gradually loses moisture until the target dryness is achieved, at which point it passes into a cooling zone. Here the hot air is replaced by cool ambient air, which reduces the product temperature to the desired [19, 20].

Combination product [14, 16, 18]

Powdered and granulated excipients can be combined to overcome some disadvantages of granulated products. Less energy and equipment for granulation may be required if the majority of the diluents can be added after granulation. Also heat sensitive excipients such as flavors can be added after drying of the granulation to avoid exposure to elevated temperatures.

The general method is first to granulate some of the excipients, then blending the remaining excipients with the dried granules before filling the container. The presence of the diluents helps to improve flow and reduces both segregation and dust formation.

Disadvantages

- Risk of non-uniformity
- Particle sizes of various fractions should be carefully controlled

Advantages and Disadvantages of types of Dry mixtures

Dry mixtures have some advantages along with disadvantages which are discuss in table no. 3.

Table no.3: Advantages and disadvantages 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 & excipients
Combination product	Reduced cost Use of heat sensitive ingredients	Ensuring non segagating mix of granular & nongranular ingredients

Condition for manufacturing Dry Syrup:[17]

For manufacturing of dry syrup following conditions should be maintained.

- Relative humidity: Not more than 60%.
- Temperature: Below 25°C
- All relevant materials are removed
- Equipment is cleaned
- Balanced is calibrate

- Bottle drying date

Evaluation of oral reconstitutable suspension^[14]

After preparation of reconstitutable suspension it will evaluate for below parameters.

- (1) Flow properties: Flow properties such as angle of repose, bulk density, tap density and porosity of powder mixture, granulations and combination product should be carried out.
- (2) Rheological behavior: The rheological behavior of the reconstituted suspensions is determined using Brookfield viscometer (Model – RVT).
- (3) Sedimentation behavior:-
 - a.) Redispersibility: The redispersibility is determined by studying the number of strokes to redisperse the formed sediment at the end of 7 days of storage of the formulations (not more than 100 strokes = Redispersibility).
 - b.) Sedimentation Volume Ratio (SVR): Sedimentation volume of a suspension is expressed by the ratio of the equilibrium volume of the sediment, V_u , to the total volume, V_o of the suspension. i.e. $F = V_u/V_o$. The value of F normally lies between 0 to 1 for any pharmaceutical suspension. The value of F provides a qualitative knowledge about the physical stability of the suspension.
- (4) Drug content: The required weight of drug mixture is taken and extracted with 100ml solvent and solution is filtered through nylon filter membrane. 0.1ml of the solution is further diluted to 10ml with solvent and absorbance of the solution is read on UV Spectroscopy. The drug concentration is extrapolated from the calibration curve in solvent.
- (5) In vitro drug release: The in vitro dissolution studies were carried out using USP apparatus Type II at 100 rpm. The dissolution medium consisted of 900 ml distilled water maintained at $37^\circ\text{C} \pm 0.50\text{C}$. The drug release at different time intervals was measured for two hours using UV spectrophotometer.
- (6) Particle size: The oral reconstitutable suspension is evaluated, the average particle size of the formulation is examined using standard microscopy method average and standard deviations of 100 particles are estimated.
- (7) Viscosity: The rheological behavior of the suspension is determined by using Brookfield viscometer (Model - LVDI).
- (8) Zeta potential measurement: Suspension is diluted with distilled water and the measurements are taken in triplicate.
- (9) Stability study: The reconstitutable suspension is stored in air tight amber coloured glass bottles for 36 days at 45°C and then reconstituted with distilled water to make up the volume to 60 ml with gentle shaking. The reconstituted suspension is stored at 4°C , 25°C and 45°C for 15 days.
- (10) pH values: The pH of suspensions was measured with the aid of a pH meter.

Packaging and storage^[16]

Dry powder for reconstitution packaged in wide mouth container or in sachet in case of unit dosing.

1. The dry powders for reconstitution should be packaged in wide mouth container having sufficient air space above the liquid.
2. The dry powders should be stored in tight container protected from freezing, excessive heat and light.
3. The label should contain the direction stating: "Shake Before Use" to ensure uniform distribution of solid particles and thereby to obtain uniform and proper dosage.
4. The dry powders should be stored at room temperature.
5. After reconstitution the suspension should be stored in the refrigerator (freezing should be avoided to prevent aggregation)
6. For single dosage packing, sachets are used made up of 4 layers of aluminum foil.

ICH guidelines (q6a) for reconstitutable oral suspensions^[14, 21, 22]

International conference on harmonization (ICH) provides some guidelines for reconstitutable oral suspension.

a) Uniformity of dosage units: This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopoeial procedure should be used. In general, the specification should include one or the other but not both. 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. The dosage unit is considered to be the typical dose taken by the patient.

If dispensing equipment (such as medicine droppers or dropper tips for bottles) is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used. For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

b) pH: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

c) Microbial limits: Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. In general, it is 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. It should be noted that, whereas this Guideline does not directly address excipients, the principles discussed here may be applicable to excipients as well as to new drug products. With acceptable scientific justification, it may be possible to propose no microbial limit testing for powders intended for reconstitution as oral liquids.

Acceptance criteria should be set for the total count of aerobic microorganisms, total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa*). These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience. Decision tree #8 provides additional guidance on the use of microbial limits testing.

d) 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. Testing for antimicrobial preservative content should normally be performed at release. Under certain circumstances, in-process testing may suffice in lieu of release testing.

When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. Antimicrobial preservative effectiveness should be demonstrated during development, during scaleup, and throughout the shelf-life (e.g., in stability testing: see the ICH Guideline, “Stability Testing of New Drug Substances and Products”), although chemical testing for preservative content is the attribute normally included in the specification.

e) Antioxidant preservative content: Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary, and in-process testing may suffice in lieu of release testing where permitted. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.

f) Extractable: Generally, where development and stability data show evidence that extractable from the container/closure systems are consistently below levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted. This should be reinvestigated if the container/closure system or formulation changes.

g) Alcohol content: Where it is declared quantitatively on the label in accordance with pertinent regulations, the alcohol content should be specified. It may be assayed or calculated.

h) 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. Dissolution procedures using either pharmacopoeial or non-pharmacopoeial apparatus or conditions should be validated. Singlepoint measurements are normally considered suitable for immediate-release dosage forms. Multiple-point sampling, at appropriate intervals, should be performed for modified-release dosage forms. Developmental data should be

considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

i) Particle size distribution: Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for oral suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure for these formulations. Particle size distribution testing should be performed at release. Particle size distribution testing may also be proposed in place of dissolution testing; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges.

j) Redispersibility: For oral suspensions which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate procedure. The procedure (mechanical or manual) should be indicated. Time required to achieve resuspension by the indicated procedure should be clearly defined.

k) Rheological properties: For relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity/specific gravity) in the specification. The test and acceptance criteria should be stated. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

l) Reconstitution time: Acceptance criteria for reconstitution time should be provided for dry powder products which require reconstitution. The choice of diluent should be justified. Data generated during product development may be sufficient to justify skip lot testing or elimination of this attribute from the specification may be proposed.

Typical Reconstitutable Oral Suspensions

Some reconstitutable oral suspension mentioned in table no. 4.

Table no. 4: Reconstitutable oral suspensions

Drug	Manufacturers
Amoxicillin trihydrate	SmithklineBeecham
Ampicillin	Biocraft
Cefalexin	Dista
Dicloxacillin sodium	Apothecan
Erythromycin ethylsuccinate	Abbott
Ampicillin & probencid	Biocraft

Future Perspective: Sustained release powder for oral suspension formulate by using sustained release polymer.

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