

MEDICINES CONTROL COUNCIL



DISSOLUTION

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines and the website.

First publication	May 2003
Release for comment	November 2003
Deadline for comment	November 2003
Date for finalisation/implementation	December 2003
Version 2	June 2006
Amendment of sections 1, 2, 3, 4, 5	
Deadline for comment	14 August 2006
Date of implementation, excluding 4.1 b)	2 July 2007
Date of implementation 4.1 b)	2 July 2008
Version 3:	June 2012
Date of implementation	With immediate effect
New section 3.2 viii)	
Date of implementation	1 September 2010
Version 4:	March 2011
Date of implementation	With immediate effect
Version 5:	June 2015
Date of implementation	July 2015 With immediate effect

DR JC GOUWS
REGISTRAR OF MEDICINES

TABLE OF CONTENTS

	Page
1 INTRODUCTION	3
2 SETTING DISSOLUTION SPECIFICATIONS	4
2.1 PHARMACOPOEIAL PRODUCT DISSOLUTION TEST AVAILABLE	5
2.2 PHARMACOPOEIAL PRODUCT DISSOLUTION TEST NOT AVAILABLE	5
2.3 SPECIAL CASES	6
3 DISSOLUTION PROFILES	6
3.1 REQUIREMENTS	6
3.2 COMPARISON OF DISSOLUTION PROFILES	7
3.3 NON-COMPARATIVE DISSOLUTION PROFILES	8
3.4 REPORT ON COMPARATIVE AND NON-COMPARATIVE DISSOLUTION STUDIES	8
4 IN VITRO DISSOLUTION TESTING IN SUPPORT OF A BIOWAIVER	8
4.1 PROPORTIONALLY SIMILAR DOSAGE FORMS	8
4.1.1 Immediate release tablets	9
4.1.2 Modified release products (<i>refer to Pharmaceutical & Analytical Guideline for definitions</i>)	9
4.1.2.1 Extended release beaded capsules	9
4.1.2.2 Extended release tablets	9
4.2 REFERENCE PRODUCTS REGISTERED IN SOUTH AFRICA BUT PROCURED IN ANOTHER COUNTRY, THE HEALTH REGULATORY AUTHORITY OF WHICH THE MCC ALIGNS ITSELF WITH (<i>refer also to Pharmaceutical & Analytical and Biostudies Guidelines</i>)	9
4.3 AMENDMENTS	9
4.3.1 Types of dissolution testing	10
4.3.2 Types of amendments (<i>refer to Amendments Guideline</i>)	10
4.4 BIOWAIVERS BASED ON BCS (<i>refer also to the Biostudies Guideline</i>)	11
4.4.1 Biopharmaceutics Classification System (BCS)	11
4.4.1.1 High solubility	11
4.4.1.2 High permeability	11
4.4.2 Determination of dissolution characteristics of multisource products in consideration of a biowaiver based on the BCS	12
4.4.2.1 Very rapidly dissolving	12
4.4.2.2 Rapidly dissolving	12
5 REFERENCES	13
UPDATE HISTORY	14

1 INTRODUCTION

This guideline describes the setting of dissolution specifications as a quality control requirement and also describes how to conduct dissolution testing in support of a request for a waiver for bioequivalence testing.

Although intrinsic dissolution of the active pharmaceutical ingredient (API) is an important consideration when formulating solid oral dosage forms, the dissolution behaviour of solid oral dosage forms provides important information to ensure pharmaceutical product quality. Hence, dissolution testing has been established as an extremely valuable tool to monitor batch-to-batch consistency. The primary utility of a dissolution test is, therefore, to establish dissolution specifications for relevant pharmaceutical products for the purposes of quality assurance.

Dissolution testing can also be useful in providing information on pharmaceutical product quality following certain post-approval changes made to the product, such as changes in formulation, manufacturing process, site of manufacture and the scale-up of the manufacturing process. The various types of changes where dissolution can be used in support of a biowaiver are described in the Amendments guideline, also refer 4.3.2 below.

In addition, where solid oral dosage forms have been proportionally formulated in different strengths, and the API follows linear kinetics, dissolution data can be used in support of a biowaiver for lower strengths of such dosage forms, provided an acceptable bioequivalence study has been carried out on one strength, usually the highest strength.

