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6. PRIMARY PACKAGES FOR PHARMACEUTICALS

6.1. INTRODUCTION

Pharmaceutical products are delivered to the intended consumers in a variety of packages.

A package for a pharmaceutical is a form that is intended to contain, protect/preserve the contents throughout the shelf life; aid in the safe, efficient transportation and distribution; and to inform the user about the drug substance or drug product. A package comprises a container that usually has a closure (e.g. cap, lid, dispensing system) and a label (e.g. a separate label or printed matter). The closure may or may not have a liner.

A package is also conventionally referred to as a container-closure system.

NOTE 1:

This section covers the primary package i.e. the materials that come in direct contact with pharmaceutical contents. Secondary and tertiary packaging is not addressed in this pharmacopoeia.

This chapter deals with the specific requirements, guidance and information on containers used for packaging of pharmaceutical products. The materials that are used in the manufacture of containers, particularly plastic containers, the raw materials and additives used and the formulations employed should be agreed with the users of the containers.

A container-closure system for pharmacopoeial article is intended to contain a drug substance or drug product with which it is, or may be in direct contact.

A container-closure system for pharmacopoeial article must be chosen with care and after taking into consideration the nature of the articles and the likely effects of transportation and storage, even for short periods of time.

A container-closure system for pharmacopoeial article should be designed so that the contents may be removed in a manner suitable for the intended use of the article in it. It should also provide an adequate degree of protection, minimise the loss of constituents and should not interact physically or chemically with the contents in a way that will alter their quality to an extent beyond the limits given in the individual monograph, or present a risk of toxicity.

The choice of a container-closure system for pharmacopoeial article is also governed by the likely period of storage of the article during which its quality will not be compromised to a degree where it will be unfit for use. Under the heading Storage, the pharmacopoeia indicates the measures to be taken to protect the article from contamination and deterioration during its entire shelf-life. Technical Specifications for the package to be used for any article have not been given but in certain cases, the type of package that is recommended is stated in terms that have the following meanings.

6.1.1. Terminology

a. ***Package***. A package comprises a container that usually has a closure (e.g. cap, lid, dispensing system) and a label (e.g. a separate label or printed matter). The closure may or may not have a liner.

A package is also conventionally referred to as a container-closure system.

b. ***Well-closed Package.*** A container-closure system for a pharmacopoeial article that protects the contents from extraneous solids and liquids and loss of the article in process of handling, shipment, storage and distribution.

c. ***Airtight or Tightly-closed Package*.** A container-closure system for a pharmacopoeial article that protects the contents from contamination by extraneous solids, liquids, or vapours, loss or deterioration of the article from effervescence, deliquescence or evaporation during handling, shipment, storage and distribution. A tightly-closed container-closure system for a pharmacopoeial article must be capable of being tightly re-closed after use.

d. ***Hermetically Sealed Package*.** A container-closure system for a pharmacopoeial article that is impervious to air or any other gas under normal conditions of handling, shipment, storage and distribution, e.g. sealed glass ampoule, gas cylinder etc. A hermetically sealed container-closure system must be used for a single dose.

e. ***Light-resistant Package*.** A container-closure system for a pharmacopoeial article that protects the contents from the effects of actinic light by virtue of the specific properties of the material of which it is made. Alternatively, a clear and colourless or a translucent container may be made light-resistant by means of an opaque (light-resistant) covering and/or in such cases, the label on the container should bear a statement that the opaque covering or storage in dark place is needed until the contents have been used up.

f. ***Single-dose Package*.** A container-closure system for pharmacopoeial article that holds a quantity of the preparation intended for total or partial use as a single administration.

g. ***Multi-dose Package*.** A container-closure system for a pharmacopoeial article that holds a quantity of the preparation suitable for two or more doses.

h. ***Sealed Package*.** A container-closure system for pharmacopoeial article closed by fusion of the material of the container.

i. ***Tamper-evident Package*.** A container-closure system for a pharmacopoeial article fitted with a device or mechanism that reveals irreversibly whether the container has been opened.

The user of the container-closure system must obtain an assurance from the supplier that the composition of the closure does not vary from batch to batch and that it is identical to that of the container used during compatibility testing. When the user is informed of changes in the composition, compatibility testing and biological testing must be repeated, totally or partly depending on the nature of the changes.

A container-closure system for a pharmacopoeial article is available in different forms. However, one of the form is container which is widely used for pharmaceuticals. The details are given below:

6.2. CONTAINERS

Containers for pharmaceutical products are made of a variety of materials such as different types of plastics, glass, metal and their combination. This section covers the guideline for each type of these container materials.

6.2.1. Plastic Containers

The commonly used plastic resins conforming to Indian Standards for the manufacture of plastic container and closures are Polyethylene terephthalate (PET) (IS 12252), Polyethylene (IS 10146), Polyvinyl Chloride (IS 10151), Polypropylene (IS 10910), Cyclic Olefins, Polyamides [nylon 6 (IS 12247)], Polycarbonate (IS 14971), Poly (ethylene-vinyl acetate) (IS 13601). However, if the manufacturer of pharmacopoeial articles intends to use plastics made from polymers other than listed above, it should be justified and authorised by appropriate competent authority.

The resin identification codes as mentioned in IS 14534 may be visibly marked on the plastic containers and/ or the label, wherever possible.

The plastic containers should be manufactured from materials that do not include in their composition any substances that can be extracted by any contents in such quantities so as to alter the efficacy or stability of the product or present a toxic hazard. Recycling of excess material of well-defined nature and proportions may be permitted after appropriate validation.

A summary of the manufacture and usage of plastic container and closures is provided in the **Table 1**.

Table 1 - Overview of the life cycle (stages) of Plastic Materials for Pharmacopoeial Articles

Stakeholder	Activity Involved	Governing Regulations in force	Examples
Plastic Resin Manufacturers	**Monomers** (Raw material) ↓ conversion into ↓ **Polymer** **(**Plastic Resin)	BIS Standards on composition of various packaging polymers (plastic resins)	Polyethylene terephthalate (PET) = IS 12252 Polyethylene (PE) = IS 10146 Polyvinyl chloride (PVC) = IS 10151 Polypropylene (PP) = IS 10910 Polyamides [nylon 6] = IS 12247 Polycarbonate = IS 14971 Poly (ethylene-vinyl acetate) = IS 13601
Manufacturers of Packaging components (Convertors)	Addition of Colourant/ Additives to Resin if needed and converting the mixture into shaped articles (Plastics Articles)	BIS Standard for Resin Identification Codes IS - 14534	Bottles, Containers, Tubes, Caps, Closures and other forms of Packages **Identification Codes** Code No.1 = PET Code No.2 = HDPE (High Density PE) Code No.3 = V (PVC, Polyvinyl Chloride) Code No.4 = LDPE (Low Density PE) Code No.5 = PP Code No.6 = PS (Polystyrene) Code No.7 = Other plastics
Manufacturer of Pharmacopoeial Articles (Users)	Filling of Pharmaceutical Formulations (Packaged Products)	The Drugs and Cosmetics Act, 1940 The Drugs and Cosmetics Rules, 1945	Substances, Preparations, Articles
Consumer	Consumption/ Usage	-	Patients, Health care chain (Doctors, Hospitals)
All stakeholders	Disposal	Plastic Waste Management Rules, 2016	Various responsibilities on Manufacturers, Local Bodies, Citizens, etc.

The selection of a suitable plastic container should be based on a knowledge, obtained from the supplier of the raw materials used and of the composition of the plastic so that potential hazards can be assessed. The plastic container chosen for any particular product should be such that the ingredients of the product in contact with the plastic material are not significantly adsorbed on its surface and do not significantly migrate into or through the plastic. Type samples (specimen) of the intended container should be packed with the product and tested under conditions that reproduce those that would be encountered in use. These tests should include examination of the product to ensure absence of any sensory, chemical or physical change, an assessment of changes in the quality of contents due to permeability of the plastic, detection of changes in pH, an assessment of the effects of light, chemical tests and where necessary, biological tests. Containers from bulk production should conform to the type sample (specimen) in every respect. It should be ensured that there is no change in the composition or any change in the manufacturing method used by the manufacturer and more importantly, that no use is made of post-consumer recycled material. It must be emphasized that changes in the composition of the plastic or reworking or inadequate control of processing can bring about changes which may invalidate the results of type testing. Samples from production should be tested to ensure conformance to type samples (specimen) and test schedules should be designed to check deviations from the characteristic of the type sample (specimen).

The biological and chemical tests described below are intended for plastic containers in which pharmaceutical formulations are packaged. It should be appreciated that these tests by themselves are not sufficient to establish safety or suitability of the plastic containers for the preparations and it is necessary to consider the results of the tests in conjunction with the information given above. Specification should be agreed with the container manufacture and

should be revised if the composition of the plastic or the ingredient quality is altered or the processing treatment is changed.

It shall be the responsibility of the user/manufacturer to ensure the compatibility of the pharmaceutical products with the package and stability of the product in the package system. Towards this the user / manufacturer shall have in place a system of quality assurance with the supplier / convertor to ensure compliance of the components of the package with the requirement stated in this chapter at all times. The user should take the "risk-based approach" to determine the testing and its frequency required to ensure this.

Applicability of Biological Tests for Plastic Packages

- Packages used for oral and topical dosage forms do not need any biological testing.
- *In vitro* testing described in Appendix 2.2.23 is applicable to the packages used for all dosage forms except for oral and topical dosage forms.
- Packages that meet the requirements of the *in vitro* tests are not required to undergo any further *in vivo* testing (2.2.24).
- Packages that do not meet the requirements of the *in vitro* tests where applicable are required to undergo further *in vivo* testing.

Packages that do not meet the requirements of the biological reactivity tests [(2.2.23) and (2.2.24), if appropriate] are not suitable as packages for pharmaceutical use.

6.2.1.1. Plastic Containers for Parenteral Preparations

General Requirements

Material. Plastic containers for parenteral preparations are manufactured from one or more polymers. The polymers most commonly used are polyethylene, polypropylene and polyvinyl chloride. Only virgin plastic material, which is practically odourless, is used in the manufacture of the containers. Additives such as antioxidants, lubricants, plasticisers, stabilisers, etc. may be used but no pigment may be used for purposes of colouring.

Characteristics. The containers may be bags or bottles. They have a site suitable for the attachment of an infusion set designed to ensure a secure connection. They may have a site that allows an injection to be made at the time of use. They usually have a part that allows them to be suspeended and which will withstand the tension occurring during use. Although it may not be feasible to include parameters for construction and design of containers in terms of size, shape and weight, for example those meant for large volume parenterals (LVP), of different materials and made on different machines, both manufactured indigenously and internationally, involved in the production of such plastic containers, nevertheless the integrity of neck and shoulders of the containers should be suitably and appropriately strengthened and it shall be the responsibility of such LVP manufacturers to ensure that the containers withstand the stress conditions and rigors of transportation and packaging. The containers must withstand the sterilisation conditions to which they will be submitted. The design of the container and the method of sterilisation chosen are such that all parts of the containers that may be in contact with the infusion are sterilised. The containers are impermeable to micro-organisms after closure. The containers are such that after filling them, they are resistant to damage from accidental freezing which may occur during transport of the final preparation. The containers are and remain sufficiently transparent to allow the appearance of the contents to be examined at any time, unless otherwise justified and authorised.

Labelling. The label accompanying a batch of empty containers states (1) the name and address of the manufacturer; (2) a batch number which enables tracing the history of the container and of the plastic material of which it is manufactured.

Visual inspection. The empty containers display no defects that may lead to leakage and the filled and closed container shows no leakage.

NOTE 2:

For satisfactory storage of some preparations, the container should be enclosed in a protective envelope. The initial evaluation of storage is then to be carried out using the container enclosed in the envelope.

Tests on Containers

Leakage test. Fill ten containers with water, fit with the intended closures and keep them inverted at room temperature for 24 hours.

There are no signs of leakage from any container.

Collapsibility test. This test is applicable to containers which are to be squeezed in order to remove the contents. A container, by collapsing inward during use, yields at least 90% of its nominal contents at the required rate of flow at ambient temperature.

NOTE 3:

For Parenterals in Plastic Containers, other suitable means of ensuring package integrity may be used.

NOTE 4:

Plastic Containers for Parenteral Preparations shall be governed by all considerations covered in details in the Plastic Containers for Non-parenteral Preparations (6.2.1.2).

