5.17. RECOMMENDATIONS ON METHODS FOR DOSAGE FORMS TESTING

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5.17.1. RECOMMENDATIONS ON DISSOLUTION TESTING

This general chapter is non-mandatory; it provides information on dissolution testing, on recommended dissolution media and on the expression of dissolution specifications for oral dosage forms (see general chapter 2.9.3. Dissolution test for solid dosage forms). This information represents generally accepted parameters used in the field of dissolution.

In the determination of the dissolution rate of the active substance(s) of a solid dosage form, the following are to be specified:

- the apparatus to be used, and in cases where the flow-through apparatus is specified, which flow-through cell is to be used;
- the composition, the volume and the temperature of the dissolution medium;
- the rotation speed or the flow rate of the dissolution medium;
- the time, the method and the amount for sampling of the test solution or the conditions for continuous monitoring;
- the method of analysis;
- the acceptance criteria.

The choice of apparatus to be used depends on the physico-chemical characteristics of the dosage form. When a large quantity of dissolution medium is required to ensure sink conditions, or when a change of pH is necessary, the flow-through apparatus may be preferred.

EXPERIMENTAL TESTING CONDITIONS

The use of the basket and the paddle apparatus and the reciprocating cylinder apparatus is generally based on the principle of operating under sink conditions, i.e. in such a manner that the material already in solution does not exert a significant modifying effect on the rate of dissolution of the remainder. Sink conditions normally occur in a volume of dissolution medium that is at least 3-10 times the saturation volume.

In general, an aqueous medium is used. The composition of the medium is chosen on the basis of the physico-chemical characteristics of the active substance(s) and excipient(s) within the range of conditions to which the dosage form is likely to be exposed after its administration. This applies in particular to the pH and the ionic strength of the dissolution medium.

The pH of the dissolution medium is usually set between pH 1 and pH 8. In justified cases, a higher pH may be needed. For the lower pH values in the acidic range, *0.1 M hydrochloric acid* is normally used. Recommended dissolution media are described hereafter.

Water is recommended as a dissolution medium only when it is proven that the pH variations do not have an influence on the dissolution characteristics.

In specific cases, and subject to approval by the competent authority, dissolution media may contain enzymes, surfactants, further inorganic substances and organic substances. For the testing of preparations containing poorly aqueous-soluble active substances, modification of the medium may be necessary. In such circumstances, a low concentration of surfactant is recommended; it is recommended to avoid the use of organic solvents.

Gases dissolved in the dissolution medium can affect the results of the dissolution test. This is true in particular for the flow-through apparatus, where de-aeration of the medium is necessary to avoid the formation of gas bubbles in the flow-through cell. A suitable method of de-aeration is as follows: heat the medium while stirring gently to about 41 °C, immediately filter under vacuum using a filter with a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 min. Other de-aeration techniques for removal of dissolved gases may be used.

Using the paddle or basket apparatus, the volume of dissolution medium is normally 500-1000 mL. A stirring speed of between 50 r/min and 100 r/min is normally chosen; it must not exceed 150 r/min.

For the flow-through apparatus, the liquid flow rate is normally set between 4 mL/min and 50 mL/min.

RECOMMENDED DISSOLUTION MEDIA

The following dissolution media may be used.

Table 5.17.1.-1. – *Examples of dissolution media*

pH	Dissolution media
pH 1.0	HCl
pH 1.2	NaCl, HCl
pH 1.5	NaCl, HCl
pH 4.5	Phosphate or acetate buffer
pH 5.5 and pH 5.8	Phosphate or acetate buffer
pH 6.8	Phosphate buffer
pH 7.2 and pH 7.5	Phosphate buffer

The composition and preparation of these various media are indicated below.

Hydrochloric acid media

- *0.2 M hydrochloric acid*.
- *0.2 M sodium chloride*. Dissolve 11.69 g of *sodium chloride R* in *water R* and dilute to 1000.0 mL with the same solvent.

