6.4 **TABLETS FOR DIRECT APPLICATION (DT)**

**Introduction**

Tablets are preformed solids of uniform shape and dimensions, usually circular, with either flat or convex faces. Their size and weight is determined by manufacturing and/or use requirements. For some physical tests the tablets must be broken and their fragments be used. Tablets for direct application (DT) are intended for application in the field (e.g. rice paddies) without prior dispersal or dissolution in water.

Tablets for direct application are often not coated or highly compacted and possess lower mechanical strength. Such tablets require commercial packaging that minimizes or eliminates mechanical stress during normal handling and transport. Selection of physical tests methods must take into account the commercial packaging of tablets.

Certain clauses are not applicable to effervescent tablets. These types of tablets, are defined by the European Pharmacopoeia as "uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates which react rapidly in the presence of water to release carbon dioxide” (EDQM, 2022). The excess of acid and base will mask possible acidity or alkalinity that are conveyed by the active ingredient or coformulants in the tablet. For this reason, the clauses for acidity/alkalinity or pH range are not applicable to effervescent tablets.

*Note for preparation of draft specifications. Do not omit clauses or insert additional clauses, nor insert limits that are more lax than those than given in the guidelines, without referring to Section 4. From the “Notes” provided at the end of this guideline, incorporate only those which are applicable to the particular specification.*

**...... [ISO common name] TABLETS FOR DIRECT APPLICATION**

[CIPAC number]/DT (month & year of publication)

6.4.1 **Description**

The material shall consist of an homogeneous mixture of technical ...... [ISO common name], complying with the requirements of FAO/WHO specification […..], in the form of ....... (see Section 4.2), together with carriers and any other necessary formulants. It shall be in the form of tablets for application without prior disintegration and dispersion/dissolution in water. The formulation shall consist of dry, unbroken, free-flowing tablets and shall be free from extraneous matter.

6.4.2 **Active ingredient** (Note 1)

6.4.2.1 **Identity tests** (Note 2)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

6.4.2.2 ...... **[ISO common name] content** (Note 2)

The ...... [ISO common name] content shall be declared (g/kg) and, when determined, the average content measured shall not differ from that declared by more than the appropriate tolerance, given in the table of tolerances, Section 4.3.2.

6.4.2.3 **Tablet dose uniformity**, if required

The ...... [ISO common name] content, measured separately in ... tablets, shall have a relative standard deviation (RSD) of not more than …%.

6.4.3 **Relevant impurities** (Note 1)

6.4.3.1 **By-products of manufacture or storage** (Note 3), if required

Maximum: …… % of the …… [ISO common name] content found under 6.4.2.2.

6.4.3.2 **Water** (MT 30.6), if required

Maximum: ….. g/kg

6.4.4 **Physical properties**

6.4.4.1 **Acidity** and/or **alkalinity** (MT 191) or **pH range** (MT 75.3) (Notes 4, 5 & 6), if required (Note 7)

 Maximum acidity: … g/kg calculated as H2SO4.

Maximum alkalinity: … g/kg calculated as NaOH.

pH range: … to …

6.4.4.2 **Tablet integrity** (Note 8)

No broken, soft or sticky tablets should be present

Fragments: yes/no

Soft/sticky: yes/no

6.4.4.3 **Attrition resistance of tablets** (MT 178.2) (Notes 9 & 10) if required

Minimum attrition resistance: ......%.

6.4.5 **Storage stability**

6.4.5.1 **Stability at elevated temperature** (MT 46.4)

After storage at 54 ± 2°C for 14 days (Note 11) without pressure (Note 12) the determined average active ingredient content must not be lower than … % relative to the determined average content found before storage (Note 13) and the formulation shall continue to comply with the clauses for:

- by-products of manufacture or storage (6.4.3.1),

- acidity/alkalinity/pH range (6.4.4.1),

- tablet integrity (6.4.4.2),

- attrition resistance of tablets (6.4.4.3),

as required.

Note 1 Measuring the active ingredient content or relevant impurities requires a representative sample of the tablet. A representative sample is obtained by grinding one or several tablets and then sampling the homogeneous powder.

Note 2 Method(s) of analysis must be CIPAC, AOAC or equivalent. Where methods have not yet been published, full details and appropriate method validation data must be submitted to FAO/WHO by the proposer.

Note 3 This clause should include only relevant impurities and the title should be changed to reflect the name of the relevant impurity. Method(s) of analysis must be peer validated.

Note 4 The method to be used shall be stated. If several methods are available, a referee method shall be selected.

Note 5 The following tests may require breaking tablets to adjust the test concentration:

|  |  |  |  |
| --- | --- | --- | --- |
| Point | Property | CIPAC | Rate |
| 6.4.4.1 | Acidity or alkalinity | MT 191 | 10 g add 100 ml  |
| pH range | MT 75.3 | 1 g make up 100 ml |

Tablets or fragments of tablets must be completely disintegrated for the purposes of
CIPAC methods MT 191 and MT 75.3.

Note 6 Before performing the CIPAC test, it is necessary to let the tablet(s) or fragments of a tablet disintegrate completely in a 250 ml beaker containing 50 ml of the water required by the method. A gentle stirring may be needed.

Note 7 This clause is not applicable to effervescent tablets, as they incorporate an effervescent system.

Note 8 This requirement describes the physical state of the tablet for example whether it is broken or dusty with fragments or soft and sticky. Visual observation only. Unless otherwise indicated, at least one pack/package containing multiple tablets should be inspected for color, texture, fragments and dust.

Note 9 An attrition test is only required for bulk packaged tablets with a diameter < 1 cm that may exhibit surface wear during transport and handling.

Note 10 The scope of CIPAC MT 178.2 is to measure attrition resistance of water dispersible granules but the method is considered to be applicable to DT, WT and ST with a diameter of < 1 cm as well.

Note 11 Unless other temperatures and/or times are specified. Refer to Section 4.6.2 of this manual for alternative storage conditions. Whole tablets must be stored. After storage tablets may be broken for tests as specified in Note 8.

Note 12 Without pressure means that the test is performed as specified by CIPAC MT 46.4, but no pressure is applied to the sample during its aging.

Note 13 Samples of the formulation taken before and after the accelerated storage stability test may be analysed concurrently after the test in order to reduce the analytical error.