Active absorption from oral dosage forms depends on adequate release of the active pharmaceutical ingredient (API) from the product. Physico-chemical factors, such as dissolution or solubility of the API under physiologic conditions, and its permeability through the membranes of the gastrointestinal tract, play pivotal roles in this respect. Due to the critical nature of these factors, dissolution of a pharmaceutical product *in vitro* can, in certain instances, be relevant to anticipate the *in vivo* characteristics/results.

During the development of a pharmaceutical product dissolution testing is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the API. As soon as the composition and the manufacturing process are defined dissolution testing is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches.

Furthermore, dissolution testing can be used to support the bioavailability of a new pharmaceutical product, the bioequivalence of an essentially similar product or variations.

- i) Quality assurance
 - To get information on the product and API test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for quality control.
 - To be used as a tool in quality control to demonstrate consistence in product manufacture.
 - To get information on the reference products used in bioavailability/ bioequivalence studies and pivotal clinical studies.
- ii) Bioequivalence surrogate inference
 - To demonstrate similarity between reference products registered in South Africa but procured in another country, the health authority of which the South African MCC aligns itself with, and the corresponding innovator products in South Africa.
 - To demonstrate similarity between different product formulations of an active substance (variations and new, essentially similar products included) and the reference medicinal product.
 - To collect information on batch to batch consistency of the products (test and reference) to be used as bases for the selection of appropriate batches for the *in vivo* study.

1 INTRODUCTION - continued

If an active substance is considered highly soluble, it is reasonable to expect that it will not cause any bioavailability problems if, in addition, the dosage system is rapidly dissolved in the physiological pH-interval expected after product administration. A bioequivalence study may in those situations be waived based on case history and similarity of dissolution profiles, which are based on discriminatory testing, provided that the other exemption criteria are met.

If an active substance is considered to have a low solubility and a high permeability, the rate limiting step for absorption may be dosage form dissolution. This is also the case when one or more of the excipients are controlling the release and subsequent dissolution step of the active substance. In those cases a variety of test conditions is recommended and adequate sampling should be performed to characterise the dissolution profile completely e.g. at 10, 15, 20, 30, 45 and 60 minutes

In summary, dissolution testing is performed

- a) as an essential part of product development
- b) in support of an application for a waiver of bioequivalence testing
- c) to obtain information on test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for quality control
- d) to demonstrate batch-to-batch and lot-to-lot consistency during manufacture, and to indicate potential problems of bioavailability i.e. as a tool in quality control.

In vitro dissolution characterization is encouraged for all product formulations investigated (including prototype formulations), particularly if *in vivo* absorption characteristics are being defined for the different product formulations. Such efforts may enable the establishment of an *in vitro-in vivo* correlation. When an *in vitro-in vivo* correlation or association is available the *in vitro* test can serve not only as a quality control specification for the manufacturing process, but also as an indicator of how the product will perform *in vivo*.

2 SETTING DISSOLUTION SPECIFICATIONS

The dissolution test method and specifications must be capable of:

- discriminating between batches with respect to critical manufacturing variables which may have an impact on the desired bioavailability
 - showing batch to batch consistency of pivotal clinical, bioavailability and routine production batches
 - determining stability of the relevant release characteristics of the product.
- a) For new pharmaceutical products, dissolution specifications should be based on data obtained from acceptable clinical, pivotal bioavailability and/or bioequivalence batches.
 - b) In the case of multisource pharmaceutical products, the dissolution specifications are generally the same as the reference product.

These specifications should be confirmed by comparison of the dissolution performance of the multisource pharmaceutical product and reference product from an acceptable bioequivalence study.

If the dissolution performance of the multisource pharmaceutical product is substantially different from that of the reference product and the *in vivo* data remain acceptable, a different dissolution specification for the multisource pharmaceutical product may be set.

- c) A single point specification for immediate release dosage forms and a multipoint specification for modified release dosage forms are generally applicable for quality control, batch release and stability testing purposes.

2 SETTING DISSOLUTION SPECIFICATIONS - continued

In general a minimum of three sampling time points should be included in the specification of an oral prolonged release product. An early time point to exclude dose dumping (typically 20 to 30 % dissolved), at least one point to ensure compliance with the shape of the dissolution profiles around 50 % dissolved and one to ensure that the majority of the API has been released (generally more than 80 % dissolved).

