REVISION OF MONOGRAPH ON TABLETS
Draft proposal for The International Pharmacopoeia
(September 2009)

DRAFT FOR COMMENT

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**SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/09.324 Rev.**

*Revision of International Pharmacopoeia monograph on Tablets*

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**Explanatory note:**

*Suggested text for deletion in “strike-through”.
Suggested text to be added or changed is underlined.*
Proposed revision

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 they are tablets may be obtained by moulding or extrusion techniques. They may be uncoated or coated. They are usually intended for oral administration, but preparations for alternative applications, such as implants, solution-tablets for injections, irrigations, or for external use, vaginal tablets, etc., are also available in this presentation. These preparations may require a special formulation, method of manufacture, or form of presentation, appropriate to their particular use. For this reason they may not comply with certain sections of this monograph.

[Note from Secretariat: see italic statement added above.]

The different categories of tablet that exist include soluble tablets, effervescent tablets, tablets for use in the mouth, and modified-release tablets. Unless otherwise specified in the individual monograph, Tablets are normally right circular solid cylinders in shape, and their end surfaces of which are flat or convex and the edges of which may be bevelled. They Tablets 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.

They should be sufficiently hard to withstand handling, including packaging, storage, and transportation, without crumbling or breaking.

[Note from Secretariat: this part is dealt with below under Manufacture.]

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 authorised 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 that exist 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) and sustained-release (extended-/prolonged-release tablets).

*new section

Manufacture

The manufacturing processes for tablets should meet the requirements of good manufacturing practice (GMP), especially with regard to cross-contamination.

The following information is intended to provide very broad guidelines concerning the main critical steps to be followed during production of tablets, indicating those that are the most important.

In the manufacture of tablets, measures are taken to:

• ensure that the active ingredient(s) are of an 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 of the subdivided parts in order to ensure so that the patient receives the intended dose.

A suitable test to assess this aspect of product quality 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.

In order to obtain a suitable formulation, it is usually necessary to mix the active ingredient(s) with a number of excipients. It is essential that such mixing is carried out in a manner that ensures homogeneity. 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 particular 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 or slugging 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 lubricants before the compression stage to improve the powder flow and to reduce sticking and adhesion to die walls and punches during compression and/or disintegrating agents. 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.

The final tablet mixture is volumetrically fed into the die cavity to ensure that the tablets are of a uniform mass when compressed. The tablets may be coated, either in coating pans or by an air suspension technique. A hydrophobic subcoat applied to the core of sugar-coated tablets may reduce dissolution.
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 particle size of the active ingredient(s), the homogeneity and moisture content of the mixture and/or granulate, 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 included in Supplementary Information (section to be determined).

[Note from the Secretariat: It is intended to include tests for friability, resistance to crushing and uniformity of dosage units within a new sub-section of the Supplementary Information section of The International Pharmacopoeia.]

Packaging must be adequate to protect the tablets from light, moisture, and damage during packaging and 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

A requirement for compliance with the test for 5.1 Uniformity of content for single-dose preparations is specified in certain individual tablet monographs for sugar coated or enteric coated tablets, where the test for 5.2 Uniformity of mass for single-dose preparations does not apply. In addition, a requirement is specified in certain individual monographs where the active ingredient is 5% or less of the total.
formulation. In such cases the test for 5.2 Uniformity of mass for single-dose preparations is not required.

**Dissolution/disintegration test**

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 the "Dissolution test" compliance with a dissolution test is specified in the individual monograph, the 5.3 Disintegration test for tablets and capsules is not required.

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

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

9. the storage conditions for and 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. Any special storage conditions should be stated on the label. [Note from Secretariat: this part is covered under Labelling.] 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.

Additional special packaging, storage, and transportation recommendations are specified provided, where necessary, in the individual monograph.
Requirements for specific types of tablets

Note from Secretariat: It is proposed to modify the order of the sections of the monograph to that given in the list under Definition, that is to describe the “physical” categories of uncoated and coated first, followed by the categories based on intended use/administration/release characteristics.

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 (multi-layer tablets), but no signs of coating.

Disintegration test

Uncoated tablets, except soluble tablets, dispersible tablets, effervescent tablets, and tablets for use in the mouth, and chewable tablets, 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 (tablets for solutions)

Definition

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

Disintegration test

Soluble tablets comply with disintegrate within 3 minutes when examined by 5.3 Disintegration test for tablets and capsules, but use using water R at room temperature 15 – 25°C, and operate the apparatus for 5 minutes, unless otherwise specified in the individual monograph.
**Dispersible tablets**

[Note from Secretariat: new section]

**Definition**

Dispersible tablets are uncoated 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 required to be carried out in premises where the low-humidity conditions is so low 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**

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

[Note from Secretariat: new section]

**Definition**

Chewable tablets are usually uncoated. They are intended to be chewed before being swallowed.

**Manufacture**

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

- ensure that the tablets are easily crushed by chewing.

**Tablets for use in the mouth (sublingual, buccal) and chewable tablets**

**Definition**

Tablets for use in the mouth and chewable tablets 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, 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**

Extended-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 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.