Tests using Special Solution "S"

Preparation of Special Solution "S"

Fill a container under examination to its nominal capacity with water and close it, using the usual means of closure; otherwise closed using a suitable sheet / foil of aluminium. Heat in an autoclave so that a temperature of 121± 2°C is reached within 20 to 30 minutes and maintain at this temperature for 30 minutes. If heating at 121°C leads to deterioration/deformation of the container, heat at 100°C for 2 hours.

Note: Use solution S within 4 hours of its preparation.

Blank. Prepare a blank by heating water in a borosilicate-glass flask closed by an aluminium foil at the temperature and for the time used for the preparation of solution S.

Tests Using Solution "S"

Clarity and Colour of solution S. Solution S is clear (2.4.1) and is colourless (2.4.1).

Acidity or Alkalinity. To a volume of solution S corresponding to 4% of the nominal capacity of the container add 0.1mL of *phenolphthalein solution*. The solution is colourless.

Add 0.4mL of *0.01M sodium hydroxide.* The solution is pink. Add 0.8mL of *0.01M hydrochloric acid* and 0.1mL of *methyl red solution*. The solution is orange-red or red.

Light absorption. The light absorption in the range 230nm to 360nm of solution S using a blank prepared as described under Solution S is not more than 0.20 (2.4.7).

Reducing substances. To 20.0mL of solution S add 1mL of *dilute sulphuric acid* and 20.0mL of *0.002M potassium permanganate*. Boil for 3 minutes. Cool immediately. Add 1g of *potassium iodide* and titrate immediately with *0.01M sodium thiosulphate*, using 0.25mL of *starch solution* as indicator.

Carry out a titration using 20.0mL of the blank prepared as described under Solution S.

The difference between the titration volumes is not more than 1.5mL.

Transparency. Fill the container previously used for the preparation of solution S to its nominal capacity with a 1 in 200 dilution of the standard suspension (2.4.1) when made from polyethylene or polypropylene. For containers made of other plastics, use a 1 in 400 dilution.

The cloudiness of the suspension is perceptible when viewed through the container and compared with a similar container filled with *water* (2.4.1).

6.2.1.1.1. Sterile Plastic Containers for Blood and Blood Components

Plastic containers for the collection, storage, processing and administration of blood and its components are manufactured from one or more polymers, if necessary with additives. The composition and the conditions for manufacture of the containers are approved/ registered by the appropriate competent authorities in accordance with the relevant national legislation and international agreements.

When the composition of the materials of the different parts of the containers corresponds to the appropriate specifications, their quality is controlled by the methods indicated in the specifications, described under Plastic Containers for Parenteral Preparations (6.2.1.1).

Materials other than those described in the Pharmacopoeia may be used provided that their composition is authorised by the Licensing Authority and that the containers manufactured from them comply with the requirements prescribed for Sterile Plastic Containers for Human Blood and Blood Components.

In normal conditions of use the materials do not release monomers, or other substances, in amounts likely to be harmful and do not lead to any abnormal modifications of the blood. The containers may contain anticoagulant solutions, depending on their intended use, and are supplied sterile.

Each container is fitted with attachments suitable for the intended use. The container may be in the form of a single unit or the collecting container may be connected by one or more tubes to one or more secondary containers to allow separation of the blood components to be effected within a closed system.

The outlets are of a shape and size allowing for adequate connection of the container with the blood-giving equipment. The protective coverings on the blood-taking needle and on the appendages should be such as to ensure the maintenance of sterility. They should be easily removable but should be tamper-proof.

The capacity of the containers is related to the nominal capacity prescribed by the national authorities and to the appropriate volume of anticoagulant solution. The nominal capacity is the volume of blood to be collected in the container. The containers are of a shape such that when filled they may be centrifuged.

The containers are fitted with a suitable device for sending or fixing which does not hinder the collection, storage, processing or administration of the blood.

The containers are enclosed in sealed, protective envelopes.

Description. The container is sufficiently transparent to allow adequate visual examination of its contents before and after the taking of the blood and is sufficiently flexible to offer minimum resistance during filling and emptying under normal conditions of use. The container contains not more than 5mL of air.

Tests

Solution S_1. Fill the container with 100mL of sodium chloride injection. Close the container and heat it in an autoclave so that the contents are maintained at 110°C for 30 minutes.

If the container under examination contains an anticoagulant solution, first empty it, rinse the container with 250 mL of *water for injections* at 20±1ºC and discard the rinsings.

Solution S_2. Introduce into the container a volume of *water for injections* corresponding to the intended volume of anticoagulant solution. Close the container and heat it in an autoclave so that the contents are maintained at 110°C for 30 minutes. After cooling, add sufficient water for injections to fill the container to its nominal capacity.

If the container under examination contains an anticoagulant solution, first empty it and rinse it as indicated above.

Resistance to centrifugation. Introduce into the container a volume of *water*, acidified by the addition of 1mL of *dilute hydrochloric acid*, sufficient to fill it to its nominal capacity. Envelop the container with absorbent paper impregnated with a 1 in 5 dilution of *bromophenol blue* reagent or other suitable indicator and then dried. Centrifuge at 5000rpm for 10 minutes.

No leakage is perceptible on the indicator paper and no permanent distortion occurs.

Resistance to stretch. Introduce into the container a volume of *water*, acidified by the addition of 1mL of *dilute hydrochloric acid*, sufficient to fill it to its nominal capacity. Send the container by the sending device at the opposite end from the blood-taking tube and apply along the axis of this tube an immediate force of 20 N (2.05 kgf). Maintain the traction for 5 seconds. Repeat the test with the force applied to each of the parts for filling and emptying.

No break and no deterioration occurs.

Leakage. Place the container that has been submitted to the stretch test between two plates covered with absorbent paper impregnated with a 1 in 5 dilution of *bromophenol blue* reagent or other suitable indicator and then dried. Progressively apply force to the plates to press the container so that its internal pressure (i.e. the difference between the applied pressure and atmospheric pressure) reaches 67 kPa within 1 minute. Maintain the pressure for 10 minutes.

No signs of leakage are detectable on the indicator paper or at any point of attachment (seals, joints, etc.).

Vapour permeability. For a container containing an anticoagulant solution, fill with a volume of *sodium chloride injection* equal to the volume of blood for which the container is intended.

For an empty container, fill with the same mixture of anticoagulant solution and *sodium chloride injection*. Close the container, weigh it and store it at 5 ± 1°C in an atmosphere with a relative humidity of 50 ± 5% for 21 days.

At the end of this period the loss in weight is not more than 1%.

Emptying under pressure. Fill the container with a volume of *water* at 5 ± 1°C equal to the nominal capacity. Attach a transfusion set without an intravenous cannula to one of the connectors. Compress the container so as to maintain throughout the emptying an internal pressure (i.e. the difference between the applied pressure and atmospheric pressure) of 40 kPa.

The container empties in less than 2 minutes.

Speed of filling. Attach the container by means of the blood-taking tube fitted with the needle to a reservoir containing a suitable solution having a viscosity equal to that of blood, such as a 33.5% w/v solution of *sucrose* at 37°C. Maintain the internal pressure of the reservoir (i.e. the difference between the applied pressure and atmospheric pressure) at 9.3 kPa with the base of the reservoir and the upper part of the container at the same level. The volume of liquid which flows into the container in 8 minutes is not less than the nominal capacity of the container.

Resistance to temperature variations. Place the container in a suitable chamber having an initial temperature of 20°C to 23°C. Cool it rapidly in a deep-freeze to –80°C and maintain it at this temperature for 24 hours. Raise the temperature to 50ºC and maintain for 12 hours. Allow to cool to room temperature. The container complies with the tests for Resistance to centrifugation, Resistance to stretch, Leakage, Vapour permeability, Emptying under pressure and Speed of filling described above.

Transparency. Fill the empty container with a volume equal to its nominal capacity of the standard suspension (2.4.1), diluted so as to have an absorbance at 640nm of 0.37 to 0.43 (dilution factor about 1 in 16) (2.4.7).
The cloudiness of the suspension must be perceptible when viewed through the bag, as compared with a similar container filled with *water*.

Extractable matter. Tests are carried out by methods designed to simulate as far as possible the conditions of contact between the container and its contents which occur in conditions of use.
The conditions of contact and the tests to be carried out on the eluates are described, according to the nature of the constituent materials, in the particular requirements for each type of container.

Haemolytic effects in buffered systems

Stock buffer solution. Dissolve 90.0g of *sodium chloride*, 34.6g of *sodium phosphate* and 2.4g of *sodium dihydrogen phosphate dihydrate* in *water* and dilute to 1000mL with the same solvent. Prepare three buffer solutions as follows

Buffer solution A_0. To 30.0mL of stock buffer solution add 10.0mL of *water*.

Buffer solution B_0. To 30.0mL of stock buffer solution add 20.0mL of *water*.

Buffer solution C_0. To 15.0mL of stock buffer solution add 85.0mL of *water*.

Introduce 1.4mL of solution S_2 into each of three centrifuge tubes. To tube I add 0.1mL of buffer solution A_0, to tube II add 0.1mL of buffer solution B_0 and to tube III add 0.1mL of buffer solution C_0. To each tube add 0.02mL of fresh, heparinised human blood, mix well and warm on a water-bath at 30±1°C for 40 min. Use blood collected less than 3 hours previously or blood collected into either an Anticoagulant Citrate Phosphate Dextrose Solution (CPD solution) or Anticoagulant Citrate phosphate Dextrose Adenine Solution (CPDA solution) less than 24 hours previously.
Prepare further three solutions as follows:
3.0mL of buffer solution A_0 and 12.0mL of *water* (solution A_1),
4.0mL of buffer solution B_0 and 11.0mL of *water* (solution B_1),
4.75mL of buffer solution B_0 and 10.25mL of *water* (solution C_1),
To tubes I, II and III add, respectively, 1.5mL of solution A_1, 1.5mL of solution B_1 and 1.5mL of solution C_1. At the same time and in the same manner, prepare three other tubes, replacing solution S_2 by *water*.

Centrifuge simultaneously the tubes to be examined and the control tubes at exactly 2500g in the same horizontal centrifuge for 5 minutes. After centrifuging, measure the absorbance of the liquids at about 540nm (2.4.7), using the stock buffer solution as blank. Calculate the haemolytic value as a percentage from the expression

$$\frac{A_{exp}}{A_{100}} \times 100$$

where, A_{100} = absorbance of tube III,

A_{exp} = absorbance of tube I or II or of the corresponding control tubes.

The solution in tube I give a haemolytic value not greater than 10% and the haemolytic value of the solution in tube II does not differ by more than 10% from that of the corresponding control tube.

Sterility. Introduce aseptically into the container 100mL of *sodium chloride injection* and shake the container to ensure that the internal surfaces have been entirely wetted. Filter the contents of the container through a membrane filter. Complete the test as described under Method of Test for aqueous solutions (2.2.11), paragraph 2, beginning at the words 'After filtration, ……..'.

Pyrogens. Solution S_1 complies with the test for pyrogens (2.2.8). Inject 10mL of the solution/kilogram of the rabbit's weight.

Abnormal toxicity. Solution S_1 complies with the general test for abnormal toxicity (2.2.1). Inject 0.5mL of the solution into each mouse.

Container and Closures. Sterile plastic containers for human blood and blood components are packed in protective tamper-evident envelopes. On removal from its protective envelope the container shows no leakage and no growth of micro-organisms. The protective envelope is sufficiently robust to withstand normal handling.

The protective envelope is sealed in such a manner that it cannot be opened and re-closed without leaving visible traces that the seal has been broken.

Labelling. The label states that once withdrawn from its protective envelope, the content must be used within 10 days.

A part of the label is reserved for the information required concerning the blood or blood components for which the container is intended to be used.

The ink, or other substance used to print the labels or the writing must not diffuse into the plastic material of the container and must remain legible up to the time of use.

6.2.1.1.2. Sterile PVC (Polyvinyl chloride) Containers for Blood and Blood Components

Sterile PVC (Polyvinyl chloride) containers for blood and blood components should meet the requirements described under the introductory part of section 6.2.1.of chapter 6.2. They also comply with the tests described under Sterile Plastic Containers for Blood and Blood Components and with the following additional tests.