The acceptable variation allowed around each time point (upper and lower limits) can be determined in different ways.

The limits may be derived from the spread of dissolution data of biobatches demonstrating bioequivalence or by demonstrating bioequivalence between batches at the proposed upper and lower limit of dissolution range – “side batch” concept in the case where IVIVC has not been established. Refer to the relevant ICH/CPMP guidelines in the case where IVIVC has been established.

Once dissolution specifications are set, the pharmaceutical product should comply with those specifications throughout its shelf-life. If the stability studies indicate release rate changes the release limits should be narrowed or the shelf-life reduced to guarantee that the product complies with the limits derived from batches which have demonstrated acceptable *in vivo* performance, at the expiry date. CPMP/QWP/604/96 EMEA 1999 2.2 Setting specifications page 4/15 and CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** sections 4.1.2, 4.2.1 and Annex 1.

Routine testing of the finished product is always necessary unless it can be demonstrated that this is not possible or justified. In these cases, routine testing of intermediates e.g. cores, pellets, may be acceptable.

Testing should continue through the three stages of testing (according to the USP) unless the product conforms at stage 1 or 2.

Setting dissolution specifications for multisource pharmaceutical products may be classified in three categories as described below. The dissolution method should specify in-line filtration for drawing the dissolution samples to ensure that the dissolution of the sample is stopped immediately on withdrawal of the sample unless filtration is demonstrated to be unnecessary or inappropriate as could be the case when a surfactant is present. A method stating that the samples should be drawn and filtered does not necessarily imply or ensure that the dissolution of undissolved particles in the sample is stopped at the time of sampling. (USP “Test specimens are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary”.)

2.1 PHARMACOPOEIAL PRODUCT DISSOLUTION TEST AVAILABLE

In this instance the quality control dissolution test should be the test described in the BP or USP. Use of any other pharmacopoeia should be justified and acceptable to the MCC.

It is recommended that a dissolution profile be generated by taking samples at 15-minute intervals, or less, using the specified pharmacopoeial method for test and reference products (12 units each).

Additional dissolution data may also be required when scientifically justified, e.g. when the pharmacopoeia does not specify a dissolution test for all APIs in a combination product.

If appropriate the pharmacopoeial specification may be adopted.

2.2 PHARMACOPOEIAL PRODUCT DISSOLUTION TEST NOT AVAILABLE

If there is no pharmacopoeial method available, the FDA method for the reference listed product may be considered (<http://www.fda.gov/cder/dmethods>). Alternatively a dissolution method developed according to the criteria below should be submitted.

Comparative dissolution testing, using test and reference products under a variety of test conditions, is recommended.

2.2 PHARMACOPOEIAL PRODUCT DISSOLUTION TEST NOT AVAILABLE - continued

Criteria to be considered include:

- The pH solubility profile of the API
- Dissolution profiles generated at different agitation speeds (e.g. 100 revolutions per minute (rpm) for USP Apparatus I (basket), or e.g. 75 rpm for USP apparatus II (paddle)
- Dissolution profiles generated on all strengths in at least three dissolution media (e.g. pH 1,2, 4,5, and 6,8 buffer). If the API being considered is poorly soluble, appropriate concentrations of surfactant are recommended.

In all cases, profiles should be generated as previously recommended.

The medium which exhibits optimum discrimination should be selected.

The method used should be justified and validated.

For modified release products, as above. Where relevant, products should be tested on gastro resistance. Dissolution should preferably be tested routinely both at

- low pH (e.g. pH 2) to identify possible damage to the gastro-resistance coating or diffusion of the API through the coating and
- a pH simulating the intestinal segment for release (e.g. pH 6,8).

Where relevant one test system should be used, i.e. after exposure for at least 1 hour to acidic medium the medium should be changed (e.g. pH 6,8) and the release of the API determined.

