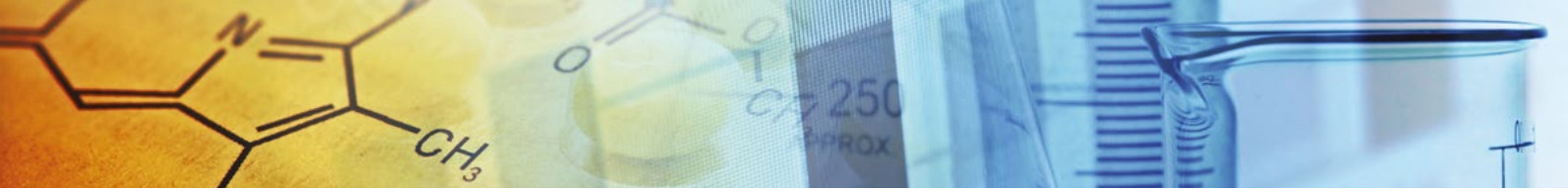


British Pharmacopoeia

How to use the BP

The BP is the only comprehensive collection of authoritative official standards for UK pharmaceutical substances and medicinal products. It contains all texts and monographs of the European Pharmacopoeia (signposted with a chaplet of stars), as well as the national standards developed by the BP. Unsurprisingly, this means the BP contains a lot of information.

This guide is designed to help you become more familiar with the requirements of the BP, where to locate the different types of information and how to apply a formulated preparation monograph.

Getting started

If a drug product is licensed in a country where the BP is a legal standard:

- it should be able to comply with the requirements of the BP at any time throughout its shelf life
- it should meet the standards of the BP regardless of whether compliance with the BP is claimed or it is not called by the name at the head of the monograph

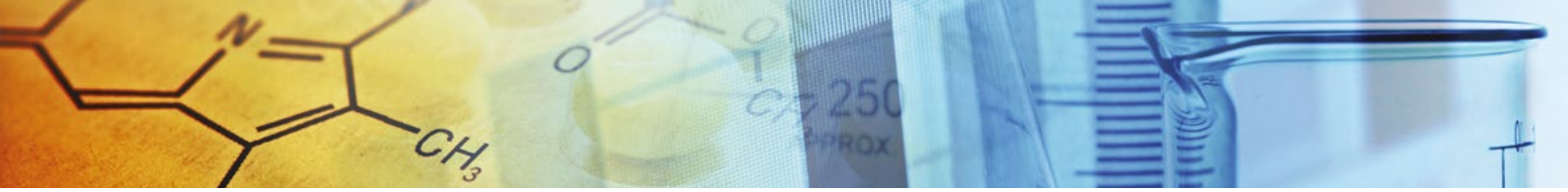
For a drug product to be compliant with a BP monograph:

- the monograph that was in force at the date of product manufacture should be applied e.g. BP 2019 is legally effective between 01/01/2019 and 31/12/2019. The effective date can be found in the Introduction section of the BP
- all ingredients (drug substances and excipients) that are used to make the product should comply with the published BP or Ph. Eur. monograph for those substances
- the product should comply with the relevant general monographs
- the product should comply with the requirements of the monograph for the formulated preparation

What you should do if:

- you have developed a method which is an improvement on the current BP procedure and want to propose a revision to the monograph
- you believe that there is an error in the BP

contact bpcom@mhra.gov.uk with the information needed to contribute to monograph development (described on the Monograph Development page on the BP website) or, providing details of the error with data if appropriate.



Navigating the BP

Guidance on where certain types of information is located within the BP is given below:

BP CONTENT

Preliminaries

The Preliminaries (Volume I of the hard copy) consist of several informative texts, including the Introduction which details the new, revised and omitted monographs in any given edition of the BP, the legally effective date and an update on high profile BP activities.

General Notices

The General Notices contain information applicable to all texts in the BP and are essential reading. General notices explain which statements are mandatory and non-mandatory, and the definition of terms. They can be found in the online BP using the 'Table of Contents' or following the 'General Notices' link in monographs (the pink pages in all volumes of the hard copy).

