Liquid preparation for oral use

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This monograph does not apply to liquids intended for oromucosal administration (e.g. gargles and mouthwashes).

Definition

Liquid preparations for oral use are usually solutions, emulsions or suspensions containing one or more active ingredients in a suitable vehicle; they may in some cases consist simply of a liquid active ingredient used as such. Liquid preparations for oral use are either supplied in the finished form or, with the exception of Oral emulsions, may also be prepared just before issue for use by dissolving or dispersing granules or powder in the vehicle stated on the label.

The vehicle for any liquid preparation for oral use is chosen having regard to the nature of the active ingredient(s) and to provide organoleptic characteristics appropriate to the intended use of the preparation. Liquid preparations for oral use may contain suitable antimicrobial preservatives, antioxidants and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilizing, stabilizing, flavouring and sweetening agents and authorized colouring matter.

Liquid preparations for oral use may be supplied as multidose or as single-dose preparations. Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 mL or multiples thereof, or an oral syringe for other volumes or, for Oral drops, a suitable dropper.

Additional information

Liquid preparations for oral use are often the dosage form of choice for paediatric use.

Owing to the wide range of liquid preparations for oral use and their long history of use, a variety of terms has been used to describe different members of this category of preparation. These terms, which are not mutually exclusive and the definitions of which have changed over time, include elixirs, linctuses, milks, mixtures and syrups. Such terms are still used within the titles of certain specific, long-established, traditional preparations (e.g. ephedrine elixir, codeine linctus, acid gentian mixture). With such exceptions, however, it is recommended that the titles of liquid dosage forms for oral use are based on the terms used as sub-monograph headings in this general monograph. The term syrup (denoting a solution containing a high proportion of sucrose) is used, inter alia, for certain solutions (e.g. black currant syrup, lemon syrup) that are used as vehicle ingredients for their sweetening and flavouring properties. Such syrups are not dosage forms in the pharmacopoeial sense: they do not contain any active ingredient and are not intended to be administered as such.

Oral solutions containing one or more active ingredients dissolved in a vehicle containing a high proportion of sucrose or a suitable polyhydric alcohol or alcohols and which may contain ethanol, have traditionally been called elixirs. Viscous oral solutions containing one or more active ingredients dissolved in a vehicle containing a high proportion of sucrose, other sugars or a suitable polyhydric alcohol or alcohols and which are intended for use in the treatment or relief of cough have traditionally been called linctuses. They are intended to be sipped and swallowed slowly without the addition of water.

Manufacture

The manufacturing process for liquid preparations for oral use should meet the requirements of Good Manufacturing Practice (GMP).

The following information is intended to provide broad guidelines concerning the critical steps to be followed during production of liquid preparations for oral use.

In the manufacture of liquid preparations for oral use, measures are taken to:

- ensure that all ingredients are of appropriate quality
- minimize the risk of microbial contamination (see recommendations in chapter *Microbiological quality of non-sterile products: recommended acceptance criteria for pharmaceutical preparations* of the supplementary information section.);
- minimize the risk of cross-contamination

During the development of a preparation, the formulation for which contains one or more antimicrobial preservatives, the effectiveness of the chosen preservative system shall be demonstrated to the satisfaction of the relevant regulatory authority.

Appropriate measures should also be taken to optimize the stability of the active ingredient(s) in liquid formulations including those prepared from powder or granules. Additional measures should be taken so that, when stored under the conditions stated on the label, oral solutions are not subject to precipitation and oral suspensions are not subject to fast sedimentation, lump formation or caking.

During development of a single-dose liquid preparation for oral use, it shall be demonstrated that the nominal content can be withdrawn from the container.

In the production of liquid preparations for oral use containing dispersed particles, measures are taken to ensure a suitable and controlled particle size and, where appropriate, crystal structure (polymorphic and/or solvated forms) with regard to the intended use.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production. In-process controls during the manufacture of oral liquids should include pH and fill volume. The validation of the manufacturing process and the in-process controls are documented.

Safety concerns

An important aspect of GMP for all pharmaceutical products is assuring the quality of all the starting materials used. The need for analytical testing to check the identity and quality of starting materials is explained in detail in section 14 of the current WHO GMP guidelines [1]. Failure to ensure that starting materials are of the required quality can have very serious consequences.

Increasingly, countries are dependent on the importation of starting materials for use in the production of medicines. Starting materials often change hands many times before reaching the manufacturer of the final marketed product and there are many opportunities for the material to undergo re-labelling along the distribution and trade chain (see WHO guideline on *Good Trade and Distribution Practices for Pharmaceutical Starting Materials* [1]). As a result, starting materials required for production of pharmaceutical products can become contaminated or materials may be supplied that no longer correspond to what is stated on the label in terms of quality or identity, either accidentally or as a result of negligence and sometimes fraud.