2.3 SPECIAL CASES

- 2.3.1 For poorly water soluble drug products (e.g. glyburide), dissolution testing at more than one time point, and preferably a dissolution profile, is recommended for quality control purposes. Alternatively, the use of the USP apparatus 4 (Flow-Through Method) should be considered for the development of dissolution specifications for such products.
- 2.3.2 If a monograph for a fixed-dose combination is not included in the USP or BP, the monographs for the individual components should be used to set the dissolution requirements for each, or a dissolution method should be developed according to the criteria in paragraph 2.2.

3 DISSOLUTION PROFILES**3.1 REQUIREMENTS**

Dissolution studies of test and/or reference products as relevant, should be conducted in at least each of the following three media:

- pH 1,0 – 1,2 buffer: acidic media such as 0,1 N HCl or SGF without enzymes
- pH 4,5 buffer
- pH 6,8 buffer or SIF without enzymes

The use of any surfactant is not acceptable.

Further evidence in the main/specification dissolution medium, if not one of the required dissolution media, should be provided. The discriminating ability of the specification dissolution if not one of the three specified dissolution media, should be demonstrated and justified especially if the API being considered is poorly soluble and the specification dissolution medium contains a surfactant.

In case of gelatine capsules or tablets with gelatine coatings the use of enzymes may be acceptable. Such use should be justified.

3.1 REQUIREMENTS - continued

It is advisable to investigate more than one single batch of the test and reference products to ensure representativeness.

Usual experimental conditions are e.g.:

- Apparatus: paddle or basket
- Volume of dissolution medium: 900 ml or less
- Temperature of the dissolution medium: 37±1 °C
- Agitation: paddle apparatus - usually 50 or 75 rpm,
basket apparatus - usually 100 rpm

3.2 COMPARISON OF DISSOLUTION PROFILES

Two scenarios for comparing the profiles obtained from multipoint dissolution are operative:

1. If both the test and reference product show more than 85 % dissolution within 15 minutes, the profiles are considered similar (no calculations required). If not, see the next point.
2. Calculate the f_2 value. If $f_2 \geq 50$, the profiles are normally regarded similar such that further *in vivo* studies are not necessary. Note that only one measurement should be considered after 85 % dissolution of both products has occurred and excluding point zero.

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared errors, and is a measurement of the similarity in the percentage (%) dissolution between the two curves.

$$f_2 = 50 \cdot \log\left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\}$$

Where n is the number of time points, R_t is the dissolution value of the reference batch at time t , and T_t is the dissolution value of the test batch at time t .

A specific procedure to determine difference and similarity factor is as follows:

- a) Determine the dissolution profile of two products, i.e. of the test and reference products (using 12 units each).
- b) For f_2 calculations a minimum of three time points (excluding point zero) must be used, and only one measurement included after 85 % dissolution of both products has occurred.
- c) For curves to be considered similar, f_2 values should be close to 100. Generally, f_2 values greater than 50 (50 to 100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products.

This model-independent method is most suitable for dissolution profile comparisons when three to four or more dissolution time points are available. The following recommendations should also be considered:

- i) The dissolution measurements of the test and reference batches should be made under exactly the same conditions. The dissolution time points for both profiles should be the same (e.g. 10, 15, 20, 30, 45, 60 minutes, etc.). For rapidly dissolving products (profiles reaching 85 % at 30 minutes) the minimum time points are 10, 15, 20 and 30 minutes.
- ii) Only one measurement should be considered after 85 % dissolution of both products have occurred.
- iii) To allow use of mean data, the percent coefficient of variation (CV) at the earlier time points (e.g. 15 minutes) should not be more than 20 %, and at other time points should not be more than 10 %.

3.3 NON-COMPARATIVE DISSOLUTION PROFILES

Sufficient sample withdrawal time points should be used to adequately characterise the dissolution profiles of the active ingredient(s) from the final product. For rapidly dissolving products (profiles reaching 85 % at 30 minutes) the minimum sample withdrawal time points are 10, 15, 20 and 30 minutes.

