Tablets

The requirements of this monograph do not necessarily apply to preparations that are intended for use other than by oral administration, such as implants, solution-tablets for injections and irrigations, tablets for external use, vaginal tablets, etc. Such preparations may require a special formulation, method of manufacture, or form of presentation, appropriate to their particular use.

Definition

Tablets are solid dosage forms usually obtained by single or multiple compression of powders or granules. In certain cases tablets may be obtained by moulding or extrusion techniques. They are uncoated or coated.

Tablets are normally right circular solid cylinders, the end surfaces of which are flat or convex and the edges of which may be bevelled. They may have lines or break-marks (scoring), symbols or other markings.

If the break-mark(s) is/are intended to facilitate breaking the tablet for ease of swallowing a dose consisting of one or more whole tablets, the scoring is not critical. However, if the break-mark(s) is/are intended to permit accurate subdivision of the tablet in order to provide doses of less than one tablet, the scoring is critical. Tablets containing active ingredients having a narrow therapeutic window should generally not be presented with break-marks for subdivision. Non-functional break-marks should be avoided.

Tablets contain one or more active ingredients. They may contain excipients such as diluents, binders, disintegrating agents, glidants, lubricants, substances capable of modifying the behaviour of the dosage forms and the active ingredient(s) in the gastrointestinal tract, colouring matter authorized by the appropriate national or regional authority and flavouring substances. When such 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.

Tablets are single-dose preparations intended for oral administration. Some are intended to be swallowed whole, some after being chewed and some after being crushed, some are intended to be dissolved or dispersed in water before being taken and some are intended to be retained in the mouth where the active ingredient(s) is/are liberated.

The different categories of tablet include:

- -uncoated tablets;
- -coated tablets (including film-coated and sugar-coated tablets);
- -soluble tablets;
- -dispersible tablets;
- -effervescent tablets;
- -chewable tablets;
- -tablets for use in the mouth (including sublingual and buccal tablets);
- -modified-release tablets (including delayed-release tablets (gastro- resistant/enteric-coated tablets) and sustained-release tablets (extended-/prolonged-release tablets)).

Manufacture

The manufacturing processes for tablets should meet the requirements of good manufacturing practices (GMP).

The following information is intended to provide broad guidelines concerning the critical steps to be followed during production of tablets.

In the manufacture of tablets, measures are taken to:

- -ensure that the active ingredient(s) 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;
- -ensure that the tablets possess a suitable mechanical strength to avoid crumbling or breaking on subsequent processing, e.g. coating, storage and distribution;
- -minimize the degradation of the active ingredient(s);
- -minimize the risk of microbial contamination;
- -minimize the risk of cross-contamination.

In addition, in the manufacture of those scored tablets (tablets bearing a break-mark or marks) for which subdivision is intended in order to provide doses of less than one tablet measures are taken to:

- -ensure the effectiveness of break-marks with respect to the uniformity of mass or content, as appropriate, of the subdivided parts so that the patient receives the intended dose.

A suitable test to assess the uniformity of mass during development is as follows:

Take 30 tablets at random. Break each tablet by hand and take one part for the test and reject the other part(s). Weigh each of the 30 parts thus obtained and calculate the average mass. No individual mass is outside the limits of 75% to 125% and not more than one individual mass is outside the limits of 85% to 115% of the average mass.

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

Sometimes the physical characteristics of the mixture allow it to be directly compressed; in this case the particle size distribution and flowability of the ingredients becomes particularly important because of the risk for segregation during handling of the mix. However, it is usually necessary to granulate before compression, preferably by wet-granulation but in certain cases dry-granulation may be preferred. Generally wet-granulation of the mix before compression reduces the risk for segregation. When a wet-granulation technique is employed control of the residual moisture after the drying step is important for smooth tablet compression. Too low or too high moisture contents may influence the chemical and physical stability of the final tablet. The granulate and powders normally need to be mixed with glidants and/or lubricants before the compression stage to improve the powder flow and to reduce sticking and adhesion to walls and punches during compression. The use of excessive amounts of glidants and lubricants should be avoided since these will deleteriously affect the tablets. Some lubricants like magnesium stearate may in excessive amounts or by long mixing times reduce the mechanical resistance of tablets and prolong disintegration and dissolution time.