Acidity or Alkalinity. Introduce into the container a volume of *water for injections* corresponding to the intended volume of anticoagulant solution. Close the container and heat in an autoclave so that the contents are maintained at 110ºC for 30 minutes. Cool and add sufficient *water for injections* to fill the container to its nominal capacity (solution A). To a volume of solution A corresponding to 4% of the nominal capacity of the container add 0.1mL of *phenolphthalein solution;* the solution remains colourless.

Add 0.4mL of *0.1M sodium hydroxide;* the solution is pink. Add 0.8mL of *0.01M hydrochloric acid* and 0.1mL of *methyl red solution;* the solution is orange-red or red.

Light absorption. Heat *water for injections* in a round bottom flask in an autoclave at 110ºC for 30 minutes (solution B). Measure the light absorption of solution A in the range 230nm to 360nm using solution B as blank. The absorbance is not more than 0.30 at any wavelength from 230nm to 250nm and not more than 0.10 at any wavelength from 251nm to 360nm (2.4.7).

Ammonium. Dilute 5mL of solution A to 14mL with *water* in a test-tube, if necessary make alkaline with *2M sodium hydroxide* and dilute further to 15mL with *water*. Add 0.3mL of *alkaline potassium mercuri-iodide solution*, stopper the tube, mix and allow to stand for 5 minutes. When viewed vertically, any yellow colour produced is not more intense than that obtained by treating a mixture of 10mL of *ammonium standard solution (1ppm NH4)* and 5mL of *water* in the same manner (2ppm).

Chlorides. 15mL of solution A complies with the limit test for chlorides (2.3.12). Prepare the standard using a mixture of 1.2mL of *chloride standard solution (5ppm Cl)* and 13.8mL of *water (0.4ppm).*

Extractable di(2-ethylhexyl)phthalate

Extraction solvent. *Ethanol* diluted with *water* to have a relative density of 0.9389 to 0.9395 (2.4.29), measured with a pycnometer.

Stock solution. Dissolve 0.1g of *di(2-ethylhexyl)phthalate* in the extraction solvent and dilute to 100mL with the same solvent.

Standard solutions

(a) Dilute 20mL of stock solution to 100mL with extraction solvent.
(b) Dilute 10mL of stock solution to 100mL with extraction solvent.
(c) Dilute 5mL of stock solution to 100mL with extraction solvent.
(d) Dilute 2mL of stock solution to 100mL with extraction solvent.
(e) Dilute 1mL of stock solution to 100mL with extraction solvent.

Measure the absorbance of the standard solutions at the maximum at about 272nm, using the extraction solvent as blank and plot a curve of absorbance against the concentration of di(2-ethylhexyl)phthalate (2.4.7).

Extraction procedure. Using the donor tubing and the needle or adaptor, fill the empty container with a volume equal to half the nominal volume with the extraction solvent, previously heated to 37ºC in a well-stoppered flask. Expel the air completely from the container and seal the donor tube. Immerse the filled container in a horizontal position in a water-bath maintained at 37±1ºC for 60±1 minute without shaking. Remove the container from the water-bath, invert it gently ten times and transfer the contents to a glass flask. Immediately measure the *absorbance* at the maximum at about 272nm, using the extraction solvent as blank (2.4.7).

Determine the concentration of di(2-ethylhexyl)phthalate in milligrams/100mL of the extract from the calibration curve. The concentration does not exceed

10mg/100mL for containers of nominal volume greater than 300mL but not greater than 500mL;

13mg/100mL for containers of nominal volume greater than 150mL but not greater than 300mL;

14mg/100mL for containers of nominal volume upto 150mL.

Oxidisable substances. Immediately after preparation of solution A, transfer to a borosilicate-glass flask a quantity corresponding to 8% of the nominal capacity of the container. At the same time, prepare a blank using an equal volume of the freshly prepared solution B in another borosilicate-glass flask. To each solution add 20.0mL of *0.002M potassium permanganate* and 1mL of *1M sulphuric acid.* Allow to stand at room temperature, protected

from light, for 15 minutes. To each solution add 0.1g of *potassium iodide.* Allow to stand protected from light for 5 minutes and titrate immediately with *0.01M sodium thiosulphate,* using 0.25mL of *starch solution* as indicator.
The difference between the two titrations is not more than 2.0mL.

Residue on evaporation. Evaporate to dryness 100mL of solution A in a borosilicate-glass beaker, previously heated to 105°C. Evaporate to dryness in the same conditions 100mL of solution B. Dry to constant weight at 105°C.
The difference between the weights of the residues is not more than 3mg.

6.2.1.1.3. Sterile PVC (Polyvinyl chloride) Containers for Blood containing an Anticoagulant Solution

Unless otherwise authorised as described in the introductory part of section 6.2.1 of chapter 6.2, the nature and composition of the material from which the containers are made complies with the requirements described under Sterile PVC (Polyvinyl chloride) containers for blood and blood components (6.2.1.1.2).
Sterile plastic containers containing an anticoagulant solution are used for the collection, storage and administration of blood. Before filling they comply with the description and characteristics described under Sterile PVC (Polyvinyl chloride) containers for blood and blood components (6.2.1.1.2).
After addition of the anticoagulant solution the containers comply with the tests described under Sterile Plastic Containers for Blood and Blood Components (6.2.1.1.1) and with the following additional tests:

Light absorption. Measure the light absorption of the anticoagulant solution from the container in the range 250nm to 350nm using an anticoagulant solution of the same composition that has not been in contact with a plastic material as blank.
The absorbance at the maximum at about 280nm is not more than 0.5 (2.4.7).

Extractable di(2-ethylhexyl)phthalate. Carefully remove the anticoagulant solution by means of the flexible transfer tube. Using a funnel fitted to the tube, completely fill the container with *water*, leave in contact for 1 minute, squeezing the container gently and empty completely. Repeat the rinsing.
The container then complies with the test described under Sterile PVC (Polyvinyl chloride) containers for blood and blood components (6.2.1.1.2).

Volume of anticoagulant solution. The volume does not differ by ±10% from the stated volume when determined by emptying the container and collecting the anticoagulant solution in a graduated cylinder.

6.2.1.2. Plastic Containers for Non-parenteral Preparations

Tests on Containers

The container used for packaging of pharmaceutical formulations shall meet all the test requirements detailed below.

Leakage test, Collapsibility test. Comply with the tests described under Plastic Containers for Parenteral Preparations (6.2.1.1).
The following tests are applicable to containers intended for filling oral liquids.

Clarity of aqueous extract. Select unlabelled, unmarked and non-laminated portions from suitable containers, taken at random, sufficient to yield a total area of sample required, taking into account the surface area of both sides. Cut these portions into strips, none of which has a total area of more than $20cm^2$. Wash the strips free from

extraneous matter by shaking them with at least two separate portions of distilled water for about 30 seconds in each case, then draining off the water thoroughly.

Select cut and washed portions of the sample with a total surface area of 1250cm^2, transfer to a flask, previously cleaned with *chromic acid mixture* and rinsed with several portions of *distilled water* and add 250mL of *distilled water*. Cover the flask with a beaker and autoclave at 121°C for 30 minutes. Carry out a blank determination using 250mL of *distilled water*. Cool and examine the extract; it is colourless and free from turbidity.

Non-volatile residue. Evaporate 100mL of the extract obtained in the test for Clarity of aqueous extract to dryness and dry to constant weight at 105°C.

The residue weighs not more than 12.5mg.

Tests on Container Material

The following tests are done:

- on portions of the container that are unlabelled, unprinted or non-laminated or
- on the granules of plastic in the case of containers made by the 'form-fill-seal' process.

6.2.1.2.1. Polyethylene Terephthalate (PET)

Polyesters are polymers containing ester linkages generated due to the condensation of di-acids and di-ols. A prominent example in the class of polyesters is Polyethylene terephthalate (PET).

PET is a polymer which comprises at least 85% units of terephthalic acid or dimethyl terephthalate condensed with ethylene glycol. Co-monomers such as isophthalic acid, dimethyl isophthalate or diethylene glycol may also be used in the PET polymerisation.

Production of PET

The polymerisation of PET is catalysed with catalyst (usually certain metal oxides), at temperatures greater than 280°C and high vacuum. The manufacturing process of the PET pellets (resin) shall ensure that the residual acetaldehyde content is not greater than 10ppm.

The resin is then given shape into bottles or any other shape through a conversion process involving injection moulding and blow moulding.

The resin and its conversion into PET containers may involve the use of colourants conforming to Indian Standards IS-9833 and/or additives conforming to IS-12252.

The manufacturers of containers should receive the certificate of analysis for each lot of resins procured from to confirm the quality of resins that the grade of resins used is as agreed and meets the relevant specification. The certificate of analysis from the resin manufacturer shall provide the necessary assurance about the quality of resin.

Quality assessment of PET Containers

The container used for packaging of pharmaceutical formulations shall meet all the test requirements detailed below.

A] IDENTIFICATION OF CONTAINER MATERIAL

Test 1 – By FTIR Spectrophotometry

Dissolve 50mg of the PET container specimen under examination in 2mL of solvent blend of *phenol* and *tetrachloroethane* (60:40 *w/w)* with heating followed by centrifuging or *1,1,1,3,3,3-hexafluoropropan-2-ol* or other appropriate solvent systems. Apply several drops of this solution on a glass plate. Keep this plate on a water-bath in a fume cupboard to produce a thin film of about 15mm by 15mm. Allow the solvent to

evaporate completely. Remove the film using a stream of water and a scraper. Dry the film in an oven (typically at 100-105°C for about 1 hour).

Examine the film by infrared absorption spectrophotometry (2.4.6). The spectrum should show absorption maxima substantially at about 3053cm^{-1}, 1955cm^{-1}, 1725cm^{-1}, 1613cm^{-1}, 1455cm^{-1},1410cm^{-1}, 1265cm^{-1}, 1020cm^{-1}, 973cm^{-1}, 875cm^{-1}, and 730cm^{-1}.

Note: Substantial, as opposed to exact, allows for minor spectral differences arising from the natural compositional and/or physical variation and/or instrumental capabilities.

Test 2 – By UV Spectrophotometry

Reflux 100mg of the PET container under examination with 250mL of a 20% *w/v* solution of *potassium hydroxide* in a 50% v/v solution of *ethanol* for 30 minutes in a round bottom flask. Allow to cool and dilute to 100mL with *water*. Filter if necessary. Dilute 1.0mL of the filtrate to 100mL with *water*.

Examine this solution in the range 210nm and 330nm (2.4.7), the absorption maximum should be at about 240nm.

Test 3 – By Differential Scanning Calorimetry (2.4.31)

Compare the thermogram of the sample with that obtained with PET and the melting peak temperature obtained from the thermogram of the sample does not differ from that of the reference thermogram by more than 8.0°C.

B] CHEMICAL TESTS

B1] TESTS USING SPECIAL SOLUTIONS

Preparation of Special Solutions for Subsequent Tests on PET

Select unlabelled, unmarked and non-laminated portions from suitable containers, taken at random, sufficient to yield a total area of sample required, cut these portions into strips, none of which has a total area of more than 1cm^2.

Solution S1 (Aqueous Extract)

Place 10g of the sample in a round bottom flask. Add 200mL of *water* and heat at 50°C for 5 hours. Allow to cool and then decant the solution.

Use solution S1 within 4 hours of its preparation.

Solution S2 (Ethanolic Extract)

Place 10g of the sample in a round bottom flask. Add 100mL of *ethanol (95%)* and heat at 50°C for 5 hours. Allow to cool and decant the solution.

Use solution S2 within 4 hours of its preparation.

Solution S3 (Acidic Extract)

Place 20g of the sample in a round bottom flask. Add 50mL of *0.1M hydrochloric acid* and heat at 50°C for 5 hours. Allow to cool and decant the solution.

Use solution S3 within 4 hours of its preparation.

Solution S4 (Alkaline Extract)

Place 20g of the sample into a round bottom flask. Add 50mL of *0.01M sodium hydroxide* and heat at 50°C for 5 hours. Allow to cool and decant.

Use solution S4 within 4 hours of its preparation.

TESTS USING SPECIAL SOLUTION S1

B1.1] Appearance

Solution S1 has to be clear (2.4.1).

B1.2] Absorbance of solution S1 (2.4.7)

- In the UV- range (220nm to 340nm): absorbance should be not more than 0.20
- In the visible range (400nm to 800nm): absorbance should be not more than 0.05

B1.3] Acidity

To 50mL of solution S1 add 0.15mL of *BRP indicator solution.* The solution turns yellow. Not more than 0.5mL of *0.01M sodium hydroxide* is required to change the colour of the indicator to blue.