Monographs: Medicinal and Pharmaceutical Substances

Monographs: Medicinal and Pharmaceutical substances (Volumes I and II of the hard copy) contains monographs for active pharmaceutical ingredients and excipients.

Formulated Preparations: General Monographs

All pharmaceutical products should comply with the general monographs for pharmaceutical preparations and the dosage form (the product should also comply with the specific preparation monograph where one is published). These are found in Formulated Preparations: General Monographs online (Volume III of the hard copy).

Formulated Preparations: Specific Monographs

Monographs for specific drug formulations, incorporating small molecule, biological and unlicensed medicines, can be found in this section of the online BP (Volume III of the hard copy). A more detailed explanation of a formulated preparation BP monograph can be found in the next section of this guide.

Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products / Materials for use in the Manufacture of Homoeopathic Preparations / Blood-related Products / Immunological Products / Radiopharmaceutical Preparations / Surgical Materials

All monographs relating to herbal drugs and homoeopathics, blood related products, immunological products and vaccines, radiopharmaceuticals and surgical materials, can be found from the relevant section in the online table of contents (Volume IV of the hard copy).

Infrared Reference Spectra

There is a link to relevant infrared reference spectra in formulated preparation monographs (Volume V of the hard copy). Determining concordancy of IR spectra is explained in the General Notices.

Appendices

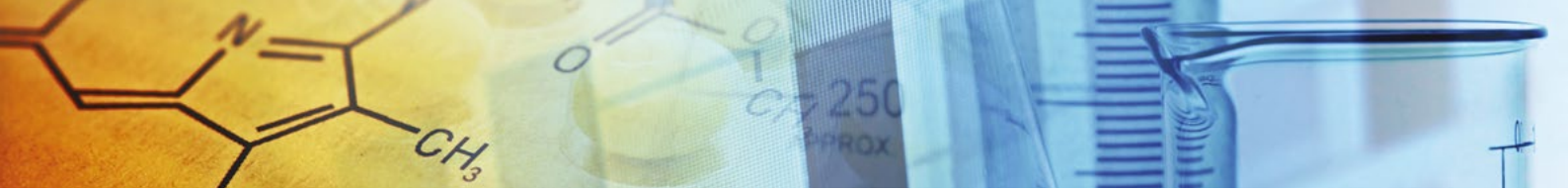
The Appendices (Volume V of the hard copy) contain methods of analysis and calibration requirements for analytical techniques (Ph. Eur. section 2), texts relating to containers (Ph. Eur. section 3), reagents and volumetric solution preparation (Ph. Eur. section 4) and the majority of the general texts of Ph. Eur section 5. When an appendix is referenced in a monograph, the requirements of that appendix are mandatory unless stated otherwise. The European Pharmacopoeia Equivalent Texts page correlates Ph. Eur. texts to the Appendix reference of the BP.

Supplementary Chapters

The Supplementary Chapters contain non-mandatory information and guidance. If you need advice to understand a test or calculate results in the BP, the supplementary chapters may contain the information you are looking for (Volume V of the hard copy).

British Pharmacopoeia (Veterinary)

The BP (Vet) contains the sections described above for pharmaceutical and medicinal products that are only used in veterinary medicine (Volume VI of the hard copy).



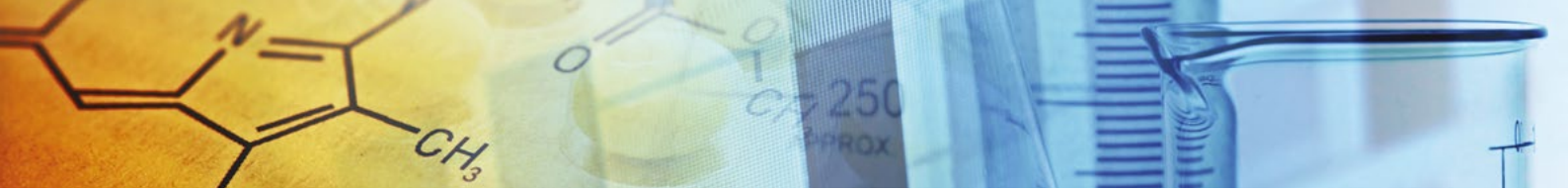
Following a monograph

This section is designed to provide a broad explanation of how to apply and interpret a BP formulated preparation monograph, using the BP 2019 Aspirin Tablets monograph as an example.