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 tablet production should include the moisture content of the final lubricated blend, the size of granules, the flow of the final mixture and, where relevant, the uniformity of mass of tablet cores before coating. In-process controls during tablet production should also include the dimensions (thickness, diameter), uniformity of mass, hardness and/or crushing force, friability, disintegration or dissolution rate (for example, for modified-release tablets) of the finished dosage form. Suitable test methods that may be used to demonstrate certain of these attributes are provided in Section 3 of Supplementary information.

In the manufacture, packaging, storage and distribution of tablets, suitable measures are taken to ensure their microbiological quality (see Supplementary information, 3.6 Microbiological quality of non-sterile products: recommended acceptance criteria of pharmaceutical preparations).

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

The validation of the manufacturing process and the in-process controls are documented.

Visual inspection

Unpack and inspect at least 20 tablets. They should be undamaged, smooth and usually of uniform colour.

Evidence of physical instability is demonstrated by:

- -presence of excessive powder and/or pieces of tablets at the bottom of the container (from abraded, crushed, or broken tablets);
- -cracks or capping, chipping in the tablet surfaces or coating, swelling, mottling, discoloration, fusion between tablets;
- -the appearance of crystals on the container walls or on the tablets.

Uniformity of mass

Tablets comply with the test for 5.2 Uniformity of mass for single-dose preparations, unless otherwise specified below or 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 tablet 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 requirements for disintegration stated in the sections below do not apply.

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 (INN) should be used wherever possible;

(3) the amount of the active ingredient(s) in each tablet and the number of tablets 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;

(8) the name and address of the manufacturer or the person responsible for placing the product on the market;

(9) for scored tablets where the directions for use include subdivision to provide doses of less than one tablet, the label should also include:

- the storage conditions for and the period of use of those subdivided part(s) not immediately taken or administered.

Storage

Tablets should be kept in well-closed containers and protected from light, moisture, crushing and mechanical shock. Tablets should be able to withstand handling, including packaging and transportation, without losing their integrity. Moisture-sensitive forms, such as effervescent tablets, should be stored in tightly closed containers or moisture-proof packs and may require the use of separate packages containing water-adsorbent agents, such as silica gel, or in unit dose packaging (blister cards).

Additional special packaging, storage and transportation recommendations are provided, where necessary, in the individual monograph.

Requirements for specific types of tablets

Uncoated tablets

Definition

The majority of uncoated tablets are made in such a way that the release of active ingredients is unmodified. A broken section, when examined under a lens, shows either a relatively uniform texture (single-layer tablets) or a stratified texture (multilayer tablets), but no signs of coating.

Disintegration test

Uncoated tablets, except soluble tablets, dispersible tablets, effervescent tablets and tablets for use in the mouth comply with 5.3 Disintegration test for tablets and capsules . Operate the apparatus for 15 minutes, unless otherwise specified in the individual monograph, and examine the state of the tablets.

Soluble tablets

Definition

Soluble tablets are uncoated or film-coated tablets that are intended to be dissolved in water giving a clear or slightly opalescent solution.

Disintegration test

Soluble tablets disintegrate within 3 minutes when examined by 5.3 Disintegration test for tablets and capsules , but using water R at 15–25° C.

Dispersible tablets

Definition

Dispersible tablets are uncoated tablets or film-coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion.

Disintegration test

Dispersible tablets disintegrate within 3 minutes when examined by 5.3 Disintegration test for tablets and capsules, but using water R at 15–25° C.

Fineness of dispersion

Place 2 tablets in 100 mL of water R and stir until completely dispersed. A smooth dispersion is produced, which passes through a sieve screen with a nominal mesh aperture of 710 µm.

Effervescent tablets

Definition

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

Manufacture

The manufacture of effervescent tablets is carried out in low-humidity conditions so that the reaction between acidic and basic components of the formulation does not take place.