B1.4] Alkalinity

To 50mL of solution S1, add 0.2mL of *methyl orange solution*. The solution turns yellow. Not more than 0.5mL of *0.01M hydrochloric acid* is required to reach the beginning of the colour change of the indicator to orange.

B1.5] Reducing substances

To 20mL of solution S1, add 2mL of *0.5M sulphuric acid* and 20mL of *0.002M potassium permanganate*. Boil for 3 minutes. Immediately cool to room temperature. Add 1.0g of *potassium iodide*, 0.25mL of *starch solution* as indicator and titrate with *0.01M sodium thiosulphate*. Perform a blank titration using 20mL of *water*.

The difference in volume used in the 2 titrations is not greater than 0.5mL.

TESTS USING SPECIAL SOLUTION S2

B1.6] Appearance

Solution S2 has to be clear and colourless (2.4.1).

B1.7] Absorbance of solution S2 (2.4.7)

In the visible range (400nm to 800nm): absorbance should be not more than 0.05.

B1.8.] Extractable Metals

NOTE 5:

a) For quantitative determination of the extractable metals described hereunder, Inductively Coupled Plasma Spectrometry (2.4.42) may be used. Alternatively, Atomic Absorption Spectrometry (2.4.2) can be used provided it has the appropriate sensitivity.

b) Extractable metals are measured using special solutions S3 and S4.

c) *Permissible limits mentioned in the paragraphs below are extractable metals in the PET/Plastics. These have been expressed as ppm (µg of extracted metal/ /g of PET/Plastics in the special solutions, after appropriate calculations).*

NOTE 6:

The above extractable elements have been chosen to be estimated based on their historical presence in various PET manufacturing processes.

TESTS USING THE SPECIAL SOLUTION S3

B1.8.1] Aluminium. Not more than 1ppm.

Reference solutions. Prepare the reference standard solutions of *aluminium (200ppm Al)* with *0.1M hydrochloric acid*.

Wavelength. 396.15nm, the spectral background being taken at 396.25nm.

Verify the absence of aluminium in the *0.1M hydrochloric acid* used.

B1.8.2] Barium. Not more than 1ppm.

Reference solutions. Prepare the reference standard solutions of *barium (50ppm Ba)* with *0.1M hydrochloric acid*.

Wavelength 455.40nm, the spectral background being taken at 455.30nm.

Verify the absence of barium in the *0.1M hydrochloric acid* used.

B1.8.3] Cobalt. Not more than 1ppm.

Reference solutions. Prepare the reference standard solutions of *cobalt (100ppm Co)* with *0.1M hydrochloric acid*.

Wavelength 228.62nm, the spectral background being taken at 228.50nm.

Verify the absence of cobalt in the *0.1M hydrochloric acid* used.

B1.8.4] Manganese. Not more than 1ppm**.**

Reference solutions. Prepare the reference standard solutions of *manganese (100ppm Mn)* with *0.1M hydrochloric acid*.

Wavelength 257.61nm, the spectral background being taken at 257.50nm.

Verify the absence of manganese in the *0.1M hydrochloric acid* used.

B1.8.5]Titanium. Not more than 1ppm.

Reference solutions. Prepare the reference standard solutions of *titanium (100ppm Ti)* with *0.1M hydrochloric acid*.

Wavelength 323.45nm or 334.94nm, the spectral background being taken at 323.35nm.

Verify the absence of titanium in the *0.1M hydrochloric acid* used.

B1.8.6] Zinc. Not more than 1ppm**.**

Reference solutions. Prepare the reference standard solutions of *zinc (100ppm Zn)* with *0.1M hydrochloric acid*.

Wavelength 213.86nm, the spectral background being taken at 213.75nm.

Verify the absence of zinc in the *0.1 M hydrochloric acid* used.

TESTS USING THE SPECIAL SOLUTION S4

B1.8.7] Antimony. Not more than 1ppm**.**

Reference solutions. Prepare the reference standard solutions of *antimony (100ppm Sb)* with *0.01M sodium hydroxide*.

Wavelength. 231.15nm or 217.58nm, the spectral background being taken at 231.05nm.

B1.8.8] Germanium. Not more than 1ppm**.**

Reference solutions. Prepare the reference standard solutions of *germanium (100ppm Ge)* with *0.01M sodium hydroxide*.

Wavelength 206.87nm or 265.12nm, the spectral background being taken at 206.75nm.

B2] OTHER TESTS

B2.1] Substances soluble in dioxane. Not more than 3.0%

Place 2g of the material to be examined in a round bottom flask. Add 20mL of *dioxane* and heat under reflux for 2 hours. Evaporate 10mL of the solution to dryness on a water-bath and then dry the residue at 100-105°C.

The residue weighs a maximum of 30.0mg.

B2.2] Sulphated ash (2.3.18). Not more than 0.5% determined on 1.0g.

B2.3] Total Terephthaloyl moieties. Not more than 1ppm

Polyethylene terephthalate extracting media. *(1)* 50% *ethanol*(dilute 125mL of *ethanol (95%)*, with *Purified Water* to 238mL, and mix), (2) *n-heptane* and (3) *water*.

For each extracting media fill a sufficient number of test containers to 90% of its nominal capacity to obtain not less than 30mL.

Fill a corresponding number of glass bottles with each extracting medium for use as a blank. Fit the bottles with impervious seals, such as aluminium foil, or apply closures. Incubate the test packaging system and the glass bottles at 49°C for 10 days. Remove the test systems and glass bottles and store at room temperature. Do not transfer the *extracting medium* samples to alternative storage vessel.

Determine the absorbance of 50% ethanol extract at the wavelength of maximum absorbance at about 244nm (2.4.7). For the blank use corresponding extracting medium blank.

Determine the absorbance of *n-heptane* extract at the wavelength of maximum absorbance at about 240nm (2.4.7). For the blank use corresponding extracting medium blank.

The absorbance of the 50% *ethanol* and *n-heptane* extracts does not exceed 0.150, corresponding to not more than 1ppm of total terephthaloyl moieties.

B2.4] Ethylene glycol. Not more than 1ppm

Periodic acid solution. Dissolve 125 mg of periodic acid in 10mL of *water*.

Dilute sulphuric acid. To 50mL of *water*, slowly add and with constant stirring 50mL of *sulphuric acid*, allow to cool to room temperature.

Note: Dilution of sulphuric acid produces substantial heat and can cause the solution to boil. Perform this addition carefully sulphur dioxide gas will be evolved. Use fume hood is recommended.

Sodium bisulphite solution. Dissolve 100mg of *sodium bisulphite* in 10mL of *water.*

Disodium chromotropate solution. Dissolve 100mg of *disodium chromotropate* in 100mL of *sulphuric acid*.

Reference solution. Dissolve quantity of ethylene glycol in the *water*, to obtain a solution containing 0.0001% w/v of ethylene glycol.

Test solution. Use the water extract from Total Terephthaloyl moieties

Procedure. Transfer 1mL of the reference solution, test solution and purified water extracting medium in three separate volumetric flasks. Add 0.1mL of *periodic acid solution* to each flask swirl to mix, and allow to stand for 60 minutes. Add 1mL of *sodium bisulphite solution* to each flask, and mix. Add 0.1mL of *disodium chromotropate solution* to each flask, and mix. (Note- All the solutions should be analysed within 1 hour after addition of *disodium chromotropate solution*) Slowly add 6mL of *sulphuric acid* to each flask, mix, and allow the solutions to cool to room temperature. Dilute each solution with dilute sulphuric acid to volume, and mix. Measure the absorbance of the resulting solutions at the maximum at about 575nm (2.4.7), using *water extracting medium* as the blank.

The absorbance of the *Sample solution* does not exceed that of the *Standard solution*, corresponding to not more than 1ppm of *ethylene glycol*.

C] BIOLOGICAL TESTS

Applicability of the test.

1. PET Containers to be used for the packaging of dosage forms other than oral and topical shall comply with the requirements stated in 6.2.1.
2. PET Containers to be used for the packaging of oral and topical dosage forms do not require the biological tests.

6.2.1.2.2. Polyethylene

A] Identification of Container Material

- **High-density polyethylene**

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from $3800cm^{-1}$ to $650cm^{-1}$ (2.6–15 µm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of High-Density *Polyethylene RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and RS spectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

The thermogram of the specimen is similar to the thermogram of High-Density *Polyethylene RS*, and (T_g) the melting peak temperature obtained from the thermogram of the specimen does not differ from that of the RS by more than 6.0°.

- **Low-density polyethylene**

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800cm^{-1} to 650cm^{-1} (2.6–15 µm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of the Low-Density *Polyethylene RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and RS spectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

The thermogram of the specimen is similar to the thermogram of Low-Density *Polyethylene RS*, and (T_g) the melting peak temperature obtained from the thermogram of the specimen does not differ from that of the RS by more than 8.0°.

B] Chemical Tests

Preparation of Special Solutions for subsequent tests on Polyethylene

Solution S1 (Water extraction)

Place 25g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500mL of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500mL volumetric flask and dilute with purified water to volume; the diluted solution is *Solution S1*.

Use Solution S1 within 4 hours of preparation.

Solution S2 (Toluene extraction)

Place 2.0g of the test material in a 250mL borosilicate glass flask with a ground-glass neck. Add 80mL of *toluene* and boil under a reflux condenser for 1.5 hours, stirring constantly. Allow to cool to 60°C and add 120mL of methanol with continued stirring. Pass the resulting solution through a sintered-glass filter. Rinse the flask and the filter with 25mL of a mixture of 40 volumes of *toluene* and 60 volumes of *methanol* add the rinsing to the filtrate, and dilute to 250mL with the same mixture of solvents to produce *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5g in a borosilicate glass flask with a ground-glass neck. Add 100mL of *0.1M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100mL volumetric flask, and dilute to volume with *0.1M hydrochloric acid*; the diluted solution is *Solution S3.*

Tests Using Special Solutions

B.1] Absorbance (2.4.7)

Determine the spectrum between 220 and 340nm in Solution S1.

Absorbance should be not more than 0.2.

B.2] Acidity or alkalinity

To 100mL of Solution S1 add 0.15mL of *BRP indicator solution*. Determine the titration volume of *0.01M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100mL portion of Solution S, add 0.2mL of *methyl orange solution*. Determine the titration volume of *0.01M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5mL of *0.01N sodium hydroxide* is required to change the colour of the indicator to blue. Not more than 1.0mL of *0.01N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3] Plastic Additives

These tests should be carried out in whole or in part as required due to the stated composition of the material.

B.3.1] Phenolic Antioxidant

*Solvent mixture***.** Mixture of equal volumes of *acetonitrile* and *tetrahydrofuran*.

Sample solution S2A. Evaporate 50mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the resulting residue with 5.0mL of the solvent mixture. Prepare a blank solution from the blank solution corresponding to Solution S2.

Sample solution S2B. Evaporate 50mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the residue with 5.0mL of *methylene chloride*. Prepare a blank solution from the blank solution corresponding to SolutionS2.

Reference solutions of the following reference solutions; prepare only those that are necessary for the analysis of the phenolic antioxidants stated in the composition of the substance to be examined.

Reference solution (a). A 0.01% w/v of *Butylated Hydroxytoluene RS* and 0.024% w/v of *Plastic Additive 01 RS* in the solvent mixture.

Reference solution (b). A 0.024% w/v of *Plastic Additive 02 RS* and 0.024% of *Plastic Additive 03 RS* in the solvent mixture

Reference solution *(c)*. A 0.024% of *Plastic Additive 04 RS* and 0.024% of *Plastic Additive 05 RS* in *methylene chloride*

Reference solution (d). A 0.01% of *Butylated Hydroxy toluene RS* in the solvent mixture

Reference solution (e). A 0.024% of *Plastic Additive 01 RS* in the solvent mixture

Reference solution (f). A 0.024% of *Plastic Additive 06 RS* prepared in the solvent mixture

Reference solution (g). A 0.024% of *Plastic Additive 02 RS* prepared in the solvent mixture

Reference solution (*h*). A 0.024% of *Plastic Additive 03 RS* prepared in the solvent mixture

Reference solution (i). A 0.024% of Plastic *Additive 04 RS* prepared in *methylene chloride*

Reference solution (j). A 0.024% of *Plastic Additive 05 RS* prepared in *methylene chloride*

Test A

Determine by liquid chromatography (2.4.14).

