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GRANULES

Granulata

Requirements for granules to be used for the preparation of oral solutions or suspensions are given in the monograph Liquid preparations for oral use (0672). Where justified and authorised, the requirements of this monograph do not apply to granules for veterinary use.

DEFINITION

Granules are preparations consisting of solid, dry aggregates of powder particles sufficiently robust to withstand handling. They are intended for oral administration. Some are swallowed as such, some are chewed and some are dissolved or dispersed in water or another suitable liquid before being administered.

For reasons of patient safety and to ensure the correct administration of the medicinal product, this term may also be used where very small tablets (rather than granules) are presented in a sachet, and where the entire contents of the sachet are intended for oral administration as a single dose.

Granules contain one or more active substances with or without excipients and, if necessary, colouring matter authorised by the competent authority and flavouring substances.

Granules are presented as single-dose or multidose preparations. Each dose of a multidose preparation is administered by means of a device suitable for measuring the quantity prescribed. For single-dose granules, each dose is enclosed in an individual container, for example a sachet or a vial.

Where applicable, containers for granules comply with the requirements of *Materials used for the manufacture of containers* (*3.1* and subsections) and *Containers* (*3.2* and subsections).

Several categories of granules may be distinguished:

- effervescent granules;
- coated granules;
- gastro-resistant granules;
- modified-release granules.

PRODUCTION

In the manufacture, packaging, storage and distribution of granules, suitable measures are taken to ensure their microbial quality; recommendations on this aspect are provided in general chapter *5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use*.

TESTS

Uniformity of dosage units. Single-dose granules comply with the test for uniformity of dosage units (*2.9.40*) or, where justified and authorised, with the tests for uniformity of content and/or uniformity of mass shown below. Herbal drugs and herbal drug preparations present in the dosage form are not subject to the provisions of this paragraph.

Uniformity of content (*2.9.6*). Unless otherwise prescribed or justified and authorised, single-dose granules with a content of active substance less than 2 mg or less than 2 per cent of the total mass comply with test B for uniformity of content of single-dose preparations. If the preparation has more than one active substance, the requirement applies only to those substances that correspond to the above conditions.

Uniformity of mass (*2.9.5*). Single-dose granules except for coated granules comply with the test for uniformity of mass of single-dose preparations. If the test for uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required.

Uniformity of mass of delivered doses from multidose containers (*2.9.27*). Granules supplied in multidose containers comply with the test.

STORAGE

If the preparation contains volatile ingredients or the contents have to be protected, store in an airtight container.

Effervescent granules

DEFINITION

Effervescent granules are uncoated granules generally containing acid substances and carbonates or hydrogen carbonates which react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in water before administration.

TESTS

Disintegration. Place 1 dose of the effervescent granules in a beaker containing 200 mL of *water R* at 15-25 °C; numerous bubbles of gas are evolved. When the evolution of gas around the individual grains ceases, the granules have disintegrated, being either dissolved or dispersed in the water. Repeat the operation on 5 further doses. The preparation complies with the test if each of the 6 doses used disintegrates within 5 min.

STORAGE

In an airtight container.

Coated granules

DEFINITION

Coated granules are usually multidose preparations and consist of granules coated with one or more layers of mixtures of various excipients.

PRODUCTION

The substances used as coatings are usually applied as a solution or suspension in conditions in which evaporation of the vehicle occurs.

TESTS

Dissolution. A suitable test may be carried out to demonstrate the appropriate release of the active substance(s), for example one of the tests described in general chapter *2.9.3. Dissolution test for solid dosage forms*.

Modified-release granules

DEFINITION

Modified-release granules are coated or uncoated granules that contain special excipients or that are prepared by special procedures, or both, designed to modify the rate, the place or the time at which the active substance or substances are released.

Modified-release granules include prolonged-release granules and delayed-release granules.

PRODUCTION

A suitable test is carried out to demonstrate the appropriate release of the active substance(s).

TESTS

Dissolution. Carry out a suitable test to demonstrate the appropriate release of the active substance(s), for example the test described in general chapter *2.9.3. Dissolution test for solid dosage forms*.

Gastro-resistant granules

DEFINITION

Gastro-resistant granules are delayed-release granules that are intended to resist the gastric fluid and to release the active substance(s) in the intestinal fluid. These properties are achieved by covering the granules with a gastro-resistant material or by other suitable means.

