WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 4, Issue 3, 462-484. Review Article ISSN 2277– 7105

RECONSTITUTABLE ORAL SUSPENSIONS (DRY SYRUPS): AN OVERVIEW

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Article Received on
20 Dec 2014,

Revised on 14 Jan 2015,
Accepted on 08 Feb 2015

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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. Dry syrups are the dry mixtures that require the addition of water at the time of dispensing. It is packed dry in bottles to preserve the stability of sensitive pharmaceutical ingredients. After reconstitution such formulations are to be administered in a specific period as indicated in the label claim of dry syrup packing. A number of commercial and official preparations are available as dry powder mixtures. Most of the drugs prepared as dry powders for oral suspension are antibiotics. The present review gives an account of the excipients used, methods of preparation of dry syrups along with the instruments used, their evaluations, ICH guidelines, the packaging materials used, examples of research articles, few marketed preparations and few of the patents obtained.

KEYWORDS: Administration, patient compliance and stability of formulation.

INTRODUCTION

Since decades among all the pharmaceutical products available, oral drug delivery has gained a higher scope and popularity and has been widely employed for the systemic delivery of drugs. The positive aspect regarding the oral dosage form which created its high level of acceptance was its ease of administration, patient compliance and stability of formulation.

Although conventional oral suspensions can be administered immediately, there is an important category of suspensions that requires mixing prior to administration. These suspensions are commercial dry mixtures that require the addition of water at the time of dispensing. The reconstituted system is the formulation of choice when the drug stability is a major concern. A number of commercial and official preparations are available as dry powder mixturesor granules that are intended to be suspended in water or some other vehicle prior to oral administration. Most of the drugs prepared as dry powders for oral suspension are antibiotics. The dry mix for oral suspension is prepared commercially to contain 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 also shows improved bioavailability as compared to tablets and capsules as it is in the dispersed state at the time of administration. The granules in the sachets must be taken as a suspension in a glass containing prescribed amount of ingestible liquid, mostly water. Although studies have demonstrated that the dry oral suspension after constitution in a liquid is stable for 24 hours after preparation, it is recommended that the suspension should be consumed immediately after preparation.[2]

Disadvantages of liquid oral suspensions

- It is a bulk formulation so there are chances of inaccuracy in single dosing.
- 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.
- Stability of the liquid suspension largely depends on the temperature of storage.
- Caking occurs upon storage.[2]

Advantages of dry granules for oral suspension.

- There is accurate single dosing as the dose is packed in single dose sachets.

- Drug dose is comparatively independent of any physical factors like temperature, sedimentation rate and liquid flow properties.
- Packaging of the powder mixture is done in sachets making the formulation easy to carry.
- Enhanced convenience of single dosage regimen.
- Colored, flavored, sweetened formulation is advantageous for administration to the pediatric population.
- 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.[2]

Reasons for formulation of such suspensions

The most common reason for the formulation of suspensions for reconstitution is inadequate chemical stability of the drug in an aqueous vehicle. In such cases, dissolution or even suspension of the drug results in a very short shelf life. For example, reconstituted suspensions of penicillin have a maximum shelf life of 14 days. The manufactured dry mixture, however, has a shelf life of at least 2 years.

Another reason for the formulating suspensions for reconstitution is to avoid the physical stability problems often encountered in conventional suspensions. 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.

Formulation for reconstitution reduces the weight of the final product because the aqueous vehicle is absent and consequently, transportation expenses may be reduced. The dry mixture may be shipped without regard to seasonal temperatures because its physical stability is less susceptible to temperature extremes as compared with conventional suspensions.[3]

Desired attributes

During manufacture the dry blend, or mixture, must be a uniform mixture of the appropriate concentration of each ingredient. It must not segregate into a non uniform mix because errors in dosage may result. During reconstitution the powder blend must disperse quickly and completely in the aqueous vehicle. The reconstituted suspension must be easily redispersed and poured by the patient to provide an accurate and uniform dose. After reconstitution the high viscosity caused by the refrigerated storage temperatures should not obstruct dose

administration by the patient. The final product must have an acceptable appearance, taste, odor.[3]

Excipients used

The criteria for selecting excipients are based both on suitability for reconstitution and on the physical type of powder mixture desired.