If the substance to be examined contains additive butylated hydroxytoluene and/or additive ethylene bis[3,3-bis[3-(1,1dimethylethyl)-4-hydroxyphenyl]butanoate

Chromatographic system

- a stainless steel column 25cm x 4.6mm, packed with octadecylsilane bonded to porous silica microparticles (5µm)
- mobile phase: a mixture of 70 volumes of a *acetronitrile* and 30 volumes of *water*
- flow rate: 2.0mL/minute
- spectrophotometer set at 280nm
- injection volume: 20µL

Inject reference solution (a). The test is not valid unless the resolution between the peaks due to additive butylated hydroxytoluene and additive ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate] peaks is not less than 8.0.

Inject Sample solution S2A corresponding blank solution, Reference solution (a), and Reference solution (d), Reference solution (e), or both. Run the chromatogram for about 30 minutes.

The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solution (d) or Reference solution (e).

Note: Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test B

If the substance to be examined contains one or more of the following antioxidants pentaerythrityl tetrakis[3-(3,5-di tert-butyl-4-hydroxyphenyl)propionate; 2,2,2″,6,6,6″-hexa-tert-butyl-4,4,4″-[(2,4,6-trimethyl-1,3,5-benzene-triyl)trismethylene]triphenol; octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate; tris(2,4-di-tert-butylphenyl) phosphate; 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6(1H,3H,5H)-trione

Determine by liquid chromatography (2.4.14).

Chromatographic system

Carry out the test as described in Test A with the following modifications

- a stainless steel column 25cm x 4.6mm, packed with octadecylsilane bonded to porous silica microparticles (5µm),
- mobile phase: a mixture of 60 volumes of *acetronitrile* 30 volumes of *tetrahydrofuran* and 10 volumes of *water*,
- flow rate: 1.5mL/minute,
- spectrophotometer set at 280nm,
- injection volume: 20µL

Inject reference solution (b).The test is not valid unless the resolution between the peaks due to additive pentaerythrityl tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and additive 2,2’,2″,6,6’,6″-hexa-tert-butyl-4,4’,4″-[(2,4,6-trimethyl-1,3,5-benzene-triyl)trismethylene]triphenol peaks is not less than 2.0.

Inject Sample solution S2A corresponding blank solution, Reference solution (b), and any Reference solutions of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

Note: Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test C

If the substance to be examined contains additive octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and/or additive tris(2,4-di-tert-butylphenyl) phosphite.

Determine by liquid chromatography (2.4.14).

Chromatographic system

Carry out the test as described in Test A with the following modifications

- a stainless steel column 25cm x 4.6mm, packed with octadecylsilane bonded to porous silica microparticles (5µm)
- mobile phase: a mixture of 50 volumes of *methanol*, 40 volumes of 2 *propanol* and 5.0 volumes of *water*
- flow rate: 1.5mL/minute
- spectrophotometer set at 280nm injection volume: 20µL

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to additive octadecyl-3-(3, 5-di-tert-butyl-4-hydroxyphenyl) propionate and additive tris(2,4-di-tert-butylphenyl) phosphite peaks is not less than 2.0.

Inject Sample solution S2B corresponding blank solution, Reference solution (c), and any Reference solutions (i) or Reference solution (j) of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2B are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

Note: Sample solution S2B shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

B.3.2] Non-phenolic Antioxidant

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase A. Hexane

Mobile phase B. Methylene chloride

Methylene chloride, acidified. To 100mL of *methylene chloride* add 10mL of *hydrochloric acid*, shake, allow to stand, and separate the two layers. Use the lower layer.

Sample solution S2C. Evaporate 100mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the resulting residue with 2mL of *methylene chloride* acidified.

Reference solution (m). A 0.6% w/v of *Plastic Additive 08 RS* in *methylene chloride*. Dilute 2mL of the solution with *methylene chloride*, acidified to 10 mL.

Reference solution (n). A 0.6% w/v of *Plastic Additive 09 RS* in *methylene chloride*. Dilute 2mL of the solution with *methylene chloride*, acidified to 10mL.

Reference solution (o). A 0.6% w/v of *Plastic Additive 10 RS* in *methylene chloride*. Dilute 2mL of the solution with *methylene chloride*, acidified to 10mL.

Reference solution (p). A 0.6% of *Plastic Additive 10 RS*, and 0.6% of *Plastic Additive 09 RS* in *methylene chloride*. Dilute 2mL of the solution with *methylene chloride*, acidified to 10mL.

Apply to the plate 20µL of sample solution S2C, reference solution and the reference solution corresponding to all the phenolic and non-phenolic antioxidants expected to be present. Development the plates Over a path of 18cm with Mobile phase A and over a path of 17cm with Mobile phase B

respectively. After development, dry the plate in air and examine under ultraviolet light at 254nm and spray with alcoholic iodine solution.

The test is not valid unless the chromatogram obtained with reference solution (p) shows two separate spot. Any spot in the chromatogram obtained with sample solution S2C is not more intense than the spot in the same position in the chromatogram of the corresponding reference solution.

B.3.3] Amides and Stearates

Use sample solution as sample solution S2C as described in Non-phenolic Antioxidants.

Reference solution (r). A 0.2% of *Stearic Acid RS* prepared in *methylene chloride*.

Reference solution (s). A 0.2% of *Plastic Additive 12 RS* prepared in *methylene chloride*.

Reference solution (t). A 0.2% of *Plastic Additive 13 RS* prepared in *methylene chloride*.

Test A

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*

Mobile phase. a mixture of 75 volume of *trimethylpantane* and 25 volumes of *alcohol*

Apply to the plate 10µL of sample solution S2C, reference solution (r). Develop the plates over a path of 10 cm with Mobile phase. After development, dry the plate in air and examine by spray with 2% 2,6-dichlorophenol-indophenol sodium in dehydrated alcohol heat in an oven at 120°C for a few minutes to intensify the spots.

Any spot corresponding to additive stearic acid in the chromatogram obtained with sample solution S2C (R_f = about 0.5) is not more intense than the spot in the same position in the chromatogram of reference solution (r).

Test B

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*

Mobile phase A. *Hexane*

Mobile phase B. A mixture of 95 volumes of *methylene chloride* and 5.0 volumes of *methanol.*

Apply to the plate 10µL of sample solution S2C, reference solution (s) and reference solution (t). Develop the plates Over a path of 13cm with Mobile phase A and Over a path of 10cm with Mobile phase B respectively. After development, dry the plate in air and examine by spray with 40% *phosphomolybdic acid* in *alcohol* heat in an oven at 120°C for a few minutes to intensify the spots. Any spot corresponding to additive oleamide or erucamide in the chromatogram obtained with sample solution S2C (R_f = about 0.2) is not more intense than the spot in the same position in the chromatogram of reference solution (s) and reference solution (t).

B.4] Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the total organic carbon analyses should have a limit of detection of 0.2mg/L (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20mg/L (which encompasses the total organic carbon limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank total organic carbon concentrations is not more than 5mg/L.

B.5] Extractable Metals

Solution S3 is used for extracting acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A)

Aluminum. Solution S3 contains not more than 0.4mg/L (ppm), corresponding to 1µg/g.

Arsenic, cadmium, lead, mercury, cobalt, and nickel. Report the measured value in Solution S3 at values above 0.01mg/L (ppm), corresponding to 0.025µg/g. If the measured values are below these values, report the result as less than 0.01mg/L (ppm), corresponding to less than 0.025µg/g.

Chromium. Solution S3 contains not more than 0.02mg/L (ppm), corresponding to 0.05µg/g.

Titanium. Solution S3 contains not more than 0.4mg/L (ppm), corresponding to 1µg/g.

Vanadium. Solution S3 contains not more than 0.04mg/L (ppm), corresponding to 0.1µg/g.

Zinc. Solution S3 contains not more than 0.4mg/L (ppm), corresponding to 1µg/g.

Zirconium. Solution S3 contains not more than 0.04mg/L (ppm), corresponding to 0.1µg/g.

6.2.1.2.3. Polyvinyl Chloride, Non-Plasticized

A] Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800cm^{-1} to 650cm^{-1} (2.6–16 µm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of the *Polyvinyl Chloride, Non-plasticized RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and RS spectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

The thermogram of the specimen is similar to the thermogram of *Polyvinyl Chloride, Non-plasticized RS*, and the melting peak temperature obtained from the thermogram of the specimen does not differ from that of the RS by more than 8.0°. Note that the results of the DSC analysis are strongly dependent on the amount of plasticizer in the test article.

B] Chemical Tests

<u>Preparation of Special Solutions for subsequent tests on Polyvinyl Chloride</u>

Solution S1 (Water extraction)

Place 25g of the test material into a borosilicate glass flask. Add 500mL of purified water, cover the flask's neck with aluminium foil or a borosilicate beaker, and heat in an autoclave at 121 ± 2°C for 20 min. Allow the solution to cool and the solids to settle, decant the solution into a 500mL volumetric flask, and dilute with purified water to volume; the diluted solution is *Solution S1*.

Solution S2 (Tetrahydrofuran extraction)

Dissolve 5.0g of the test material in 80mL of *tetrahydrofuran* and dilute to a volume of 100mL with the same solvent. Filter if necessary; the solution may remain opaque. Slowly and drop wise add 70mL *ethanol*

to 20mL of this solution. Cool the mixture in ice for 1 hours. Filter or centrifuge the mixture, collecting residue A. Wash residue A with *ethanol*. Collect the washings and add them to the solution remaining after filtration or centrifugation. Transfer the solution to a 100mL volumetric flask and dilute to volume with ethanol. This process produces *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5g in a borosilicate glass flask with a ground-glass neck. Add 100mL of *0.1M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100mL volumetric flask, and dilute to volume with *0.1M hydrochloric acid*; the diluted solution is *Solution S3.*

Tests Using Special Solutions

B.1] Absorbance (2.4.7)

Evaporate 100mL of Solution S1 to dryness. Dissolve the residue in 5mL of hexane. If necessary, pass through a filter that has been previously rinsed with hexane. Determine the spectrum between 250 and 330 nm in the dissolved residue.

Polyvinyl chloride, non-plasticized contains 1-phenyleicosane-1, 3-dione for dry dosage forms for oral administration

Dilute 1.0 volume of Solution S2 to 10 volumes with ethanol prior to measurement. In all other situations, analyze Solution S2 with no further preparation. Determine the spectrum between 250 and 330nm in the dissolved residue

Absorbance should be not more than 0.25 for containers for non-injectable aqueous solutions.

Absorbance should be not more than 0.30 for containers for dry dosage forms for oral administration

B.2] Plastic Additives and Stabilizers

The supplier of the material must be able to provide sufficient compositional information to establish whether the material meets the specifications for additives and stabilizers.

B.2.1] Vinyl Chloride

Determine by gas chromatography (2.4.13).

Test solution. Place 1.0g of the test material in a 50mL vial, and add 10.0mL of the internal standard solution. Close the vial, and secure with a stopper. Shake by avoiding contact between the stopper and the liquid. Place the vial in a water bath at 60±1°C for 2.0 hours.

Internal standard solution. Inject 10µL of ethyl ether into 20.0mL of *N,N-dimethylacetamide* by immersing the tip of the needle in the solvent using a microsyringe. Immediately before use, dilute the solution with *N,N-dimethylacetamide* to 1000 times its volume.

Vinyl chloride primary solution:

NOTE—Prepare under a ventilated hood.

Place 50mL of *N,N-dimethylacetamide* in a 50-mL vial, stopper the vial, secure the stopper, and weigh to the nearest 0.1mg. Fill a 50-mL polyethylene or polypropylene syringe with gaseous vinyl chloride, allow the gas to remain in contact with the syringe for about 3 min, empty the syringe, and fill again with 50mL of gaseous vinyl chloride. Fit a hypodermic needle to the syringe, and reduce the volume of gas in the syringe from 50 to 25mL. Inject the remaining 25mL of vinyl chloride slowly into the vial, shaking gently

and avoiding contact between the liquid and the needle. Weigh the vial again; the increase in mass is about 60mg (1µL of the solution obtained contains about 1.2µg of vinyl chloride). Allow to stand for 2 hours. Store the primary solution in a refrigerator.

Vinyl chloride standard solution.