[1] For the current edition of WHO guidelines, please consult the WHO Medicines web site: http://www.who.int/medicines/en/

The most documented incidents of contamination involve liquid preparations for oral use manufactured with excipients such as glycerol and propylene glycol that have been contaminated, adulterated or mixed up with diethylene glycol or ethylene glycol. Such incidents have been responsible for hundreds of deaths throughout the world (see, for example, editorial in *WHO Bulletin* 2001, 79(2)). Ingestion of diethylene glycol or ethylene glycol often leads to death through kidney failure. National Quality Control Laboratories, tasked with the analysis of suspicious finished pharmaceutical products, may use the Test for Diethylene glycol and Ethylene Glycol in Liquid Preparations for Oral Use in the Supplementary Information section to test for these contaminants.

Uniformity of mass

Liquid preparations for oral use that are presented as single-dose preparations comply with the following test. Weigh individually the contents of 20 containers, emptied as completely as possible, and determine the average mass. Not more than 2 of the individual masses deviate by more than 10% from the average mass and none deviates by more than 20%.

Uniformity of mass of doses delivered by the measuring device

The measuring device provided with a multidose liquid preparation for oral use complies with the following test. Weigh individually 20 doses taken at random from one or more multidose containers with the measuring device provided and determine the individual and average masses. Not more than two of the individual masses deviate by more than 10% from the average mass and none deviates by more than 20%.

Containers

The containers should be made of material that will not adversely affect the quality of the preparation by, for example, leaching or sorption. Liquid preparations for oral use that contain light-sensitive active ingredients are supplied in containers that are light-resistant.

Except where indicated in the individual monograph, containers should be made from material that is sufficiently transparent to permit the visual inspection of the contents.

If the preparation contains volatile ingredients, the liquid preparation for oral use should be kept in a tightly closed container.

Labelling

Every pharmaceutical preparation must comply with the labelling requirements established under GMP.

The label should include:

(1) the name of the pharmaceutical product;
(2) the name(s) of the active ingredients; International Nonproprietary Names (INNs) should be used wherever possible;
(3) the amount of active ingredient in a suitable dose-volume;
(4) the name and concentration of any antimicrobial preservative and the name of any other excipient;
(5) the batch (lot) number assigned by the manufacturer;
(6) the expiry date and, when required, the date of manufacture;
(7) any special storage conditions or handling precautions that may be necessary;

(8) directions for use, warnings, and precautions that may be necessary; and
(9) the name and address of the manufacturer or the person responsible for placing the product on the market.

If the Liquid preparation for oral use is supplied as granules or powder to be constituted just before issue for use, the label should include:

(1) that the contents of the container are granules or powder for the preparation of an oral liquid;
(2) the strength as the amount of the active ingredient in a suitable dose-volume of the constituted preparation;
(3) the directions for preparing the oral liquid including the nature and quantity of liquid to be used; and
(4) the storage conditions and shelf-life of the constituted preparation.

Requirements for specific types of liquid preparations for oral use

Oral solutions

Definition. Oral solutions are clear Liquid preparations for oral use containing one or more active ingredients dissolved in a suitable vehicle.

Visual inspection. Inspect the solution. It should be clear and free from any precipitate. A change in colour or cloudiness of solutions may indicate chemical degradation or microbial contamination.

Oral suspensions

Definition. Oral suspensions are Liquid preparations for oral use containing one or more active ingredients suspended in a suitable vehicle. For oral suspensions containing more than one active ingredient, some of the active ingredients may be in solution.

Oral suspensions may show a sediment which is readily dispersed on shaking to give a uniform suspension which remains sufficiently stable to enable the correct dose to be delivered.

Visual inspection. Inspect the suspension. Evidence of physical instability is demonstrated by the formation of flocculants or sediments that do not readily disperse on gentle shaking. A change in colour may indicate chemical degradation or microbial contamination.

Dissolution. Where a requirement for compliance is specified in the individual monograph, the oral suspension complies with the test *5.5 Dissolution test for oral dosage forms*.

Uniformity of content. For oral suspensions that are presented as single-dose preparations and that contain less than 5 mg of active ingredient per dose or in which the active ingredient is less than 5% of the total weight per dose, carry out the following test. Shake and empty each container as completely as possible and carry out the test as described under *5.1 Uniformity of content for single-dose preparations*. In such cases, the test for Uniformity of mass prescribed above is not required.