- Number of excipients should be kept to a 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. Greater processing is required to incorporate more excipients. More excipients will require sampling and testing for quality control. A common method of reducing the number of excipients is to 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.
- Many preservatives are also not suitable.[3]

FREQUENT	INFREQUENT
Suspending agent	Anticaking agent
Wetting agent	Flocculating agent
Sweetener	Granule disintegrant
Preservative	Granule binder
Color	Lubricant
Flavor	Solid diluents
Buffer	Antioxidant

Granule disintegrant: It results in prevention of the particle aggregation. The swelling of disintegrant grains in water plays an important part in the deaggregation of drug particles.

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 by vigorous hand shaking during reconstitution. This 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, Povidone, Propylene glycol alginate, Silicon dioxide, Sodium starch glycolate, Tragacanth, Xanthan gum.

The combination of microcrystalline cellulose and sodium carboxymethylcellulose is a common suspending agent. Total concentrations of the combination greater than 1 % in the reconstituted product can result in thixotropic gels. This agent and sodium carboxymethylcellulose alone are anionic; they are incompatible with many cationic excipients.

The natural gums are usually anionic and include exudates of tree and extract from seaweed. Acacia and tragacanth have been used as suspending agents for many years. The carrageenan and alginate suspending agents are seaweed extracts. The alginates produce highly viscous solutions and the iota-carrageenans produce thixotropic dispersions. A disadvantage of these natural products is batch variation in color, viscosity, gel strength and hydration rate.

Xanthan gum is a common suspending agent in suspensions for reconstitution. Because it is produced by microbial fermentation there is good batch-to-batch uniformity and few microbial problems. Its solution viscosity is practically independent of pH and temperature.[3]

Sweeteners

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. Sweeteners can mask the unfavourable taste and enhance patient acceptance in the pediatric population that uses this produce. An increased viscosity as a result of the sweetener aids suspension of the drug particles. The sweeteners used are Sucrose, Mannitol, Aspartame, Sodium saccharin, Dextrose.

Sucrose can perform both functions of sweetener and suspending agent and can serve as a diluents in the dry mixture. Aspartame has fair acid stability but poor heat stability. Saccharin may become restricted by the Food and Drug Administration because of its carcinogenic potential.[3]

Wetting agents

Many drugs in suspension are hydrophobic, they repel water and are not easily wetted. Surfactants are commonly used to aid in the dispersion of hydrophobic drugs. The formulator 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.

Polysorbate 80 is a common wetting agent. It is nonionic and is chemically compatible with both cationic and anionic excipients and drugs. It is used in concentrations lesser than or equal to 0.1%. Another common wetting agent is Sodium lauryl sulfate. This agent is anionic and may be incompatible with cationic drugs.[3]

Other excipients

The other excipients include buffers, preservatives, flavors and colors. Flocculating agents are not commonly used in suspensions for reconstitution because these products are usually redispersed frequently enough to prevent caking.

Buffers are used to maintain the optimum pH for all excipients. Suspension pH is often adjusted to ensure that the drug remains insoluble. The polymeric suspending agents, however have the greatest viscosity at the pH of their maximum solubility. Sodium citrate is a common buffer used in suspensions for reconstitution.

Preservatives are required in most suspensions because the suspending agents and sweetener are often good growth media for microorganisms. The choice of preservatives is limited because most of these ingredients require extended time periods for dissolution at room temperatures. Eg is sorbic acid. Sucrose in sufficient concentrations (ca.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. As relatively large cations or anions, these agents may be chemically incompatible with other ingredients. For example FD and C Red No.3 is a disodium salt, is anionic and would be incompatible with a cationic wetting agent.