When using a monograph for a drug product:

- you should read the General Notices; these form the foundation of pharmacopoeial requirements and define the terms used in monographs
- you should apply the requirements of the general monograph for the particular dosage form, e.g. Tablets, and the general monograph for Pharmaceutical Preparations. These can be found in the Formulated Preparations: General Monographs section in the publication table of contents
- the analytical techniques used should meet the specifications and requirements set out in the relevant appendices e.g. Appendix III Chromatographic Separation Techniques and Appendix III D Liquid Chromatography when using LC. Appendices form part of the official requirements of the BP where specified in a monograph. Supplementary Chapters are explanatory texts provided for information and to assist users
- you should confirm that the methods are suitable for the particular drug product being tested e.g. that excipients in the product do not affect the analysis

EXPLANATORY NOTES	MONOGRAPH EXAMPLE
The official title of the product in the UK. Aspirin is the British Approved Name (BAN) i.e. the non-proprietary name for acetylsalicylic acid in the UK (see Appendix XXI B Approved Synonyms for further details).	**Aspirin Tablets**
The General Notices: • provide useful information on using the BP • explain that a product should comply with the monograph, if tested • explain which sections of the monographs are mandatory & which are advisory • explain that alternative tests to the ones described in the monograph can be used.	General Notices
This is a subsidiary title, which is also an official title for products that should comply with this monograph. This name should not be used when marketing products in the UK.	Acetylsalicylic Acid Tablets
Advisory information on the most common indication(s). This is not exhaustive and is usually aligned with the entry in the British Approved Names (BAN) publication.	**Action and use** Salicylate; non-selective cyclo-oxygenase inhibitor; antipyretic; analgesic; anti-inflammatory.
The drug substance used to manufacture the tablets must comply with the relevant Ph Eur or BP monograph for that substance. In this case the Aspirin monograph (Ph. Eur. monograph 0309, Acetylsalicylic Acid).	**DEFINITION** Aspirin Tablets contain Aspirin. *The tablets comply with the requirements stated under Tablets and with the following requirements.*
The tablets must comply with the Tablets general monograph.	**Content of aspirin, $C_9H_8O_4$** 95.0 to 105.0% of the stated amount
The tablets must contain 95.0 to 105.0% of the amount stated on the label for the shelf life of the product. The content is written in terms of the label claim of the product, which may not match the full title of the drug substance monograph. This is common when the drug substance used to manufacture the product is in a salt form.	



BP monographs are designed for products that are manufactured within the quality framework for medicinal products. When applied within this framework, the identification test (or tests) in the monograph are sufficient to confirm that the drug product contains the drug substance on the label.

Where a word/phrase is in italics, it means it is connected to another section of the BP. In this case, the reagent entry for absolute ethanol in Appendix I A. The reagent used should comply with the criteria stated in the appendix entry.

The tests contained in this section of the monograph are to determine quality attributes of the product. The product must comply with the requirements of the tests.

The methods in the monograph are the official methods which support the standard. However, alternative methods can be used if the user can demonstrate that it gives an equivalent measure of the requirement. This is stated in the General Notices Part II, in the section on 'Assays and Tests'.

Q value limits were not applied to monographs published before BP 2008; the requirements of Appendix XII B. Monographs of the British Pharmacopoeia apply in these cases, and the monographs affected are listed in SC I E Dissolution Testing of Solid Oral Dosage Forms.

Monographs first published in BP 2008 or afterwards should comply with Appendix XII B. Dissolution and Q value limits will be given within the monograph.

