**7.33** **CAPSULE SUSPENSIONS**

**Introduction**

Capsule suspension (CS) is the designation for a stable suspension of micro-encapsulated active ingredient in an aqueous continuous phase, intended for dilution with water before use.

The parameters which best describe the performance characteristics are as follows.

* Active ingredient, determined and expressed as “total”, “free” and “release rate” (“total” is required in all cases, “free” and “release rate” are dependent upon the intended application);
* Pourability test (to ensure that the CS can be poured from its container);
* Spontaneity of dispersion, suspensibility, wet sieve and persistent foam tests (to ensure the sprayability of the diluted suspension);
* Stability to freezing/thawing. Freezing of a micro-encapsulated formulation may result in capsule failure through crystallization or by other mechanisms, with the result that the properties of the formulation may be drastically changed, including release of the active ingredient into the aqueous medium.

*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] CAPSULE SUSPENSION**

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

**7.33.1** **Description**

The material shall consist of a suspension of micro-capsules containing technical ...... [ISO common name], complying with the requirements of FAO/WHO specification ......, in the form of ....... (see Section 4.2), in an aqueous phase, together with suitable formulants. After agitation, the material shall appear homogeneous (Note 1) and suitable for further dilution in water.

**7.33.2** **Active ingredient**

7.33.2.1 **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.

7.33.2.2 **...... [ISO common name] content**

7.33.2.2.1 **Total content** (Note 2)

The ...... [ISO common name] content shall be declared (g/kg or g/l at 20 ± 2 ºC, Note 3) 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

7.33.2.2.2 **Free (non-encapsulated) content** (Notes 2 and 4), if required

The free ...... [ISO common name] average content measured shall not exceed ......% of the determined total content.

7.33.2.2.3 **Release rate** (Note 4) (for slow- or controlled release formulations), if required

The release rate measured shall comply with the following criteria: …….

**7.33.3** **Relevant impurities**

7.33.3.1 **By-products of manufacture or storage** (Note 5), if required

Maximum: ......% of the …… [ISO common name] content found under 7.33.2.2.1.

**7.33.4** **Physical properties**

7.33.4.1 **Acidity** and/or **alkalinity** (MT 191) or **pH range** (MT 75.3) (Note 6), if required

Maximum acidity: ...... g/kg calculated as H2SO4.

Maximum alkalinity: ...... g/kg calculated as NaOH.

pH range: ...... to ......

7.33.4.2 **Pourability** (MT 148.2)

Residue : ......%.

7.33.4.3 **Spontaneity of dispersion** (MT 160.1) (Note 7)

Minimum of ...% after 5 min in CIPAC Standard Water D at 25 ± 5 °C.

7.33.4.4 **Suspensibility** (MT 184.1) (Note 7)

Minimum ......% after 30 min in CIPAC standard water D at 25 ± 5°C

7.33.4.5 **Wet sieve test** (MT 185.1) (Note 8)

Maximum: ......% of the formulation shall be retained on a ......µm test sieve.

7.33.4.6 **Persistent foam** (MT 47.3) (Note 9)

Maximum: ...... ml after 1 min.

7.33.4.7 **Particle size distribution** (MT 187), if required

…% of particles shall be in the range … to … (Note 10)

**7.33.5** **Storage stability**

7.33.5.1 **Freeze/thaw stability** (Note 11)

After undergoing ...... freeze/thaw cycles and following homogenization, the formulation shall continue to comply with the clauses for:

- acidity/alkalinity/pH range (7.33.4.1),

- pourability (7.33.4.2),

- spontaneity of dispersion (7.33.4.3),

- suspensibility (7.33.4.4),

- wet sieve test (7.33.4.5),

as required.

An increase in the free ...... [ISO common name] content shall be allowed, with the maximum concentration after the test corresponding to ......% of that found for total content under 7.33.2.2.1.

7.33.5.2 **Stability at elevated temperature** (MT 46.3)

After storage at 54 ± 2 °C for 14 days (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:

- release rate (7.33.2.2.3)

- by-products of manufacture or storage (7.33.3.1),

- acidity/alkalinity/pH range (7.33.4.1),

- pourability (7.33.4.2),

- spontaneity of dispersion (7.33.4.3),

- suspensibility (7.33.4.4),

- wet sieve test (7.33.4.5),

as required.

An increase in the free ...... [ISO common name] content shall be allowed, with the maximum concentration after the test corresponding to ......% of that found for total content under 7.33.2.2.1.

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Note 1 All physical and chemical tests listed in this specification are to be performed with a sample taken after the recommended homogenization procedure.

Before sampling to verify formulation quality, the commercial container must be inspected carefully. On standing, suspensions usually develop a concentration gradient from the top to the bottom of the container. This may even result in the appearance of a clear liquid on the top and/or of sediment on the bottom. Therefore, before sampling, the formulation must be homogenized according to the instructions given by the manufacturer or, in the absence of such instructions, by gentle shaking of the commercial container (for example by inverting the closed container several times). Large containers must be opened and stirred adequately. After this procedure, the container should not contain a sticky layer of non-dispersed matter at the bottom. A suitable and simple method of checking for a non-dispersed sticky layer (“cake”) is by probing with a glass rod or similar device adapted to the size and shape of the container.

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

Note 3 Unless homogenization is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre, and in calculation of the active ingredient content (in g/l), if methods other than OECD 109 or MT 3.3 are used. If the buyer requires both g/kg and g/l at 20 °C, then in case of dispute the analytical results shall be calculated as g/kg.

Note 4 A clause for release rate is required only for slow- or controlled-release CS. A clause for free active ingredient is required only where the CS is intended to have slow- or controlled-release properties or is intended to enhance operator safety. A test method for CS release rate may be product-specific.

Note 5 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/ILV.

Note 6 The method to be used shall be stated. If several methods are available, a referee method shall be selected.

Note 7 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method may be used on a routine basis provided that it has been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the referee method.

Note 8 This test detects coarse particles (e.g. oversize capsules, crystals) or agglomerates (of capsules or from crust formation), or extraneous materials which could cause blockage of spray nozzles or filters in the spray tank.

Note 9 The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D at 25 ± 5°C.

Note 10 Percentages may be specified in one or more ranges, as appropriate to the product. The determination of particle size range by laser diffraction is not an ideal criterion to ensure the suitability of liquid formulations. This should be evaluated by Wet sieve test (MT 185.1) and Suspensibility (MT 184.1) or Dispersion stability (MT 180).

Note 11 After manufacture and during shipping it is often impossible for buyer or seller to guarantee that the formulation has not been exposed to freezing temperatures. As freezing of an aqueous capsule suspension may result in undesirable, irreversible changes, including (but not limited to) capsule failure caused by crystallization of the active ingredient, the ability of the formulation to successfully withstand repeated freezing and thawing is an important property. Unless otherwise agreed, the freeze/thaw stability test shall cycle the formulation between room temperature (e.g. 20 ± 2°C) and -10 ± 2°C on 18-hour-freeze/6-hour-melt cycles for a total of 4 cycles.

Note 12 Unless other temperatures and/or times are specified. Refer to Section 4.6.2 of this Manual for alternative storage conditions.

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