To one volume of the Vinyl chloride primary solution add three volumes of *N,N-dimethylacetamide.*

Reference solutions. Place 10.0mL of the Internal standard solution in each of six 50mL vials. Close the vials, and secure the stoppers. Inject 1, 2, 3, 5, and 10µL, respectively, of the Vinyl chloride standard solution into five of the vials. The six solutions thus obtained contain, respectively, 0, 0.3, 0.6, 0.9, 1.5, and 3µg of vinyl chloride. Shake, avoiding contact between the stopper and the liquid. Place the vials in a water bath at 60 ± 1°C for 2 hours.

Chromatographic system

- a stainless steel column 3m x 3.0mm, packed with with silanized diatomaceous earth for gas chromatography impregnated with 5% m/m of dimethylstearylamide and 5% m/m of *polyethylene glycol 400*
- temperature:
  - column. 45°C
  - inlet port. 100°C
  - detector at 150°C,
- flow rate: 30mL/minute using nitrogen as carrier gas

Inject 1mL of the head space of each vial containing the test solution and the Reference solutions.

Calculate the amount of vinyl chloride in the test solution by comparing the test result of the Sample solution with the test results of the Reference solutions. Calculate the amount of vinyl chloride in the test material by dividing the amount of vinyl chloride in the test solution by 1.0g, producing a result in µg/g or ppm.

Not more than 1ppm. Note that vinyl chloride is not an additive but is monitored as a residual monomer.

B.2.2] Tin in Tin-Stabilized Materials

Reference solution U. 0.081% of *Plastic Additive 18 RS* prepared in *tetrahydrofuran*. Dilute 20mL to 100mL with *ethanol*.

Test solution. In a test tube, add 0.1mL of Solution S2, Add 0.05mL of *1M hydrochloric acid*, 0.5mL of *potassium iodide solution*, and 5mL of *ethanol*. Mix thoroughly and wait for 5 min. Add 9mL of *water* and 0.1mL of a 5-gram/ /L solution of *sodium sulphite* and mix thoroughly. Add 1.5mL of *dithizone solution* freshly diluted 100-fold with *methylene chloride*, shake for 15 sec and allow to stand for 2 min.

Standard solution. Use 0.1mL of Reference solution U through the same procedure as the 0.1mL of Solution S2.

Compare the violet colour in the lower layer of the Sample solution to the violet colour in the lower layer of the Standard solution. The colour in the Sample solution should not be as intense as the colour in the Standard solution.

Not more than 0.25 weight %.

B.2.3] Tin in Non Tin-Stabilized Materials

Test solution. In a test tube, add 0.1mL of Solution S2, Add 0.05mL of *1M hydrochloric acid*, 0.5mL of *potassium iodide solution*, and 5mL of *ethanol*. Mix thoroughly and wait for 5 min. Add 9mL of water and 0.1mL of a 5-gram/ /L solution of *sodium sulphite* and mix thoroughly. If the solution is not colourless, add the sodium sulphate in 0.05mL fractions Add 1.5mL of dithizone solution freshly diluted 100-fold with *methylene chloride*, shake for 15 sec and allow to stand for 2 min.

Standard solution. Use 0.05mL of Reference solution U through the same procedure as the 0.1mL of Solution S2.

Compare the violet colour in the lower layer of the Sample solution to the violet colour in the lower layer of the Standard solution. The colour in the Sample solution should not be as intense as the colour in the Standard solution.

Not more than 25µg/g (ppm).

B.3] Related Substances (Residual Monomers / Residual Solvents)

B.3.1] Chlorine Content

50.0mg of the test material is processed using Oxygen Flask method (2.3.34). Absorb the combustion products with 20mL of *1M sodium hydroxide*. To this, add 2.5mL of *nitric acid*, 10mL of *0.1M silver nitrate* solution, 5mL of *ferric ammonium sulphate solution*, and 1mL of *dibutyl phthalate*. Titrate with *0.005M ammonium thiocyanate* solution until a reddish-yellow colour is obtained. Carry out a blank titration.

Calculate the titration volume by subtracting the volume of titrant used in the blank from the volume of titrant used in the Preparation. Each mL of *0.005M ammonium thiocyanate* is equal to 6.25mg of polyvinyl chloride. The chlorine content, in weight%, is calculated as follows:

Chlorine content (weight %) = {[titrant volume (in mL) × 6.25 mg/mL]/weight of sample (mg)} × 100%

Not less than 80% by weight, expressed as polyvinyl chloride.

B.4] Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the total organic carbon analyses should have a limit of detection of 0.2mg/L (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20mg/L (which encompasses the total organic carbon limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank total organic carbon concentrations is not more than 5mg/L.

B.5] Extractable Metals

Solution S3 is used for extracting acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A).

Aluminum, arsenic, lead, cadmium, mercury, cobalt, nickel, vanadium, and zinc: Report the measured value in Solution S3 at values above 0.01mg/L (ppm), corresponding to 0.025µg/g. If the measured values are below these values, report the result as less than 0.01mg/L (ppm), corresponding to less than 0.025µg/g.

Additional acceptance criteria for materials used as containers for non-injectable aqueous solutions.

Barium: Solution S3 contains not more than 0.10mg/L (ppm), corresponding to 2µg/g.

Cadmium: Solution S3 contains not more than 0.03mg/L (ppm), corresponding to 0.6µg/g.

Zinc: Solution S3 contains not more than 5mg/L (ppm), corresponding to 100µg/g.

6.2.1.2.4. Polyvinyl Chloride, Plasticized

A] Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800cm^{-1} to 600cm^{-1} (2.6–16 µm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of the *Polyvinyl Chloride, Plasticized RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and RS spectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

The thermogram of the specimen is similar to the thermogram of *Polyvinyl Chloride, Plasticized RS*, and(Tg) the melting peak temperature obtained from the thermogram of the specimen does not differ from that of the RS by more than 8.0°. Note that the results of the DSC analysis are strongly dependent on the amount of plasticizer in the test article.

B] Chemical Tests

Preparation of Special Solutions for subsequent tests on Polyvinyl Chloride

Solution S1 (Water extraction)

Place 25g of the test material into a borosilicate glass flask. Add 500mL of purified water, cover the flask's neck with aluminium foil or a borosilicate beaker, and heat in an autoclave at 121 ± 2°C for 20 min. Allow the solution to cool and the solids to settle, decant the solution into a 500-mL volumetric flask, and dilute with purified water to volume; the diluted solution is *Solution S1*.

Solution S2 (Tetrahydrofuran extraction)

Dissolve 5.0g of the test material in 80mL of *tetrahydrofuran* and dilute to a volume of 100mL with the same solvent. Filter if necessary; the solution may remain opaque. Slowly and drop wise add 70mL *ethanol* to 20mL of this solution. Cool the mixture in ice for 1 hours. Filter or centrifuge the mixture, collecting residue A. Wash residue A with ethanol. Collect the washings and add them to the solution remaining after filtration or centrifugation. Transfer the solution to a 100mL volumetric flask and dilute to volume with ethanol. This process produces *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5g in a borosilicate glass flask with a ground-glass neck. Add 100mL of *0.1M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100mL volumetric flask, and dilute to volume with *0.1M hydrochloric acid*; the diluted solution is *Solution S3.*

Tests Using Special Solutions

B.1] Absorbance (2.4.7)

Evaporate 100mL of Solution S1 to dryness. Dissolve the resulting residue in 5mL of hexane to produce the hexane sample. Pass the hexane sample, if necessary, through a filter previously rinsed with hexane. Determine the spectrum between 250 and 310nm in the hexane sample.

Absorbance should be not more than 0.25.

B.2] Acidity or alkalinity

To 100mL of Solution S1 add 0.15mL of *BRP indicator solution*. Determine the titration volume of *0.01M sodium hydroxide* required to change the colour of the indicator to blue. To 100mL of Solution S1 add 0.2 mL of *Methyl orange solution*. Determine the titration volume of *0.01M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5mL of *0.01N sodium hydroxide* is required to change the colour of the indicator to blue. Not more than 1.0mL of *0.01N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3] Plastic Additives

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254 (1 mm thick)*

Additives are di(2-ethylhexyl) phthalate, *N,N″*-diacylethylenediamines, epoxidized soya oil, and epoxidized linseed oil. Vinyl chloride monomer (VCM) is also monitored, although it is a residual monomer and not an additive.

Mobile Phase. Toluene.

Solution A1. Add 2.0g of the test material to 200mL of peroxide-free ether and heat under a reflux condenser for 8 hours. Separate the resulting residue B and extraction solution A by filtration. Evaporate extraction solution A to dryness under reduced pressure in a water bath at 30°C, producing residue C. Dissolve residue C in 10mL of toluene.

Precipitate B2. Dissolve residue B in 60mL of *ethylene chloride* heating on a water bath under a reflux condenser, producing solution D. Filter the resulting solution D. Add the filtered solution D drop wise and with vigorous shaking to 600mL of heptanes heated almost to boiling. Separate by hot filtration the coagulum B1 and the organic solution E. Allow solution E to cool; separate the precipitate B2 that forms upon cooling, and pass through a tared sintered-glass filter (pore size of 16–40µm).

Reference solution (u) 0.01% of *Plastic Additive 14 RS* prepared in *toluene.*

Reference solution (v) 0.01% of *Plastic Additive 15 RS* prepared in *toluene.*

Reference solution (w) 0.01% of *Plastic Additive 16 RS* prepared in *toluene.*

Additive di(2-ethylhexyl) phthalate.

Apply to the plate 0.5mL of solution A to the plate as 30mm × 30mm. Apply 5µL reference solution (u). Develop the plates over a path of 15cm with toluene. After development, dry the plate in air and examine under UV light at 254nm. Locate the zone corresponding to additive di(2-ethylhexyl) phthalate, *Plastic Additive 14 RS* (R_f about 0.4). Remove the area of silica gel corresponding to this zone, mix with 40mL of *ethyl ether*, and shake for 1 min. Filter, rinse filter with two quantities each of 10mL of ethyl ether, add the rinsing to the filtrate, and evaporate to dryness. The residue weighs not more than 40mg.

Residue is not more than 40 mg

Additives epoxidized soya oil and epoxidized linseed oil.

Apply to the plate 0.5mL of solution A to the plate as 30mm × 30mm. Apply 5µL reference solution (v) and reference solution (w). Develop the plates over a path of 15cm with *toluene.* After development, dry the plate in air and expose to iodine vapor for 5 min. locate the zone corresponding to additive epoxidized soya oil, *Plastic Additive 15 RS* and epoxidized linseed oil, *Plastic Additive 16 RS* (R_f 0.0). Remove the area of silica gel corresponding to this band. Similarly, remove a corresponding area of silica gel as a blank reference. Separately mix both samples with separate 40mL portions of *methanol*, shaking for 15 min. Filter, rinse the filter with two quantities of 10mL of *methanol*, add the rinsing to the filtrate, and evaporate to dryness. The difference between the masses of both residues is not more than 10mg.

Epoxidized soya oil : The difference between the masses of both residues is not more than 10mg.

Epoxidized linseed oil: The difference between the masses of both residues is not more than 10mg.

B.4] Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the Total Organic Carbon analyses should have a limit of detection of 0.2 mg/L (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20mg/L (which encompasses the total organic carbon limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank Total Organic Carbon concentrations is not more than 5 mg/L.

B.5] Extractable Metals

Solution S3 is used for extracting acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A).

Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium: Report the measured value in *Solution S3* at values above 0.01mg/L (ppm), corresponding to 0.025µg/g. If the measured values are below these values, report the result as less than 0.01mg/L (ppm), corresponding to less than 0.025µg/g.

Barium: *Solution S3* contains not more than 0.25mg/L (ppm), corresponding to 5µg/g.

Calcium: *Solution S3* contains not more than 35mg/L (ppm), corresponding to 0.07 weight %.

Tin: *Solution S3* contains not more than 1mg/L (ppm), corresponding to 20µg/g.

Zinc: *Solution S3* contains not more than 100mg/L (ppm), corresponding to 0.2 weight %.

B.6] Related Substances (Residual Monomers / Residual Solvents)

B.6.1] Vinyl Chloride

Internal standard solution. Using a microsyringe, Inject 10µL of *ethyl ether* into 20.0mL of *N,N-dimethylacetamide* by immersing the tip of the needle in the solvent. Immediately before use, dilute 1.0 volume of the solution to 1000 volumes with *N,N-dimethylacetamide*.