PRODUCTION

A suitable test is carried out to demonstrate the appropriate release of the active substance(s).

TESTS

Dissolution. Carry out a suitable test to demonstrate the appropriate release of the active substance(s), for example the test described in general chapter *2.9.3. Dissolution test for solid dosage forms*.

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INTRAMAMMARY PREPARATIONS FOR VETERINARY USE

Praeparationes intramammariae ad usum veterinarium

DEFINITION

Intramammary preparations for veterinary use are sterile preparations intended for introduction into the mammary gland via the teat canal. There are two main categories: those intended for administration to lactating animals, and those intended for administration to animals at the end of lactation or to non-lactating animals for the treatment or prevention of infection.

Intramammary preparations for veterinary use are solutions, emulsions or suspensions or semi-solid preparations containing one or more active substances in a suitable vehicle. They may contain excipients such as stabilising, emulsifying, suspending and thickening agents. Suspensions may show a sediment which is readily dispersed on shaking. Emulsions may show evidence of phase separation but are readily redispersed on shaking.

Unless otherwise justified and authorised, intramammary preparations for veterinary use are supplied in containers for use on one occasion only for introduction in a single teat canal of an animal.

If supplied in multidose containers, aqueous preparations contain a suitable antimicrobial preservative at a suitable concentration, except where the preparation itself has adequate antimicrobial properties. Precautions for administration and for storage between administrations must be taken.

Where applicable, containers for intramammary preparations for veterinary use comply with the requirements of *Materials used for the manufacture of containers* (*3.1* and subsections) and *Containers* (*3.2* and subsections).

PRODUCTION

During the development of a intramammary preparation for veterinary use, the formulation for which contains an antimicrobial preservative, the effectiveness of the chosen preservative shall be demonstrated to the satisfaction of the competent authority. A suitable test method together with criteria for judging the preservative properties of the formulation are provided in the text on *Efficacy of antimicrobial preservation* (*5.1.3*).

Intramammary preparations for veterinary use are prepared using materials and methods designed to ensure sterility and to avoid the introduction of contaminants and the growth of micro-organisms; recommendations on this aspect are provided in the text on *Methods of preparation of sterile products* (*5.1.1*).

In the manufacture of intramammary preparations for veterinary use containing dispersed particles, measures are taken to ensure a suitable and controlled particle size with regard to the intended use.

TESTS

Deliverable mass or volume. Squeeze out as much as possible of the contents of ten containers according to the instructions on the label. The mean mass or volume does not differ by more than 10 per cent from the nominal mass or volume.

Sterility (*2.6.1*). Intramammary preparations for veterinary use comply with the test for sterility; use the technique of membrane filtration or, in justified cases, direct inoculation of the culture media. Squeeze out the contents of ten containers and mix thoroughly. For each medium, use 0.5 g to 1 g (or 0.5 mL to 1 mL as appropriate) taken from the mixed sample.

STORAGE

Store in a sterile, airtight, tamper-evident container.

LABELLING

The label states:

- the name of the active substance(s) and the mass or number of International Units of the active substance(s) that may be delivered from the container using normal technique;
- whether the preparation is intended for use in a lactating animal or a non-lactating animal;
- in the case of multidose containers, the name of any added antimicrobial preservative.

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INTRARUMINAL DELIVERY SYSTEMS

Praeparationes intraruminales

The requirements of this monograph do not apply to preparations (sometimes known as boluses) such as large conventional tablets, capsules or moulded dosage forms that give immediate or prolonged release of the active substance(s). Such preparations comply with the relevant parts of the monographs Capsules (0016) or Tablets (0478).

DEFINITION

Intraruminal delivery systems are solid preparations each containing one or more active substances. They are intended for oral administration to ruminant animals, and may be administered by means of a suitable device. They are designed to be retained in the rumen to deliver the active substance(s) in a continuous or pulsatile manner. The period of release of the active substance(s) may vary from days to weeks according to the nature of the formulation and/or the delivery system.

Some intraruminal delivery systems are intended to float on the surface of the ruminal fluid while others are intended to remain on the floor of the rumen or reticulum. Each delivery system has a density appropriate for its intended purpose.

PRODUCTION

For continuous release, the intraruminal delivery system is designed to release the active substance(s) at a defined rate over a defined period of time. This may be achieved by erosion, corrosion, diffusion, osmotic pressure or any other suitable chemical, physical or physico-chemical means.