Anticaking agents such as amorphous silica gel have several 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. As a desiccant, these agents remove moisture from the dry mixture to facilitate good powder flow and prevent caking. In addition anticaking agents separate the dry particles to inhibit fusion.[3]

Preparation of dry mixture

- Powder blends
- Granulated products
- Combination products

Powder blends

Powder blends, sometimes called powder mixtures are prepared by mixing the excipients of the dry mixture in powder form. Excipients present in small quantities may require a two stage mixing operation. Such excipients can be mixed with a portion of a major excipient to aid in their dispersion. For example, milled sucrose provides a large surface area for the adsorption of the small quantities of flavor oils. The second stage comprises the mixing of the remaining excipients. The selection of the appropriate mixer involves several considerations, the most significant of which is that the mixer should rapidly and reliably produce a homogenous mixture.

Advantages

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

  Disadvantages
- Prone to homogeneity problems. Two most important properties for the mixing of these powders are Particle size and Powder flow.
- Loss of the active ingredient during mixing
- The loss during mixing is significant if potent drug which is used in very low concentrations is lost.[3]

The equipments used are mixers. So a few types of mixers are discussed below.

Dry mixer: For batch work the dry mixer is often used. This consists of a semi-cylindrical trough, usually covered and provided with two or more ribbon spirals. One spiral is right-handed 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.

Fig. A 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.

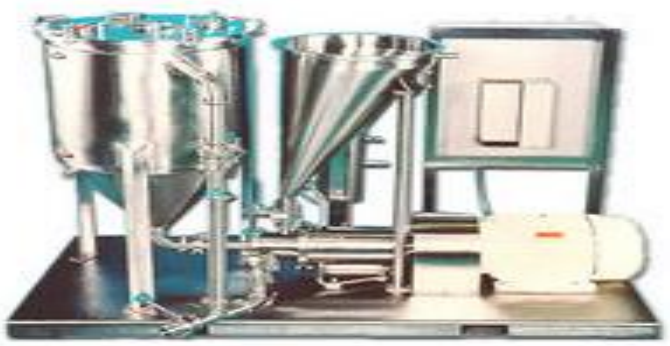

Fig. A Paddle mixer.

Vertical screw mixer: In these types of mixers, the screw rotates about its own axis whileorbiting around the centre axis of the conical tank. In another variation, the screw does not orbit but remains in the centre of the conical tank and is tapered so that theswept area steadily increases with increasing height. This type of mixer is mainly used for free flowing solids.

Fig.Vertical screw mixer.

Agitator mixers: Agitator mixers for powders can take a similar form to paddle mixers for liquids, but their efficiency is low. Planetary motion mixers are more effective, these are most commonly in the form of trough in which an arm rotates and transmits shearing action to the particles. General mixing requires an end-to-end movement which can be obtained by fitting helical blades to the agitator. In these mixers shear forces are not high, so that aggregates may remain unbroken and the movement may encourage segregation due to density or size differences. This type of mixer is most suitable for blending free-flowing materials, with components that are of uniform size and density. Special designs have been developed with modified agitators and vessels to overcome these limitations.

Tumbling mixers: In this kind of a mixer the rotation of the vessel imparts movement to the material by tilting the powder until the angle of the surface exceeds the angle of repose when the surface layers of the particles go into a slide. Simple forms use a cylindrical vessel rotating on its horizontal axis, but shear forces are low and end-to-end movement is slight. This may be overcome by including flights (a form of baffles), or the shape of the vessel may be altered to avoid symmetry. In addition, the particles hit against the wall and are deflected, causing considerable velocity and accelerationgradients. The repeated reversal of the direction of flow makes the tumbling mixer preferable where differences in density for particle size occur.

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. Tumblersof this type are available plain or with an agglomerate-breaking device or with a spray nozzle or with both of these devices. 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.

Features

- The mixing barrel and blades are made of stainless steel always keeping clean and away from dirt. The mixing barrel can be tilted freely at the angle of 0°~360° degrees for discharging and cleaning purpose.
- The conical shape at both ends enables uniform mixing and easy discharge.
- ™The cone is statically balanced to avoid any excessive load on the gear box and motor.
- ™While the powder can be loaded into the cone through a wider opening, it candischarged through a side valve.
- Depending upon the product, paddle type baffles can be provided on the shaft for better mixing.