3.4 REPORT ON COMPARATIVE AND NON-COMPARATIVE DISSOLUTION STUDIES

(refer also to *Pharmaceutical & Analytical Guideline 2.1.2* for further detail)

Only a complete report on the letterhead of the laboratory will be considered, and should contain at least the following (also refer to Documentation Requirements SA Guide to GMP Chapter 4):

- i) Purpose of study
- ii) Products / batches information, e.g.
 - Batch number, manufacturing/expiry date, packaging
 - CoA & batch size for test batches
- iii) Dissolution conditions and method

The dissolution method should specify in-line filtration for drawing the dissolution samples to ensure that the dissolution of the sample is stopped immediately on withdrawal of the sample unless filtration is demonstrated to be unnecessary. A method stating that the samples should be drawn and filtered does not necessarily imply or ensure that the dissolution of undissolved particles in the sample is stopped at the time of sampling. (USP "Test specimens are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary".)
- iv) Validated analytical method or reference to a section of the dossier
- v) Results (% API dissolved)
 - Tabulated individual and mean results and respective summary statistics
 - Graphically
 - Similarity determination / calculation for comparative dissolution studies
- vi) Discussion/conclusion
- vii) Date of analyses and date of report
- viii) A GMP/GLP compliance declaration by the laboratory, including reference to the availability of validation records of test methods and procedures for and records of the calibration of instruments and maintenance of equipment. Refer SA Guide to GMP.

4 IN VITRO DISSOLUTION TESTING IN SUPPORT OF A BIOWAIVER

(Bioequivalence Surrogate Inference) (refer also to *Biostudies Guideline*)

For certain APIs and dosage forms documentation of bioequivalence may be assessed by the use of *in vitro* dissolution testing.

4.1 PROPORTIONALLY SIMILAR DOSAGE FORMS

When a biowaiver is requested for different strengths of test/multisource products which are

- proportionally formulated (see *Biostudies guideline 2.11* and *5.1.1*),
- manufactured by the same manufacturer at the same manufacturing site, and

4.1 PROPORTIONALLY SIMILAR DOSAGE FORMS - continued

- an appropriate bioequivalence study has been performed on at least one of the strengths of the formulation (usually the highest strength unless a lower strength is chosen for reasons of safety), dissolution profiles generated for the test and other strength multisource products being applied for (i.e. lower and higher strengths) should be compared as described in section 3 of this guideline for each of the specified media.

When sink conditions do not exist in one or more media, the profiles of the higher and lower strengths may not be similar in those media due to saturation, in which case supporting data may be generated with the local innovator of the same strength.

4.1.1 Immediate release tablets

For different strengths of a multisource formulation a biowaiver may be granted if the dissolution profiles in the three dissolution media specified above are similar according to definition.

4.1.2 Modified release products (refer to Pharmaceutical & Analytical Guideline for definitions)**4.1.2.1 Extended release beaded capsules**

For extended release beaded capsules, where the strength differs only in the number of beads containing active moiety, dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition (i.e. one dissolution medium) may be considered for biowaivers for other strengths. Also refer to Biostudies guideline "Beaded Capsules".

4.1.2.2 Extended release tablets

For extended release tablets, when the drug product

- is in the same dosage form but
- in a different strength, and
- is proportionally similar in its active and inactive ingredients and
- has the same drug release mechanism

a biowaiver may be considered for other strengths if it exhibits similar dissolution profiles, $f_2 \geq 50$, in the three dissolution media specified.

4.2 REFERENCE PRODUCTS REGISTERED IN SOUTH AFRICA BUT PROCURED IN ANOTHER COUNTRY, THE HEALTH REGULATORY AUTHORITY OF WHICH THE MCC ALIGNS ITSELF WITH (refer also to Pharmaceutical & Analytical and Biostudies Guidelines)

The reference product may be procured from another country, the health regulatory authority of which the Council aligns itself with (General Information guideline PART 1D) provided that it complies with the requirements for reference products specified in the Pharmaceutical & Analytical guideline.

Demonstration of equivalence between that reference product and the corresponding innovator product marketed in South Africa is required. Dissolution profiles of the test and reference products should be compared for similarity as described in section 3 of this guideline for each of the three specified media irrespective of the solubility and/or stability profiles. Further evidence in the main/specification dissolution medium, if not one of the required dissolution media, must be provided.

4.3 AMENDMENTS

When amendments are made to pharmaceutical products, manufacturing procedures, and other associated processes including change of site, their impact on safety, efficacy and quality should be demonstrated where required. The following describes the use of dissolution testing as an indicator of quality which may be applicable as described below.