Labelling. The label on the container should include a direction that the bottle should be shaken before use.

Oral emulsions

Definition. Oral emulsions are Liquid preparations for oral use containing one or more active ingredients. They are stabilized oil-in-water dispersions, either or both phases of which may contain dissolved solids. Solids may also be suspended in Oral emulsions.

Oral emulsions may show evidence of phase separation but are readily re-dispersed on shaking.

Visual inspection. Inspect the emulsion. Evidence of physical instability is demonstrated by phase separation that is not readily reversed on gentle shaking. A change in colour of emulsions may indicate chemical degradation or microbial contamination.

Containers. When issued for use, Oral emulsions should be supplied in wide-mouthed bottles.

Labelling. The label on the container should include a direction that the bottle should be shaken before use.

Oral drops

Definition. Oral drops are Liquid preparations for oral use that are intended to be administered in small volumes with the aid of a suitable measuring device. They may be solutions, suspensions or emulsions.

Visual inspection. Inspect the drops. Drops that are solutions should be clear and free from any precipitate. Evidence of physical instability of drops that are suspensions is demonstrated by the formation of flocculants or sediments that do not readily disperse on gentle shaking. Evidence of physical instability of drops that are emulsions is demonstrated by phase separation that is not readily reversed on gentle shaking. A change in colour (or cloudiness of solutions) may indicate chemical degradation or microbial contamination of the drops.

Dose and uniformity of dose of oral drops . Into a suitable, graduated cylinder, introduce by means of the dropping device the number of drops usually prescribed for one dose or introduce by means of the measuring device the usually prescribed quantity. The dropping speed does not exceed 2 drops per second. Weigh the liquid, repeat the addition, weigh again and carry on repeating the addition and weighing until a total of 10 masses are obtained. No single mass deviates by more than 10% from the average mass. The total of 10 masses does not differ by more than 15% from the nominal mass of 10 doses. If appropriate, measure the total volume of 10 doses. The volume does not differ by more than 15% from the nominal volume of 10 doses.

Containers. Oral drops are normally supplied in suitable multidose containers that allow successive drops of the preparation to be administered.

Powders for oral solutions, oral suspensions or oral drops

Presentations of powder (usually single-dose presentations: for example, a small sachet) that are intended to be issued to the patient as a powder, to be taken in or with water or another suitable liquid, are outside the scope of this general monograph. Such preparations are controlled by the monograph for Oral powders.

Definition. Powders for oral solutions, suspensions or drops are multidose preparations consisting of solid, loose, dry particles of varying degrees of fineness. They contain one or more active ingredients, with or without excipients and, if necessary, authorized colouring matter and flavouring substances. They may contain antimicrobial preservatives and other excipients in particular to facilitate dispersion or dissolution and to prevent caking.

After dissolution or suspension in the prescribed liquid, they comply with the requirements for Oral solutions, Oral suspensions or Oral drops, as appropriate.

Manufacture. In the manufacture of powders for oral solutions, suspensions or drops, the components of the powder mixture are passed through a sieve to remove lumps and particle aggregates. The weighed masses of the sieved components, preferably of a narrow particle size distribution, are then transferred to a suitable mixer. The greatest risk of segregation of the powder mixture usually occurs when emptying the mixer container and when the powder mixture is dosed into the containers. Ensuring the suitability of the mixing equipment and the dosing devices is, therefore, critical.

Visual inspection. Inspect the powder. Evidence of physical instability is demonstrated by noticeable changes in physical appearance, including texture (e.g. clumping). A change in colour may indicate chemical degradation or microbial contamination.

Granules for oral solutions or suspensions

Presentations of granules that are intended to be issued to the patient as granules to be swallowed as such, to be chewed, or to be taken in or with water or another suitable liquid, are outside the scope of this general monograph.

Definition. Granules for oral solutions or suspensions are multidose preparations consisting of solid, dry aggregates of powder particles sufficiently resistant to withstand handling. They contain one or more active ingredients with or without excipients and, if necessary, authorized colouring matter and flavouring substances. They may contain antimicrobial preservatives and other excipients in particular to facilitate dispersion or dissolution and to prevent caking.

After dissolution or suspension in the prescribed liquid, they comply with the requirements for Oral solutions or Oral suspensions, as appropriate.

Visual inspection. Inspect the granules. Evidence of physical instability is demonstrated by noticeable changes in physical appearance, including texture (e.g. clumping of granules, presence of loose powder). A change in colour may indicate chemical degradation or microbial contamination.