World Health Organization

CAPSULES

Draft proposal for revision in *The International Pharmacopoeia*

(26 July 2024)

DRAFT FOR COMMENTS

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/23.927

CAPSULES

Description	Date
Revision drafted by the Secretariat with support from the WHO Prequalification Programme.	January 2024
Discussion at the Consultation on quality control and pharmacopoeial specifications for medicines	May 2024
Draft revision sent out for public consultation.	July – August 2024
Presentation at the 58th meeting of the Expert Committee on Specifications for Pharmaceutical Preparations.	October 2024
Further follow-up action as required.	

*[**Note from the Secretariat**. Following a request received from the WHO Prequalification Programme, a revision of the general monograph on Capsules is proposed.*

The revised text refers to the need to understand the effect of variations in the properties of gelling agents added to HPMC capsule shells on the dissolution/ disintegration performance of the finished product.

Changes to the current text are indicated by <u>insert</u> or ~~delete~~.]

CAPSULES

The requirements of this monograph do not necessarily apply to preparations that are presented as capsules intended for use other than by oral administration, such as vaginal or rectal capsules or capsules for inhalation. Such preparations may require a special formulation, method of manufacture or form of presentation, appropriate to their particular use. Starch capsules (often known as cachets) are not included in this monograph.

Definition

Capsules are solid dosage forms with hard or soft shells. They are of various shapes and sizes and contain a single dose of one or more active ingredients. They are intended for oral administration. Their surfaces may bear symbols or other markings.

Capsule shells are made of gelatin, hydroxypropyl methyl cellulose (HPMC), or other substances, the consistency of which may be adjusted by the addition of substances such as glycerol or sorbitol. The shell should disintegrate in the presence of digestive fluids so that the contents are released. The contents of capsules may be solid, liquid or of a paste-like consistency. Capsule shells and contents may contain excipients such as diluents, solvents, surface-active substances, opaque fillers, antimicrobial agents, sweeteners, colouring matter authorized by the appropriate national or regional authority, flavouring substances, disintegrating agents, glidants, lubricants, gelling agents and substances capable of modifying the behaviour of the active ingredient(s) in the gastrointestinal tract. The contents should not cause deterioration of the shell.

When excipients are used, it is necessary to ensure that they do not adversely affect the stability, dissolution rate, bioavailability, safety or efficacy of the active ingredient(s); there must be no incompatibility between any of the components of the dosage form.

The different categories of capsule include:

- hard capsules;
- soft capsules;
- modified-release capsules (including delayed-release capsules (gastro-resistant/enteric capsules) and sustained-release capsules (extended-/prolonged-release capsules)).

Manufacture

The manufacturing and filling processes for capsules should meet the requirements of good manufacturing practices (GMP).

Very broad guidelines concerning the main critical steps to be followed during production of capsules, indicating those that are the most important, are provided below.

Additional guidelines specific for hard or soft capsules are provided in the respective subsections below.

In the manufacture of capsules, measures are taken to:

- ensure that the active ingredient(s), when present in solid-state form, have appropriate solid-state properties such as particle-size distribution and polymorphic form;
- ensure that mixing with excipients is carried out in a manner that ensures homogeneity;
- minimize the degradation of the active ingredient(s);
- minimize the risk of microbial contamination;
- minimize the risk of cross contamination.

The particle size of the active ingredient(s) may be of primary significance in determining the rate and extent of dissolution and the bioavailability of the drug product, especially for substances of low solubility in aqueous media. The uniformity

of the final drug product is affected by the particle size of the active ingredient(s) as well as the excipients.

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.

Packaging is required to be adequate to protect capsules from light when required, and from moisture and damage during transportation.

Visual inspection

Unpack and inspect at least 20 capsules. They should be smooth and undamaged. Evidence of physical instability is demonstrated by gross changes in physical appearance, including hardening or softening, cracking, swelling, mottling or discoloration of the shell.

Uniformity of mass

Capsules comply with the test for *5.2 Uniformity of mass for single-dose preparations*, unless otherwise specified in the individual monograph.

Uniformity of content

Where a requirement for compliance with the test for *5.1 Uniformity of content for single-dose preparations* is specified in an individual capsule monograph, the test for *5.2 Uniformity of mass for single-dose preparations* is not required.

Dissolution/disintegration

Where a choice of test is given ("Either test A or test B may be applied"), follow the instructions in the monograph. Where a requirement for compliance with a dissolution

test is specified in the individual monograph, the requirement for disintegration stated in the sections below do not apply.

When justified and authorized, the specified disintegration and dissolution media may contain enzymes to overcome failure in the tests caused by cross-linking of the gelatin.

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 ingredient(s); International Nonproprietary Names (INNs) should be used wherever possible;
3. the amount of the active ingredient(s) in each capsule and the number of capsules in the container;
4. the batch (lot) number assigned by the manufacturer;
5. the expiry date and, when required, the date of manufacture;
6. any special storage conditions or handling precautions that may be necessary;
7. directions for use, warnings and precautions that may be necessary; and
8. the name and address of the manufacturer or the person responsible for placing the product on the market.