Fig. A double cone blender.

V- blenders: V blenders are used for dry mixing. They are totally enclosed to prevent any foreign particles to enter into the chamber.

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.[4]

Fig. A V –blender.

Granulated products

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. Wet granulation usually consists of the following steps. The solid excipients are blended and massed with the granulating fluid in a planetary mixer. The wet mass is formed into granules in one of the following before drying: vibratory sieve, oscillating granulator, grater or mill. For drugs subject to hydrolysis, non aqueous granulating fluids can be used. Most often wet massing and screening is used. The formed granules are dried in a tray oven or fluid bed drier. The dried granules are then screened in a vibratory sieve or oscillating granulator to break up or remove aggregates of granules.

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.[3]

- The equipments used in this process are.

Planetary mixers: The planetary mixer is used for mixing of dry and wet powders, light pastes, gels, and doughs. 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 it 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.

Fig.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.

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[5]

Tray dryer: In tray dryers, the pharmaceutical powder spread out, generally quite thinly, on trays in which the drying takes place. Heating may be by an air current sweeping across the trays, by conduction from heated trays or heated shelves on which the trays lie, or by radiation from heated surfaces. The hot air penetrates through the raw material via the holes punched at the tray bottom to evaporate the moisture from the raw material.

Advantages and features

1. Energy saving: Most of the air is circulating inside the drying chamber which can considerably save the energy.

2. Sanitary working condition: The inside surface is lined with stainless steel and fully welded. The sealed working condition can make sure sanitary working condition.

3. Uniform drying temperature: air distributor is fixed at each side of the drying chamber to make sure uniform air flow. So the temperature difference between the top and bottom is less than 2 °C. So the raw material can evenly dried.

4. Easy temperature control: The drying temperature can be easily controlled by PLC control system.

5. Low noise working condition: Heat resisting and low noise circulation fan is combined.

Fig.Tray dryer.

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 'fluidises', 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 fluidisation, 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.[6]

Combination product

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 blend 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.[3]

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. A general rule is 70^0 C at < 40% relative humidity.
- The finished batch should be protected from moisture. Store in lined containers with silica desiccant bags.
- Sample for batch uniformity. Test at the top, middle and bottom levels of dry mixture.[3]

Evaluation of oral reconstitutable system

(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 Brookefield 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, Vu, to the total volume, Vo of the suspension.i.e. F=Vu/VoThe 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 37^0C ± 0.5^0 C. The drug release at different time intervals was measured for two hours using UV spectrophotometer.

(6) Particle size: The oral reconstitutable suspensions 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: The zeta potential is measured in triplicates inmultimodal mode. Prior to the 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. The reconstituted suspension stored at various temperatures are evaluated after reconstitution and after 7th and 15th day of reconstitution.

10) PH values: The pH of suspensions was measured with the aid of a pH meter.[7]

ICH guidelines (q6a) for reconsitutable oral suspensions

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 testinguniformity 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 multipledose packages. The dosage unit is considered to be the typical dose taken by the patient. If the actual unit dose, as taken by the patient, is controlled, it may either be measured directly or calculated, based on the total measured weight or volume of drug divided by the total number of doses expected.

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. The dispensing equipment to be used is normally determined during development. 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 notdirectly address excipients, the principles discussed here may be applicable to excipients as well as to new drug products. Skip testing may be an appropriate approach in both cases where permissible.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. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test. 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 inprocess test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

f) Extractables: Generally, where development and stability data show evidence that extractables from the container/closure systems are consistently below levels that aredemonstrated 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. Where data demonstrate the need, tests and acceptance criteria for extractables 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 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. This test may be performed as an in-process test when justified by product development data. The testing apparatus, media, and conditions should be pharmacopoeial, if possible, or otherwise justified. Dissolution procedures using either pharmacopoeial or non-pharmacopoeial apparatus and conditions should be validated. Single-point measurements are normally considered suitable for immediate-release dosage forms. Multiple-point sampling, at appropriate intervals, should be performed for modifiedrelease dosage forms. Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo. 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. It may be performed as an inprocess test when justified by product development data. If these products have been demonstrated during development to have consistently rapid drug release characteristics, exclusion of a particle size distribution test from the specification may be proposed. 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. The mean, upper, and / or lower particle size limits should be well defined. Acceptance criteria should be set based on the observed range of variation, and 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. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

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 .Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

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.

m) 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 certain cases a more specific procedure (e.g., Karl Fischer titration) may be preferable.