For preparing media with the pH values indicated in Table 5.17.1.-2, mix 250.0 mL of 0.2 M sodium chloride and the specified volume of *0.2 M hydrochloric acid*, and dilute to 1000.0 mL with *water R*.

Table 5.17.1.-2. – *Hydrochloric acid media*

pH	HCl (mL)
1.2	425.0
1.3	336.0
1.4	266.0
1.5	207.0
1.6	162.0
1.7	130.0
1.8	102.0
1.9	81.0
2.0	65.0
2.1	51.0
2.2	39.0

The hydrochloric acid media may also be prepared by replacing sodium chloride with potassium chloride.

Acetate buffer solutions

- *2 M acetic acid.* Dilute 120.0 g of *glacial acetic acid R* to 1000.0 mL with *water R*.
- *Acetate buffer solution pH 4.5.* Dissolve 2.99 g of *sodium acetate R* in *water R*. Add 14.0 mL of 2 M acetic acid and dilute to 1000.0 mL with *water R*.
- *Acetate buffer solution pH 5.5.* Dissolve 5.98 g of *sodium acetate R* in *water R*. Add 3.0 mL of 2 M acetic acid and dilute to 1000.0 mL with *water R*.
- *Acetate buffer solution pH 5.8.* Dissolve 6.23 g of *sodium acetate R* in *water R*. Add 2.1 mL of 2 M acetic acid and dilute to 1000.0 mL with *water R*.

Phosphate buffer solutions

For preparing buffers with the pH values indicated in Table 5.17.1.-3, mix 250.0 mL of *0.2 M potassium dihydrogen phosphate R* and the specified volume of *0.2 M sodium hydroxide*, and dilute to 1000.0 mL with *water R*.

Table 5.17.1.-3. – *Phosphate buffer solutions*

pH	5.8	6.0	6.2	6.4	6.6	6.8
NaOH (mL)	18.0	28.0	40.5	58.0	82.0	112.0
pH	7.0	7.2	7.4	7.6	7.8	8.0
NaOH (mL)	145.5	173.5	195.5	212.0	222.5	230.5

Other phosphate buffer solutions

- *Phosphate buffer solution pH 4.5.* Dissolve 13.61 g of *potassium dihydrogen phosphate R* in 750 mL of *water R*. Adjust the pH if necessary with *0.1 M sodium hydroxide* or with *0.1 M hydrochloric acid*. Dilute to 1000.0 mL with *water R*.
- *Phosphate buffer solution pH 5.5 R.*
- *Phosphate buffer solution pH 6.8 R1.*
- *Buffer solution pH 7.2 R.*
- *0.33 M phosphate buffer solution pH 7.5 R.*

Simulated intestinal fluid pH 6.8

Mix 77.0 mL of *0.2 M sodium hydroxide*, 250.0 mL of a solution containing 6.8 g of *potassium dihydrogen phosphate R*, and 500 mL of *water R*. Add 10.0 g of *pancreas powder R*, mix and adjust the pH if necessary. Dilute to 1000.0 mL with *water R*.

Simulated gastric fluid

Dissolve 2.0 g of *sodium chloride R* and 3.2 g of *pepsin powder R* in *water R*, add 80 mL of *1 M hydrochloric acid* and dilute to 1000.0 mL with *water R*. If required, pepsin powder may be omitted.

Increasing pH

For a test involving increasing pH, one of the following sequences may be used:

Time (h)	0 - 1	1 - 2	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7	7
pH	1.0							
pH	1.2	6.8						
pH	1.2	2.5	4.5		7.0		7.5	
pH	1.5	4.5				7.2		

To achieve this pH variation, it is possible either:

- to substitute one buffer solution for another (whole substitution);
- to remove only half of the medium each time (half change method) and replace it with a buffer solution of higher pH: the initial pH is 1.2 and the second solution is phosphate buffer solution pH 7.5; or,
- to an initial solution at pH 1.5, to add a dose of a powder mixture containing *tris(hydroxymethyl)aminomethane R* and *anhydrous sodium acetate R* to obtain pH 4.5 and a second dose to obtain pH 7.2, as described below:
  - *hydrochloric acid pH 1.5*: dissolve 2 g of *sodium chloride R* in *water R*, add 31.6 mL of *1 M hydrochloric acid* and dilute to 1000.0 mL with *water R*;
  - *buffer solution pH 4.5*: mix 2.28 g of *tris(hydroxymethyl)aminomethane R* with 1.77 g of *anhydrous sodium acetate R*; dissolve this mixture in the hydrochloric acid pH 1.5 described above;
  - *buffer solution pH 7.2*: mix 2.28 g of *tris(hydroxymethyl)aminomethane R* with 1.77 g of *anhydrous sodium acetate R*; dissolve this mixture in the buffer solution pH 4.5 described above.

The flow-through cell may be used for the continuous change of pH.

QUALIFICATION AND VALIDATION

Due to the nature of the test method, quality by design is an important qualification aspect for *in vitro* dissolution test equipment. Any irregularities such as vibration or undesired agitation by mechanical imperfections are to be avoided.

Qualification of the dissolution test equipment has to consider the dimensions and tolerances of the apparatus. Critical test parameters, such as temperature and volume of dissolution medium, rotation speed or liquid flow rate, sampling probes and procedures, have to be monitored periodically during the periods of use.

The performance of the dissolution test equipment may be monitored by testing a reference product that is sensitive to hydrodynamic conditions. Such tests may be performed periodically or continuously for comparative reasons with other laboratories.

During testing, critical inspection and observation are required. This approach is especially important to explain any outlying results.

Validation of automated systems, whether concerning the sampling and analytical part or the dissolution media preparation and test performance, has to consider accuracy, precision, and the avoidance of contamination by any dilutions, transfers, cleaning and sample or solvent preparation procedures.

EXPRESSION OF DISSOLUTION SPECIFICATIONS FOR ORAL DOSAGE FORMS

The dissolution specification is expressed in terms of the quantity (Q) of active substance dissolved in a specified time, expressed as a percentage of the content stated on the product label.

Conventional-release dosage forms

In most cases, when tested under reasonable and justified test conditions, the acceptance criteria at level S_1 are that at least 80 per cent of the active substance is released within a specified time, typically 45 min or less. This corresponds to a Q value of 75 per cent, since, as referred to in Table 2.9.3.-1, for level S_1 the individual value of each of the 6 units tested is not less than Q + 5 per cent, i.e. not less than 80 per cent.

Typically, a single-point acceptance criterion is sufficient to demonstrate that the majority of the active substance has been released, although in certain circumstances it may be necessary to test at additional time point(s), in order to demonstrate adequate dissolution.

Prolonged-release dosage forms

The dissolution test acceptance criteria for prolonged-release dosage forms is normally expected to consist of 3 or more points. The 1st specification point is intended to prevent unintended rapid release of the active substance ('dose dumping'). It is therefore set after a testing period corresponding to a dissolved amount typically of

20 per cent to 30 per cent. The 2nd specification point defines the dissolution pattern and so is set at around 50 per cent release. The final specification point is intended to ensure almost complete release, which is generally understood as more than 80 per cent release.

Delayed-release dosage forms

A delayed-release dosage form may release the active substance(s) fractionally or totally according to the formulation design when tested in different dissolution media, e.g. in increasing pH conditions. Dissolution specifications therefore have to be decided on a case-by-case basis.

Gastro-resistant dosage forms require at least 2 specification points in a sequential test and 2 different specifications in a parallel test. In a sequential test, the 1st specification point represents an upper limit and is set after 1 h or 2 h in acidic medium, and the 2nd after a pre-set time period of testing in an adequate buffer solution (preferably pH 6.8).

In most cases the acceptance criteria at level B_1 are that at least 80 per cent of the active substance is released. This corresponds to a Q value of 75 per cent, since, as referred to in Table 2.9.3.-4, for level B_1 the individual value of each of the 6 units tested is not less than Q + 5 per cent, i.e. not less than 80 per cent.