Where there is no 'Limits' section following 'Determination of content' in the monograph, check section 3.4 of Supplementary Chapter I E Dissolution Testing of Solid Oral Dosage Forms. If the monograph title is listed here, apply a limit of not less than 70% of the label claim in 45 minutes.

If the monograph is not listed in SC I E, follow the decision tree in section 3.3 of the same supplementary chapter.

This test is designed to provide limits for potential impurities related to the drug substance, rather than all possible impurities such as adulterants or contaminants.

BPCRS Information Leaflets can be a good source of guidance e.g. reference chromatograms. Information leaflets are available free of charge in the online reference standards catalogue: https://www.pharmacopoeia.com/Catalogue/Products. Reference material with the suffix EPCRS and CRS can be obtained from the European Directorate for the Quality of Medicines & HealthCare (EDQM): https://www.edqm.eu/en/ph-eur-reference-standards-orders-catalogue

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.5 g of Aspirin with 20 mL of *absolute ethanol*, filter (Whatman GF/C is suitable), evaporate the filtrate and dry the residue at 60° for 1 hour. The *infrared absorption spectrum* of the residue, is concordant with the reference spectrum of aspirin *(RS 483)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules,* Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.

(b) Use 500 mL of a pH 4.5 buffer prepared by mixing 29.9 g of *sodium acetate* and 16.6 mL of *glacial acetic acid* with sufficient *water* to produce 10 litres at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 265 nm, *Appendix II B* using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *aspirin BPCRS* using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of aspirin, $C_9H_8O_4$, in the medium using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*.

Related substances

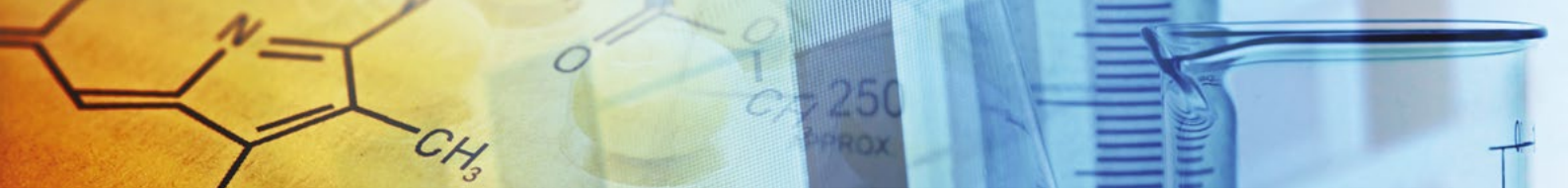
Carry out the method for *liquid chromatography*, *Appendix III D*, using the following solutions prepared immediately before use.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 0.10 g of Aspirin with 40 mL of *acetonitrile*, allow to cool, dilute to 100 mL with *water* and filter through a 0.45-µm PTFE filter.

(2) Dilute 1 volume of solution (1) to 50 volumes and further dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(3) 0.003% w/v of *salicylic acid* (impurity C) in the mobile phase.

(4) 0.1% w/v of *aspirin impurity standard BPCRS* in the mobile phase.



Appendix III Chromatographic Separation Techniques includes details on making adjustments to chromatographic conditions.

The brand/manufacturer of the column that was used when the monograph method was established is provided for information.

The General Notices require that, unless stated otherwise, assays and tests are performed between 15 to 25 °C. Ambient temperature should be taken to mean between 15 to 25 °C.

It is important to note the word 'about'. If the system suitability requirement (below) is met, and the impurities can be detected/identified, the retention time does not need to be exactly 5 minutes. There is likely to be variation due to the use of different equipment and columns. Check the More Resources section in the online BP for example test results (if there are some available).

Appendix III Chromatographic Separation Techniques gives details of how to measure resolution.

Guidance on the control of impurities and on calculating limits can be found in SC I A. Control of Impurities and SC VI A. Pharmacopoeial Calculations.

The limit is measured against the peak area of the limiting solution, in this case solution (3).

In this example, the limit of the impurity is determined against an external standard of the impurity.