Packaging and storage

(1)The dry powders for reconstitution should be packaged in wide mouth container having adequate 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 aluminium foil.[7]

Research article

A New reconstitutable oral paediatric hydrocortisone solution containing hydroxyproply beta cyclodextrin.

Hydrocortisone (HC) despite a low aqueous solubility and a very poor palatability is frequently used unlicensed in paediatric practice. Hence a reconstitutable taste masked hydrocortisone solution with the potential to be easily produced extemporaneously was developed. Excipients for the reconstitutable dry powder mix were selected based on their aqueous solubility, compatibility, safety profile in children and stability at the optimum pH for HC. HC was flavored (orange tangerine), preserved (methyl paraben sodium salt/potassium sorbate), adjusted to pH 4.2 (citric acid buffer) and included in a 1:6 hydroxypropyl-β-cyclodextrin (HP-β-CyD) complex which allowed complete solubilization of the drug following reconstitution within 1 min of handshake. Neotame 0.075% was found to be the sweetener of choice to mask the unpalatable taste and aftertaste of HC.5 mg/mL reconstituted oral palatable paediatric HC solution was stable for 1 month after reconstitution and has the potential to facilitate dosing, acceptability, availability and affordability.[8]

Marketed preparations

NAME	COMPANY	DRUGS	USE
Augmentin DS	Glaxosmithkline pharmaceuticals ltd.	Clavulanic acid, amoxicillin	Urinary tract infection, Respiratory tract infection.
Phexin DS	Glaxosmithkline pharmaceuticals ltd.	Cephalexin	Bone and joint infection, dental infections.
Nupod DS	Nicholas piramalindia ltd.	Cefpodoxime	Pharyngitis, tonsillitis
Kefloxin DS	Ranbaxy laboratories ltd	Cefadroxil	Arrythmias after myocardial infarction
Flemoxin DS	East india pharmaceutical works ltd.	Amoxicillin	Infections caused by bacteria in different parts of the body.

Patents

1) Dry syrup of teldane

(China Patent no.96103874)

The present invention discloses a kind of terfenadine drysyrup which consists of main drug terfenadine, solubilizer-beta cyclic dextrin, correctives, filler (or called excipient), disintegrating agent and cohesive and is made into granular preparation by certain method in accordance with a specific proportion. Said dry syrup possesses good taste and resolution property. The resolution degree of main drug in dry syrup is improved obviously. Said invention provided a highly effective method for changing the terfenadine from tablet into dry syrup.

2) Orally effective methylphenidate extended release powder and aqueous suspension product.

(US Patent no. 8287903)

An oral methylphenidate powder which is reconstitutable into a final oral aqueous sustained release formulation containing at least about 50%, or at least about 80% by weight water based on the total weight of the suspension, is provided. The powder is a blend containing a combination of an uncoated methylphenidate-ion exchange resin complex, a barrier coated methylphenidate-ion exchange resin complex-matrix, and a water soluble buffering agent such that upon formed into an aqueous liquid formulation, the formulation has a pH in the range of about 3.5 to about 5, or about 4 to about 4.5. Following administration of a single dose of the oral aqueous methylphenidate suspension, a therapeutically effective amount of methylphenidate is reached in less than one hour and the composition provides a twelve-hour extended release profile.[9]

CONCLUSION

The reconstituted oral suspension shows high level of acceptance in case of administration, patient compliance and stability after formulation with respect to other Dosage forms. This system shows the chemical stability of the drug during shelf life and avoids physical stability problems related to solubility and pH. This formulation is used mostly for antibiotic drugs. It is mainly formulated for the paediatric population.

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