4.3 AMENDMENTS - continued

The following dissolution tests are recommended:

4.3.1 Types of dissolution testing**a) Case A**

Dissolution testing should be conducted as a release test according to the original submission, or in accordance with compendial requirements, for the proposed and currently registered formulations, for that product.

b) Case B

Dissolution testing should be conducted as a multipoint test in the application/compendial medium, for the proposed and currently registered formulations, at intervals such as 10, 15, 20, 30, 45, 60 and 120 minutes, or until an asymptote is reached for the proposed and currently registered formulation. For rapidly dissolving products (profiles reaching 85 % at 30 minutes) the minimum time points are 10, 15, 20 and 30 minutes.

c) Case C

Dissolution testing should be conducted as a multipoint test in at least the three dissolution media as specified above for the proposed, and currently registered formulations, at intervals such as 10, 15, 20, 30, 45, 60 and 120 minutes, or until either 85 % dissolution is obtained, or an asymptote is reached. The final product dissolution medium should be included if not one of the three specified dissolution media.

4.3.2 Types of amendments (refer to Amendments Guideline)**a) Type A**

In the event that the Type A change made is such that it is unlikely to have an effect on the quality and performance of a dosage form, Case A dissolution testing is appropriate.

b) Type B

In the event that the changes, which were made, could have a significant impact on the quality and performance of a dosage form, Case B or C dissolution testing is appropriate.

Profiles of the currently used product and the proposed product should be proven to be similar, according to the requirements as describe in this Guideline.

c) Type C

In the case of changes that are likely to have a significant impact on formulation quality and performance, *in vivo* bioequivalence testing should be conducted unless otherwise justified. Case B or Case C dissolution testing may also be required. Biowaivers may also be considered if a proven *in vitro/in vivo* correlation (IVIVC) has been established.

4.4 BIOWAIVERS BASED ON BCS (refer also to the Biostudies Guideline)

In the Biopharmaceutics Classification System (BCS) an API is classified as having high or low solubility and high or low permeability.

4.4.1 Biopharmaceutics Classification System (BCS)

The Biopharmaceutics Classification System (BCS) is based on aqueous solubility and intestinal permeability of the active pharmaceutical ingredient (API). It classifies the API into one of four classes:

Class 1 - High Solubility, High Permeability

Class 2 - Low Solubility, High Permeability

Class 3 - High Solubility, Low Permeability

Class 4 - Low Solubility, Low Permeability

Combining the dissolution characteristics of the pharmaceutical product with these two properties of the API, the three major factors that govern the rate and extent of absorption from immediate release solid dosage forms are taken into account.

With respect to dissolution properties, immediate release dosage forms can be categorized as having “very rapid”, “rapid”, or “not rapid” dissolution characteristics.

On the basis of scientific principles of solubility and permeability and dissolution characteristics of the dosage form, the BCS approach provides an opportunity to waive *in vivo* pharmacokinetic bioequivalence testing for certain categories of immediate release pharmaceutical products .

Oral pharmaceutical products not eligible for a so-called “biowaiver” based on the BCS approach are described in the Biostudies Guideline.

4.4.1.1 High solubility

An API is considered highly soluble when the highest dose is soluble in 250 ml or less of aqueous media over the pH range of 1,2 to 6,8 at 37 °C

4.4.1.2 High permeability

An API is considered highly permeable when the extent of absorption in humans is 85 % or more based on a mass balance determination or in comparison to an intravenous reference dose.

Acceptable alternative test methods for permeability determination of the drug substance include:

- (i) *in vivo* intestinal perfusion in humans, or
- (ii) *in vitro* permeation using excised human or animal intestinal tissue.

When one of these two alternative methods is used for permeation studies, suitability of the methodology should be demonstrated, including determination of permeability relative to the permeability of a reference compound whose fraction dose absorbed has been documented to be at least 85 %.

4.4.1.2 High permeability - continued

Supportive data can be provided by the following additional test methods:

- (i) *in vivo* or *in situ* intestinal perfusion using animal models, or
- (ii) *in vitro* permeation across a monolayer of cultured epithelial cells (e.g. Caco-2) using a method validated using APIs with known permeabilities, although data from either of the two latter methods would not be considered acceptable on a standalone basis. In these experiments high permeability is assessed with respect to a high permeability of a series of reference compounds with documented permeabilities and fraction absorbed values, including some for which fraction dose absorbed is at least 85 %.

