Dissolution testing of tablets and capsules

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1. Introduction

Chapter *5.5 Dissolution test for solid oral dosage forms* is based on the internationally-harmonized dissolution test developed by the Pharmacopoeial Discussion Group (PDG), which comprises representatives from the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopeia. The general method presents the Paddle and Basket methods for dissolution testing. Two other general methods contained in the PDG text, namely the Reciprocating-cylinder method and the Flow-through cell, have not so far been adopted for *The International Pharmacopoeia*.

It is not the intention of *The International Pharmacopoeia* to apply retrospectively the test conditions and acceptance criteria of the revised dissolution test or to change specifications for existing products. Table 1 lists monographs with dissolution tests, which were developed applying previous versions of chapter 5.5 and which are thus not subject to the internationally-harmonized provision. In the elaboration of new monographs and revision of individual monographs in *The International Pharmacopoeia* the principles of the revised test, e.g. to base acceptance criteria on “Q” values (dissolution limits), will be applied.

Amodiaquine tablets
Artemether capsules
Artemether tablets
Artenimol tablets
Artesunate tablets
Chloroquine phosphate tablets
Chloroquine sulfate tablets
Doxycycline capsules
Doxycycline tablets
Efavirenz, emtricitabine and tenofovir tablets
Emtricitabine and tenofovir tablets
Emtricitabine capsules
Erythromycin ethylsuccinate tablets
Erythromycin stearate tablets
Ethambutol hydrochloride tablets
Griseofulvin tablets
Ibuprofen tablets
Indinavir capsules
Indometacin tablets
Isoniazid tablets
Isoniazid and ethambutol hydrochloride tablets
Levonorgestrel and ethinylestradiol tablets
Lopinavir and ritonavir tablets
Metronidazole tablets
Phenoxymethylpenicillin potassium tablets
Phenytoin sodium tablets
Pyrazinamide tablets
Quinine bisulfate tablets
Quinine sulfate tablets
Rifampicin capsules
Rifampicin tablets
Ritonavir tablets
Saquinavir tablets
Sulfadoxine and pyrimethamine tablets
Sulfamethoxazole and trimethoprim tablets
Tenofovir tablets

Table 1. Monographs on solid, oral dosage forms with dissolution test conditions and specifications elaborated before chapter *5.5 Dissolution test for solid oral dosage forms* were revised to encompass the internationally-harmonized procedure.

2. Objective of dissolution testing

While the ultimate objective of dissolution testing is to ensure adequate and reproducible bioavailability, the objective of the

dissolution tests prescribed in the individual monographs of *The International Pharmacopoeia* is to obtain information about the drug-release characteristics of a particular formulation or batch of a product under standardized test conditions. Compliance with the test provides an assurance that most of the active ingredient will be dissolved in an aqueous medium within a reasonable amount of time when the preparation is subject to a mild agitation. Compliance with the dissolution test does not by itself guarantee bioavailability.

Standardized conditions and limits are considered appropriate for a pharmacopoeial test that is intended to apply to a monograph covering multisource products.

3. Policy of *The International Pharmacopoeia*

Monographs on tablet and capsule preparations listed in Table 1 include a dissolution test, either with or without further information on the test conditions. Spectrophotometry is typically employed as an analytical test method. In the case where a dissolution test is prescribed an additional disintegration test is not required.

In the elaboration of new tablet and capsule monographs and revision of existing monographs, decisions on dissolution and disintegration testing will be taken in agreement with the guidance given by the International Conference on Harmonisation (ICH) on the application of dissolution testing to medicinal products (see www.ich.org). The monograph will contain a dissolution test and/or a disintegration test. The choice of applying disintegration or dissolution for a given product should follow ICH Q6A and Q6A decision tree 7-1. As per these guidelines consideration to establish disintegration instead of dissolution should include the solubility of the active pharmaceutical ingredient, dissolution characteristics of the product and a demonstration that a relationship has been established between dissolution and disintegration. A demonstration of robustness with respect to the chosen disintegration method may substitute for the demonstration that a relationship has been established between dissolution and disintegration. In such a case where disintegration is found suitable for control of the performance of a product the disintegration specifications should be based on the results of the validation exercise.

Chewable tablets are intended to be chewed before being swallowed; however, they may be swallowed whole and therefore performance-testing requirements for conventional-release tablets should be applied to chewable tablets.

4. Test conditions

Following a decision made at the forty-fifth meeting of the Expert Committee on Specifications for Pharmaceutical Preparations a standardized dissolution test is applied to conventional-release tablet and capsule formulations containing highly soluble active ingredients (Class I and III of the Biopharmaceutics Classification System (BCS)[1]). The following conditions for a single-time test using the Paddle method are preferred:

- dissolution medium: dissolution buffer pH 6.8;
- volume of medium: 500 mL;
- rotation speed: 75 rpm;
- sampling time: 30 min.

When test conditions are not specified in the individual monograph it is recommended to apply similar test conditions. If the Basket method is used a rotation speed of 100 rpm is recommended.

For conventional-release tablet and capsule formulations containing poorly water-soluble active ingredients (Class II and IV of the BCS) decisions on the appropriate test conditions are taken on a case-by-case basis. A single-point dissolution test is normally applied. Because of the low aqueous solubility dissolution medium of volume 900 mL and addition of a surfactant may be needed. The concentration of active ingredient at 100% dissolution should not exceed approximately 35% saturation.

For delayed-release dosage forms two-stage testing according to the procedure in *5.5 Dissolution test for solid oral dosage forms* is applied. It is important to consider the population of individuals who will be taking the dosage form when designing the test, e.g. administration of the dosage form to achlorhydric patients may require testing for resistance of the product against gastric juice at elevated pH, for example, pH 3.5.

For sustained-release dosage forms the appropriate test conditions and sampling procedures are specified in the monograph. Three time-points are applied.

5. Acceptance criteria

The revised dissolution test contains acceptance criteria for conventional-release, delayed-release and sustained-release dosage forms. The acceptance criteria are expressed according to the principles stated in the internationally-harmonized dissolution test. The harmonized dissolution limits (Q-values) are applied in new and revised monographs (i.e. monographs on solid, oral dosage forms containing a dissolution test but not listed in Table 1).

The three-level acceptance criteria, i.e. S_1, S_2 and S_3 for conventional-release dosage forms, are not applied in monographs

listed in Table 1; acceptance criteria for a two-stage test (6 + 6 dosage units) are specified in some monographs. For dosage forms for which the monograph require compliance with *5.5 Dissolution test for solid oral dosage forms*, but without specification of test conditions, it is recommended to apply a test using Q = 75% and the three-level acceptance criteria.

[1] Classification of active ingredients, included in the WHO Model List of Essential Medicines, is provided in the WHO Technical Report Series, No. 937, Annex 7 (2006).