Labelling

The label should state: "Not to be swallowed directly".

Disintegration test

Place one tablet in a 250 mL beaker containing 200 mL of water R at 15–25 °C. Numerous bubbles of gas are evolved. When the evolution of gas around the tablet or its fragments ceases, the tablet should have disintegrated, being either dissolved or dispersed in the water so that no agglomerates remain. Repeat the operation on five additional tablets. The tablets comply with the test if each of the six tablets used in the test disintegrates within 5 minutes, unless otherwise specified in the individual monograph.

Chewable tablets

Definition

Chewable tablets are usually uncoated. They are intended to be chewed before being swallowed; however, where indicated on the label, they may be swallowed whole instead.

Manufacture

In the manufacture of chewable tablets, measures are taken to:

-ensure that the tablets are easily crushed by chewing;

-ensure that the tablets are palatable.

Tablets for use in the mouth

Definition

Tablets for use in the mouth are usually uncoated. They are usually formulated to effect a slow release and local action of the active ingredient(s) (for example, compressed lozenges) or the release and absorption of the active ingredient(s) under the tongue (sublingual tablets) or in other parts of the mouth (buccal) for systemic action.

Manufacture

In the manufacture of tablets for use in the mouth, measures are taken to:

-ensure the release characteristics are appropriate to the intended use.

Coated tablets

Definition

Coated tablets are tablets covered with one or more layers of mixtures of substances such as natural or synthetic resins, polymers, gums, fillers, sugars, plasticizers, polyols, waxes, colouring matters authorized by the appropriate national or regional authority, flavouring substances and sometimes also active ingredients. A broken section, when examined under a lens, shows a core which is surrounded by a continuous layer of a different texture.

The tablets may be coated for a variety of reasons such as protection of the active ingredients from air, moisture or light, masking

of unpleasant tastes and odours or improvement of appearance. The substance used for coating is usually applied as a solution or suspension.

Three main categories of coated tablet may be distinguished: sugar-coated, film-coated, and certain modified-release tablets.

Sugar-coated tablets

Uniformity of mass

The test for 5.2 Uniformity of mass for single-dose preparations, does not apply to sugar-coated tablets (see in-process controls under Manufacture).

Disintegration test

Sugar-coated tablets comply with 5.3 Disintegration test for tablets and capsules. Operate the apparatus for 60 minutes, unless otherwise specified in the individual monograph, using water and examine the state of the tablets. If any of the tablets has not disintegrated repeat the test on an additional six tablets, using hydrochloric acid (0.1 mol/l) VS.

All six tablets must disintegrate.

Film-coated tablets

Definition

A film-coated tablet is covered with a thin layer of resins, polymers and/or plasticizers capable of forming a film.

Disintegration test

Film-coated tablets comply with 5.3 Disintegration test for tablets and capsules. Operate the apparatus for 30 minutes and examine the state of the tablets.

Modified-release tablets

Definition

Modified-release tablets are coated, uncoated or matrix tablets containing excipients or prepared by procedures which, separately or together, are designed to modify the rate, the place or the time of release of the active ingredient(s) in the gastrointestinal tract.

Sustained-release tablets (Extended-/prolonged-release tablets)

Definition

Sustained-release tablets 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 tablets (gastro-resistant/enteric-coated tablets)

Definition

Delayed-release tablets are intended to resist gastric fluid but disintegrate in intestinal fluid. This is achieved by using coating substances such as cellacefate (cellulose acetate phthalate) and anionic copolymers of methacrylic acid and its esters. It is sometimes necessary to apply more than one layer.

Uniformity of mass

The test for 5.2 Uniformity of mass for single-dose preparations does not apply to delayed-release tablets.

Disintegration test

Delayed-release tablets 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 for 2 hours, unless otherwise specified in the individual monograph (but in any case for not less than 1 hour) and examine the state of the tablets. No tablet should show signs of either disintegration (apart from fragments of coating) or cracks that would allow the contents to escape. Replace the acid by phosphate buffer solution, pH 6.8, TS. Operate the apparatus for 60 minutes and examine the state of the tablets.