Test solution. Place 1.0g of the test material in a 50mL vial, and add 10.0mL of the internal standard solution. Close the vial, and secure with a stopper. Shake, avoiding contact between the stopper and the liquid. Place the vial in a water bath at 60 ± 1°C for 2 hours.

Vinyl chloride primary solution:

Note—Prepare under a ventilated hood.

Place 50mL of *N,N-dimethylacetamide* in a 50-mL vial, stopper the vial, secure the stopper, and weigh to the nearest 0.1mg. Fill a 50-mL polyethylene or polypropylene syringe with gaseous vinyl chloride, allow the gas to remain in contact with the syringe for about 3 min, empty the syringe, and fill again with 50mL of gaseous vinyl chloride. Fit a hypodermic needle to the syringe, and reduce the volume of gas in the syringe from 50 to 25mL. Inject the remaining 25mL of vinyl chloride slowly into the vial, shaking gently and avoiding contact between the liquid and the needle. Weigh the vial again; the increase in mass is about 60mg (1µL of the solution obtained contains about 1.2µg of vinyl chloride). Allow to stand for 2 hours. Store the primary solution in a refrigerator.

Vinyl chloride standard solution. To one volume of the Vinyl chloride primary solution add three volumes of *N,N-dimethylacetamide.*

Reference solutions . Place 10.0mL of the Internal standard solution in each of six 50mL vials. Close the vials, and secure the stoppers. Inject 1, 2, 3, 5, and 10µL, respectively, of the Vinyl chloride standard solution into five of the vials. The six solutions thus obtained contain, respectively, 0, 0.3, 0.6, 0.9, 1.5, and 3µg of *vinyl chloride*. Shake, avoiding contact between the stopper and the liquid. Place the vials in a water bath at 60 ±1°C for 2 hours.

Chromatographic system

- a stainless steel column 3.0m x 3.0mm, packed with silanized diatomaceous earth for gas chromatography impregnated with 5% m/m of dimethylstearylamide and 5% m/m of *polyethylene glycol 400*
- temperature:
    - column. 45°C
    - inlet port. 100°C
    - detector at 150°C
- flow rate: 30mL/minute using nitrogen as carrier gas

Inject 1mL of the head space of each vial containing the test solution and the Reference solutions.

Calculate the amount of vinyl chloride in the test solution by comparing the test result of the Sample solution with the test results of the Reference solutions. Calculate the amount of vinyl chloride in the test material by dividing the amount of vinyl chloride in the test solution by 1.0g, producing a result in µg/g or ppm.

Not more than 1ppm.

Note that vinyl chloride is not an additive but is monitored as a residual monomer.

6.2.1.2.5. Polypropylene

A] Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800cm^{-1} to 650cm^{-1} (2.6–15 µm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of the Homopolymer *Polypropylene RS.* Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved

when all differences between the sample and RS spectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

The melting peak temperature in the thermogram does not differ from that of the Homopolymer Polypropylene RS by more than 12.0°C

B] Chemical Tests

Preparation of Special Solutions for subsequent tests on Polypropylene

Solution S1 (Water extraction)

Place 25g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500mL of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500mL volumetric flask and dilute with purified water to volume; the diluted solution is *Solution S1*.

NOTE- Use Solution S1 within 4 hours of preparation.

Solution S2 (Toluene extraction)

Place 2.0g of the test material in a 250-mL borosilicate glass flask with a ground-glass neck. Add 80mL of toluene and boil under a reflux condenser for 1.5 hours, stirring constantly. Allow to cool to 60°C and add 120mL of methanol with continued stirring. Pass the resulting solution through a sintered-glass filter. Rinse the flask and the filter with 25mL of a mixture of 40 volumes of toluene and 60 volumes of methanol add the rinsing to the filtrate, and dilute to 250mL with the same mixture of solvents to produce *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5g in a borosilicate glass flask with a ground-glass neck. Add 100 mL of *0.1M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100mL volumetric flask, and dilute to volume with *0.1M hydrochloric acid*; the diluted solution is *Solution S3.*

Tests Using Special Solutions

B.1] Absorbance (2.4.7)

Determine the spectrum between 220 and 340nm in Solution S1.

Absorbance should be not more than 0.2.

B.2] Acidity or alkalinity

To 100mL of Solution S1 add 0.15mL of BRP indicator solution. Determine the titration volume of *0.01M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100mL portion of Solution S, add 0.2mL of *Methyl orange solution*. Determine the titration volume of *0.01M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5mL of *0.01N sodium hydroxide* is required to change the colour of the indicator to blue.

Not more than 1.0mL of *0.01N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3] Plastic Additives

These tests should be carried out in whole or in part as required due to the stated composition of the material.

B.3.1] Phenolic Antioxidant

*Solvent mixture***.** Mixture of equal volumes of *Acetonitrile* and *Tetrahydrofuran*.

Sample solution S2A. Evaporate 50mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the resulting residue with 5.0mL of the Solvent mixture. Prepare a blank solution from the blank solution corresponding to Solution S2.

Sample solution S2B. Evaporate 50mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the residue with 5.0mL of methylene chloride. Prepare a blank solution from the blank solution corresponding to SolutionS2.

Reference solutions of the following reference solutions, prepare only those that are necessary for the analysis of the phenolic antioxidants stated in the composition of the substance to be examined.

Reference solution (a). A 0.01% w/v of *Butylated Hydroxytoluene RS* and 0.024% w/v of *Plastic Additive 01 RS* in the solvent mixture.

Reference solution (b). A 0.024% w/v of *Plastic Additive 02 RS* and 0.024% of *Plastic Additive 03 RS* in the solvent mixture.

Reference solution *(c).* A 0.024% of *Plastic Additive 04 RS* and 0.024% of *Plastic Additive 05 RS* in methylene chloride

Reference solution (d). A 0.01% of *Butylated Hydroxytoluene RS* in the solvent mixture

Reference solution (e). A 0.024% of *Plastic Additive 01 RS* in the solvent mixture

Reference solution (f). A 0.024% of *Plastic Additive 06 RS* prepared in the solvent mixture

Reference solution (g). A 0.024% of *Plastic Additive 02 RS* prepared in the solvent mixture

Reference solution (*h*) A 0.024% of *Plastic Additive 03 RS* prepared in the solvent mixture

Reference solution (i) A 0.024% of *Plastic Additive 04 RS* prepared in *methylene chloride*

Reference solution (j) A 0.024% of *Plastic Additive 05 RS* prepared in *methylene chloride*

Test A

Determine by liquid chromatography (2.4.14).

If the substance to be examined contains additive butylated hydroxytoluene and/or additive ethylene bis[3,3-bis[3-(1,1dimethylethyl)-4-hydroxyphenyl]butanoate

Chromatographic system

- a stainless steel column 25cm x 4.6mm, packed with octadecylsilane bonded to porous silica microparticles (5 µm),
- mobile phase: a mixture of 70 volumes of a *acetronitrile* and 30 volumes of *water*
- flow rate: 2.0 mL/minute,
- spectrophotometer set at 280 nm,
- injection volume: 20µL

Inject reference solution (a).The test is not valid unless the resolution between the peaks due to additive butylated hydroxytoluene and additive ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate] peaks is not less than 8.0.

Inject Sample solution S2A corresponding blank solution, Reference solution (a), and Reference solution (d), Reference solution (e), or both. Run the chromatogram for about 30 minutes. The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solution (d) or Reference solution (e).
Note: Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test B

If the substance to be examined contains one or more of the following antioxidants pentaerythrityl tetrakis[3-(3,5-di tert-butyl-4-hydroxyphenyl)propionate; 2,2,2″,6,6,6″-hexa-tert-butyl-4,4,4″-[(2,4,6-trimethyl-1,3,5-benzene-triyl)trismethylene]triphenol; octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate; tris(2,4-di-tert-butylphenyl) phosphate; 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6(1H,3H,5H)-trione

Determine by liquid chromatography (2.4.14).

Chromatographic system

Carry out the test as described in Test A with the following modifications

- a stainless steel column 25cm x 4.6mm, packed with octadecylsilane bonded to porous silica microparticles (5 µm)
- mobile phase: a mixture of 60 volumes of *acetronitrile* 30 volumes of *tetrahydrofuran* and 10 volumes of *water*
- flow rate: 1.5mL/minute
- spectrophotometer set at 280 nm
- injection volume: 20µL

Inject reference solution (b).The test is not valid unless the resolution between the peaks due to additive pentaerythrityl tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and additive 2,2’,2″,6,6’,6″-hexa-tert-butyl-4,4’,4″-[(2,4,6-trimethyl-1,3,5-benzene-triyl)trismethylene]triphenol peaks is not less than 2.0.

Inject Sample solution S2A corresponding blank solution, Reference solution (b), and any Reference solutions of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

Note: Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test C

If the substance to be examined contains additive octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and/or additive tris(2,4-di-tert-butylphenyl) phosphite

Determine by liquid chromatography (2.4.14).

Chromatographic system

Carry out the test as described in Test A with the following modifications

- a stainless steel column 25cm x 4.6mm, packed with octadecylsilane bonded to porous silica microparticles (5 µm)
- mobile phase: a mixture of 50 volumes of *methanol*, 40 volumes of *2 propanol* and 5.0 volumes of *water*
- flow rate: 1.5mL/minute

- spectrophotometer set at 280nm
- injection volume: 20µL

Inject reference solution (c).The test is not valid unless the resolution between the peaks due to additive octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and additive tris(2,4-di-tert-butylphenyl) phosphite peaks is not less than 2.0.

Inject Sample solution S2B corresponding blank solution, Reference solution (c), and any Reference solutions (i) or Reference solution (j) of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2B are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

Note: Sample solution S2B shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

B.3.2] Non-Phenolic Antioxidant

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phaseA. Hexane

Mobile phase B. Methylene chloride

Methylene chloride, acidified. To 100mL of methylene chloride add 10mL of *hydrochloric acid*, shake, allow to stand, and separate the two layers. Use the lower layer.

Sample solution S2C: Evaporate 100mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the resulting residue with 2mL of *methylene chloride* acidified.

Reference solution (m). A 0.6% w/v of *Plastic Additive 08 RS* in *methylene chloride*. Dilute 2mL of the solution with Methylene chloride, acidified to 10mL.

Reference solution (n): A 0.6% w/v of *Plastic Additive 09 RS* in *methylene chloride*. Dilute 2mL of the solution with Methylene chloride, acidified to 10mL.

Reference solution (o). A 0.6% w/v of *Plastic Additive 10 RS* in *methylene chloride*. Dilute 2mL of the solution with *methylene chloride*, acidified to 10mL.

Reference solution (p). A 0.6% of *Plastic Additive 10 RS*, and 0.6% of *Plastic Additive 09 RS* in *methylene chloride*. Dilute 2mL of the solution with *methylene chloride*, acidified to 10mL.

Apply to the plate 20µL of sample solution S2C, reference solution and the reference solution corresponding to all the phenolic and non-phenolic antioxidants expected to be present. Development the plates Over a path of 18 cm with Mobile phase A and over a path of 17cm with Mobile phase B respectively. After development, dry the plate in air and examine under ultraviolet light at 254nm and spray with alcoholic iodine solution. The test is not valid unless the chromatogram obtained with reference solution (p) shows two separate spot. Any spot in the chromatogram obtained with sample solution S2C is not more intense than the spot in the same position in the chromatogram of the corresponding reference solution.

B.3.3] Amides and Stearates

Use sample solution as sample solution S2C as described in Non-phenolic Antioxidants.

Reference solution (r). A 0.2% of Stearic *Acid RS* prepared in *methylene chloride*.

Reference solution (s). A 0.2% of Plastic *Additive 12 RS* prepared in *methylene chloride*.

Reference solution (t) A 0.2% of *Plastic Additive 13 RS* prepared in *methylene chloride*.

Test A

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*

Mobile phase. a mixture of 75 volume of *trimethylpantane* and 25 volumes of *alcohol*

Apply to the plate 10µL of sample solution S2C, reference solution (r). Develop the plates over a path of 10 cm with Mobile phase. After development, dry the plate in air and examine by spray with 2% 2,6-dichlorophenol-indophenol sodium in dehydrated alcohol heat in an oven at 120°C for a few minutes to intensify the spots. Any spot corresponding to additive stearic acid in the chromatogram obtained with sample solution S2C (R_f = about 0.5) is not more intense than the spot in the same position in the chromatogram of reference solution (r).