However, it is more common for the limiting solution to be a dilution of the test solution.

A dilution of the test solution (solution (1)) is another common way of preparing a limiting solution.

The (3%) figure indicates the limit as a percentage relative to the amount of Aspirin in the test solution and is given for information. It is not a numerical limit. If a numerical limit is given, the figure will be shown in the limits section without parenthesis e.g. 'the total impurities are not greater than 2.0%'.

Secondary peaks exclude the drug substance(s), reagents, internal standards and derivatising agents. Peaks that are due to the mobile phase, sample matrix, excipients and counter-ions can also be disregarded. Any other secondary peak refers to any related substance peak in the chromatogram, apart from any impurities already specified in the limits section. More details on secondary peaks can be found in Appendix III Chromatographic Separation Techniques – Quantification and Appendix III D Liquid Chromatography – Additional points for monographs of the British Pharmacopoeia.

If the limit is described as 'the sum of the area of any secondary peaks' the areas of all related substances peaks that are detected above the disregard limit should be summed. If the limit is written as 'the sum of the areas of any other secondary peaks' then the sum should not include any impurities that have specific limits applied to them. In this example, if there is a peak corresponding to impurity C in the sample, it should not be included within the sum of any 'other secondary peaks'.

As BP monographs can, in most cases, be applied to different product strengths, the disregard limit is usually based on the maximum daily dose for the drug substance and ICH guidelines.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 237 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 1.2 times the retention time of impurity F.

MOBILE PHASE

2 volumes of *orthophosphoric acid*, 400 volumes of *acetonitrile* and 600 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to aspirin (retention time about 5 minutes) are: impurity A, about 0.6; impurity B, about 0.7, impurity C, about 1.4 and impurity F, about 8.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4) the *resolution* between the peaks due to aspirin and impurity C is at least 6.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3%);

the area of any other *secondary peak* is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

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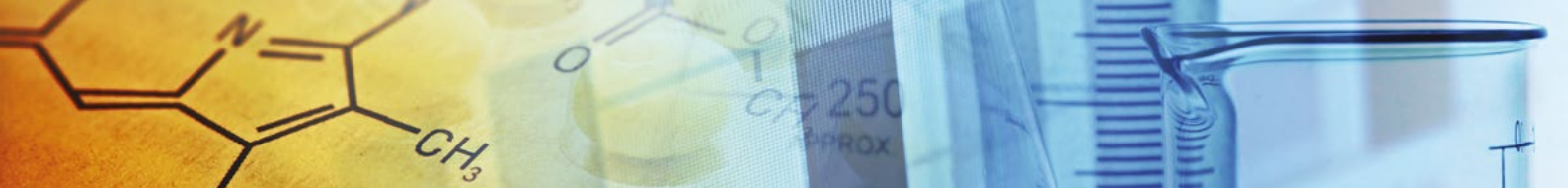

20 units is traditionally accepted as a statistical representation of a batch.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 60 mg of Aspirin with 40 mL of *acetonitrile*, allow to cool, dilute to 100 mL with *water* and filter through a 0.45-µm PTFE filter.

(2) 0.06% w/v of *aspirin BPCRS* in the mobile phase.

(3) 0.1% w/v of *aspirin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) the *resolution* between the peaks due to aspirin and impurity C is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_8O_4$ in the tablets from the chromatograms obtained using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*.

The declared content of a BPCRS can be found in the online catalogue and in the leaflet.

Labelling requirements in monographs are not comprehensive and the requirements of the regulatory authority where the product is marketed should be met. More information on the status and interpretation of the labelling section can be found in Supplementary Chapter I G Labelling.

LABELLING

The label states that the tablets contain Aspirin, unless this word appears in the name of the tablets. This requirement does not apply in countries where exclusive proprietary rights in the name Aspirin are claimed.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aspirin.

This means that the Related substances test can detect and control the impurities listed in the drug substance monograph for Aspirin (Ph. Eur. monograph 0309, Acetylsalicylic Acid).