Storage

Capsules should be kept in well-closed containers. They should be protected from light, when required, and from excessive moisture or dryness and should not be subjected to temperatures above 30 °C. Additional special packaging, storage and transportation recommendations are provided, where necessary, in the individual monograph.

Requirements for specific types of capsules

Hard capsules

Definition

Hard capsules have shells consisting of two prefabricated cylindrical sections that fit together. One end of each section is rounded and closed and the other is open. The contents of hard capsules are usually in solid form (powder or granules).

Manufacture

Sometimes the physical characteristics of the mixture of the active ingredient(s) and excipients allow it to be directly filled into the shell but it may occasionally be necessary to granulate before filling. Normally the granulate needs to be mixed with lubricants and/or disintegrating agents. The use of excessive amounts of lubricants should be avoided since these may deleteriously affect the capsules.

In-process controls during hard capsule production should include the moisture content of the mixture and/or granulate (as well as of the shells), the size of granules, the flow of the final mixture and the uniformity of mass, capsule size, integrity of the seals and disintegration or dissolution rate (e.g. for modified-release capsules) of the finished dosage form.

HPMC capsule shells can be manufactured in different ways, for example with and without the use of gelling agents. Different manufacturing methods can affect aspects of the capsule shells and thus lead to variability in product characteristics including dissolution. Manufacturer should understand these differences and minimize changes in shell supplier and/or method of manufacture (i.e. different products from the same supplier). Such changes may require significant validation to demonstrate that the change(s) have not affected the final product properties, for example, dissolution.

Disintegration test

Hard capsules comply with *5.3 Disintegration test for tablets and capsules*.

Use water as the immersion fluid unless another medium is specified in the individual monograph. Operate the apparatus for 30 minutes unless otherwise justified and authorized and examine the state of the capsules.

If capsules float, use a disc as described under 5.4 Disintegration test for suppositories.

Soft capsules

Definition

Soft capsules have thicker shells than hard capsules and antimicrobial preservatives are usually added. The shells are of one piece and various shapes. The contents of soft capsules are usually solutions or suspensions of the active ingredient(s) in non-aqueous liquids. Partial migration of the contents into the shell may occur (and vice versa) depending on the nature of the materials used and the product in question.

Manufacture

Soft capsules are usually formed, filled and sealed in one operation. However, shells for extemporaneous use are sometimes prefabricated. Liquids may be incorporated

directly. Solids are usually dissolved or dispersed in a suitable excipient(s) to give a solution, suspension or dispersion of paste-like consistency.

In-process controls during soft capsule production should include the viscosity of the contents and the uniformity of mass, capsule size, integrity of the seals and disintegration or dissolution rate (e.g. for modified-release capsules) of the finished dosage form.

Disintegration test

Soft capsules comply with *5.3 Disintegration test for tablets and capsules*, using water as the immersion fluid unless another medium is specified in the individual monograph. Add a disc to each tube. Liquid active substances dispensed in soft capsules may attack the disc; in such circumstances and where authorized, the disc may be omitted. Operate the apparatus for 30 minutes unless otherwise justified and authorized and examine the state of the capsules. If the capsules fail to comply because of adherence to the discs, the results are invalid. Repeat the test on a further 6 capsules omitting the discs.

Modified-release capsules

Definition

Modified-release capsules are hard or soft capsules in which the contents or the shell, or both, contain excipients or are prepared by special procedures such as micro-encapsulation which, separately or together, are designed to modify the rate, place or time of release of the active ingredient(s) in the gastrointestinal tract.

Sustained-release capsules (extended- or prolonged-release capsules)

Definition

Sustained-release capsules are designed to slow the rate of release of the active ingredient(s) in the gastrointestinal tract.

All requirements for these specialized dosage forms are given in the individual monographs.

Delayed-release capsules (gastro-resistant/enteric capsules)

Definition

Delayed-release capsules are hard or soft capsules prepared in such a manner that either the shell or the contents resist the action of gastric fluid but release the active ingredient(s) in the presence of intestinal fluid.

Manufacture

The additional statements given under either hard or soft capsules apply, as appropriate, to delayed-release capsules.

Disintegration test

Delayed-release capsules with a gastro-resistant shell comply with *5.3 Disintegration test for tablets and capsules*, using hydrochloric acid (0.1 mol/L) VS as the immersion fluid.

Operate the apparatus without the discs for 2 hours, unless otherwise specified in the individual monograph (but never for less than 1 hour) and examine the state of the capsules. No capsule should show signs of disintegration or rupture permitting the contents to escape. Replace the acid by phosphate buffer solution, pH 6.8, TS with added pancreatin R where specified in the individual monograph. Add a disc to each tube.

Operate the apparatus for 60 minutes and examine the state of the capsules. If the capsules fail to comply because of adherence to the discs, the results are invalid. Repeat the test on a further 6 capsules omitting the discs.

For capsules in which the contents, rather than the shell, resist the action of gastric fluid, carry out a suitable dissolution test to demonstrate the appropriate release of the active substance(s).

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