Relevant information on solubility and permeability may be provided by published data.

4.4.2 Determination of dissolution characteristics of multisource products in consideration of a biowaiver based on the BCS

For exemption from an *in vivo* pharmacokinetic bioequivalence study, an immediate release multisource product should exhibit very rapid or rapid *in vitro* dissolution characteristics (see below), depending on the BCS properties of the API. *In vitro* data should also demonstrate the similarity of dissolution profiles between the test and comparator products.

4.4.2.1 Very rapidly dissolving

A multisource product is considered to be very rapidly dissolving when no less than 85 % of the labelled amount of the API dissolves in 15 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each of the following media:

- (i) pH 1,2 HCl;
- (ii) pH 4,5 acetate buffer; and
- (iii) pH 6,8 phosphate buffer.

4.4.2.2 Rapidly dissolving

A multisource product is considered to be rapidly dissolving when no less than 85 % of the labelled amount of the API dissolves in 30 minutes using a paddle apparatus at 75 rpm or basket apparatus at 100 rpm in a volume of 900 ml or less in each of the following media:

- (i) pH 1,2 HCl;
- (ii) pH 4,5 acetate buffer; and
- (iii) pH 6,8 phosphate buffer.

5 REFERENCES

- 1 Guidance for Industry. Waiver of In-Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000.
- 2 Moore, J.W. and Flanner, H.H. (1996). Mathematical Comparison of Dissolution Profiles. *Pharm. Technol.* 20 (6):64-74.
- 3 Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 1997.
- 4 Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), September 1997.
- 5 CPMP Guideline on The Investigation of Bioequivalence. The European Agency for the Evaluation of Medicinal Products CPMP/EWP/QWP/1401/98 Rev.1/Corr**. (Date for coming into Operation August 2010).
- 6 FIP Guidelines for Dissolution Testing of Solid Oral Products. Joint report of the Section for Official Laboratories and Medicines Control Services and the Section of Industrial Pharmacists of the FIP. (Final draft 1995).
- 7 FIP Guidelines for Dissolution Testing of Solid Oral Products. Joint report of the Section for Official Laboratories and Medicines Control Services and the Section of Industrial Pharmacists of the FIP. Updated guidelines (second edition) 1997.
- 8 Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm. Res.*, 1995, 12: 413-420.
- 9 HHS/FDA Guidance for Industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system, August 2000. <http://www.fda.gov/cder/guidance/index.htm>
- 10 Yu LX, Amidon GL, Polli JE, et al. Biopharmaceutics Classification System: The scientific basis for biowaiver extensions. *Pharm. Res.* 2002, 19: 921-925.
- 11 CPMP Note for Guidance on Quality of Modified Release Products A: Oral dosage forms B: Transdermal dosage forms *Section I (Quality)* CPMP/QWP/604/96

UPDATE HISTORY

First publication	May 2003
Release for comment	November 2003
Deadline for comment	November 2003
Date for finalisation/implementation	December 2003
Version 2 Amendment of sections 1, 2, 3, 4, 5	June 2006
Deadline for comment	14 August 2006
Date of implementation, excluding 4.1 b)	2 July 2007
Date of implementation 4.1 b)	2 July 2008
Version 3: Amendment of sections 1 ii), 3.2, 4.1, 4.1.2.1, 4.2, 4.3.1 for clarification Addition of 3.2 vii) for clarification	June 2012
Date of implementation	With immediate effect
New section 3.2 viii)	
Date of implementation	1 September 2010
Version 4: Change of name of Post-registration Amendments guideline - 1, 4.2, 4.3, 4.3.2; Correction dissolution method 2c); Correction rapidly dissolving products 3.1 i)	March 2011
Date of implementation	With immediate effect
Version 5: Clarification in line with CPMP/QWP/604/96 EMEA 1999 and CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** in sections 2 and 3, updating of reporting requirements, also for non-comparative studies in line with P&A guideline, clarification of Type C for easy reference, updating of reference	March 2014/June 2015
Deadline for comment	05 May 2014
Date of implementation	July 2015 With immediate effect