Test B

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*

Mobile phaseA. Hexane

Mobile phase B. A mixture of 95 volumes of *Methylene chloride* and 5.0 volumes of *methanol.*

Apply to the plate 10µL of sample solution S2C, reference solution (s) and reference solution (t). Develop the plates Over a path of 13cm with Mobile phase A and Over a path of 10cm with Mobile phase B respectively. After development, dry the plate in air and examine by spray with 40% *phosphomolybdic acid* in *alcohol* heat in an oven at 120°C for a few minutes to intensify the spots. Any spot corresponding to additive oleamide or erucamide in the chromatogram obtained with sample solution S2C (R_f = about 0.2) is not more intense than the spot in the same position in the chromatogram of reference solution (s) and reference solution (t).

B.4] Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the Total Organic Carbon analyses should have a limit of detection of 0.2 mg/L (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20mg/L (which encompasses the total organic carbon limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank Total Organic Carbon concentrations is not more than 5mg/L.

B.5] Extractable Metals

Solution S3 is used for extracting acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A)

Aluminum: *Solution S3* contains not more than 0.4mg/L (ppm), corresponding to 1µg/g.

Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium: Report the measured value in *Solution S3* at values above 0.01mg/L (ppm), corresponding to 0.025µg/g. If the measured values are below these values, report the result as less than 0.01mg/L (ppm), corresponding to less than 0.025µg/g.

Chromium: *Solution S3* contains not more than 0.02mg/L (ppm), corresponding to 0.05µg/g.

Titanium: *Solution S3* contains not more than 0.4mg/L (ppm), corresponding to 1µg/g.

Zinc: *Solution S3* contains not more than 0.4mg/L (ppm), corresponding to 1µg/g.

6.2.1.2.6. Cyclic Olefins

A] Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800cm^{-1} to 650cm^{-1} (2.6–15 µm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of Cyclic Olefin Polymer Reference Standard (RS) or Cyclic Olefin Copolymer RS. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and RS spectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

Given the amorphous nature of these polymers and their compositional variety, material-to-material variations in the melting peak temperature can be anticipated. Thus, it is neither recommended nor required that differential scanning calorimetry (DSC) be performed.

B] Chemical Tests

Preparation of Special Solutions for subsequent tests on Cyclic Olefins

Solution S1 (Water extraction)

Place 25g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500mL of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500mL volumetric flask and dilute with purified water to volume; the diluted solution is *Solution S1*.

Use *Solution S1* within 4 hours of preparation.

Solution S2 (Toluene extraction)

Place 2.0g of the test material in a 250-mL borosilicate glass flask with a ground-glass neck. Add 80mL of toluene and boil under a reflux condenser for 1.5 hours, stirring constantly. Allow to cool to 60°C and add 120mL of methanol with continued stirring. Pass the resulting solution through a sintered-glass filter. Rinse the flask and the filter with 25mL of a mixture of 40 volumes of toluene and 60 volumes of methanol add the rinsing to the filtrate, and dilute to 250mL with the same mixture of solvents to produce *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5g in a borosilicate glass flask with a ground-glass neck. Add 100mL of *0.1M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100mL volumetric flask, and dilute to volume with *0.1M hydrochloric acid*; the diluted solution is *Solution S3.*

Tests Using Special Solutions

B.1] Absorbance (2.4.7)

Determine the spectrum between 220 and 340nm in Solution S1.

Absorbance should be not more than 0.2.

B.2] Acidity or alkalinity

To 100mL of Solution S1 add 0.15mL of BRP indicator solution. Determine the titration volume of *0.01M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100mL portion of Solution S, add 0.2mL of *Methyl orange solution*. Determine the titration volume of *0.01M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5mL of *0.01N* sodium hydroxide is required to change the colour of the indicator to blue. Not more than 1.0mL of *0.01N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3] Plastic Additives

These tests should be carried out in whole or in part as required due to the stated composition of the material.

B.3.1] Phenolic Antioxidant

*Solvent mixture***.** Mixture of equal volumes of Acetonitrile and *Tetrahydrofuran*.

Sample solution S2A. Evaporate 50mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the resulting residue with 5.0mL of the Solvent mixture. Prepare a blank solution from the blank solution corresponding to Solution S2.

Sample solution S2B. Evaporate 50mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the residue with 5.0mL of methylene chloride. Prepare a blank solution from the blank solution corresponding to SolutionS2.

Reference solutions of the following reference solutions; prepare only those that are necessary for the analysis of the phenolic antioxidants stated in the composition of the substance to be examined.

Reference solution (a). A 0.01% w/v of *Butylated Hydroxytoluene RS* and 0.024% w/v of Plastic *Additive 01 RS* in the Solvent mixture.

Reference solution (b). A 0.024% w/v of *Plastic Additive 02 RS* and 0.024% of *Plastic Additive 03 RS* in the Solvent mixture

Reference solution *(c).* A 0.024% of *Plastic Additive 04 RS* and 0.024% of *Plastic Additive 05 RS* in *methylene chloride*

Reference solution (d). A 0.01% of *Butylated Hydroxytoluene RS* in the solvent mixture

Reference solution (e). A 0.024% of *Plastic Additive 01 RS* in the solvent mixture

Reference solution (f). A 0.024% of *Plastic Additive 06 RS* prepared in the solvent mixture

Reference solution (g). A 0.024% of *Plastic Additive 02 RS* prepared in the solvent mixture

Reference solution (*h*). A 0.024% of *Plastic Additive 03 RS* prepared in the solvent mixture

Reference solution (i). A 0.024% of Plastic *Additive 04 RS* prepared in *methylene chloride*

Reference solution (j). A 0.024% of *Plastic Additive 05 RS* prepared in *methylene chloride*

Test A

Determine by liquid chromatography (2.4.14).

If the substance to be examined contains additive butylated hydroxytoluene and/or additive ethylene bis[3,3-bis[3-(1,1dimethylethyl)-4-hydroxyphenyl]butanoate

Chromatographic system

- a stainless steel column 25cm x 4.6mm, packed with octadecylsilane bonded to porous silica microparticles (5µm)

- mobile phase: a mixture of 70 volumes of *acetronitrile* and 30 volumes of *water*
- flow rate: 2.0mL/minute
- spectrophotometer set at 280nm
- injection volume: 20µL

Inject reference solution (a).The test is not valid unless the resolution between the peaks due to additive butylated hydroxytoluene and additive ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate] peaks is not less than 8.0.

Inject Sample solution S2A corresponding blank solution, Reference solution (a), and Reference solution (d), Reference solution (e), or both. Run the chromatogram for about 30 minutes. The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solution (d) or Reference solution (e).

Note: Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test B

If the substance to be examined contains one or more of the following antioxidants pentaerythrityl tetrakis[3-(3,5-di tert-butyl-4-hydroxyphenyl)propionate; 2,2,2″,6,6,6″-hexa-tert-butyl-4,4,4″-[(2,4,6-trimethyl-1,3,5-benzene-triyl)trismethylene]triphenol; octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate; tris(2,4-di-tert-butylphenyl) phosphate; 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6(1H,3H,5H)-trione

Chromatographic system Determine by liquid chromatography (2.4.14). Carry out the test as described in Test A with the following modifications

- a stainless steel column 25cm x 4.6mm, packed with octadecylsilane bonded to porous silica microparticles (5µm)
- mobile phase: a mixture of 60 volumes of *acetronitrile* 30 volumes of *tetrahydrofuran* and 10 volumes of *water*
- flow rate: 1.5mL/minute
- spectrophotometer set at 280nm
- injection volume: 20µL

Inject reference solution (b).The test is not valid unless the resolution between the peaks due to additive pentaerythrityl tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and additive 2,2',2″,6,6',6″-hexa-tert-butyl-4,4',4″-[(2,4,6-trimethyl-1,3,5-benzene-triyl)trismethylene]triphenol peaks is not less than 2.0.

Inject Sample solution S2A corresponding blank solution, Reference solution (b), and any Reference solutions of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

Note: Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test C

If the substance to be examined contains additive octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and/or additive tris(2,4-di-tert-butylphenyl) phosphite

Chromatographic system Determine by liquid chromatography (2.4.14). Carry out the test as described in Test A with the following modifications

- a stainless steel column 25cm x 4.6mm, packed with octadecylsilane bonded to porous silica microparticles (5 µm)
- mobile phase: a mixture of 50 volumes of *methanol*, 40 volumes of *2 propanol* and 5.0 volumes of *water*
- flow rate: 1.5mL/minute,
- spectrophotometer set at 280nm
- injection volume: 20µL

Inject reference solution (c).The test is not valid unless the resolution between the peaks due to additive octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and additive tris(2,4-di-tert-butylphenyl) phosphite peaks is not less than 2.0.

Inject Sample solution S2B corresponding blank solution, Reference solution (c), and any Reference solutions (i) or Reference solution (j) of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2B are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

Note: Sample solution S2B shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

B.3.2] Non-phenolic Antioxidant

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phaseA. Hexane

Mobile phase B. Methylene chloride

Methylene chloride, acidified. To 100mL of *methylene chloride* add 10mL of *hydrochloric acid*, shake, allow to stand, and separate the two layers. Use the lower layer.

Sample solution S2C: Evaporate 100mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the resulting residue with 2mL of Methylene chloride acidified.

Reference solution (m). 0.6% w/v of *Plastic Additive 08 RS* in *methylene chloride*. Dilute 2mL of the solution with *methylene chloride*, acidified to 10mL.

Reference solution (n): 0.6% w/v of *Plastic Additive 09 RS* in *methylene chloride*. Dilute 2mL of the solution with *methylene chloride*, acidified to 10mL.

Reference solution (o). 0.6% w/v of *Plastic Additive 10 RS* in *methylene chloride*. Dilute 2mL of the solution with *methylene chloride*, acidified to 10mL.

Reference solution (p). 0.6% of *Plastic Additive 10 RS*, and 0.6% of *Plastic Additive 09 RS* in *methylene chloride*. Dilute 2mL of the solution with *methylene chloride*, acidified to 10mL.

Apply to the plate 20µL of sample solution S2C, reference solution and the reference solution corresponding to all the phenolic and non-phenolic antioxidants expected to be present. Development the plates Over a path of 18cm with Mobile phase A and over a path of 17cm with Mobile phase B respectively. After development, dry the plate in air and examine under ultraviolet light at 254 nm and spray with alcoholic iodine solution.

The test is not valid unless the chromatogram obtained with reference solution (p) shows two separate spot. Any spot in the chromatogram obtained with sample solution S2C is not more intense than the spot in the same position in the chromatogram of the corresponding reference solution.

B.3.3] Copolymer of Dimethyl Succinate and (4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl) ethanol

Determine by liquid chromatography (2.4.14).

Solvent mixture. 89 volume of *Hexane* and 11 volumes of *ethanol.*

Sample solution S2D. Evaporate 25mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the residue with 10mL of toluene and 10mL of a 10% w/v solution of *tetrabutylammonium hydroxide* in a mixture of 35 volumes of *toluene* and 65 volumes of *anhydrous ethanol*. Boil under a reflux condenser for 3 hours. Allow to cool, and filter.

Reference solution (q). 0.06% w/v of *Plastic Additive 11 RS* prepared in *toluene*. Add 1.0mL of this solution to 25mL of the blank solution corresponding to Solution S2 and evaporate to dryness under vacuum at 45°C. Prepare a blank solution from the blank solution corresponding to Solution S2. Dissolve the residue with 10mL of toluene and 10mL of a 10% w/v solution of *tetrabutyl ammonium hydroxide* in a mixture of 35 volumes of toluene and 65 volumes of anhydrous ethanol. Boil under a reflux condenser for 3 hours. Allow to cool, and filter.

Chromatographic system

- a stainless steel column 25cm x 4.6mm, packed with aminopropylsilane bonded to porous silica microparticles (5µm)
- mobile phase: a mixture of 89 volume of *hexane* and 11 volumes of *ethanol*
- flow rate: 2.0mL/minute
- spectrophotometer set at 227nm
- injection volume: 20µL

Inject reference solution (q).The test is not valid unless the resolution between the peaks due to diol component and the diluents peaks is not less than 7.0.

Inject Sample solution S2D corresponding blank solution and Reference solution (q). Run the chromatogram for about 30 minutes. The peak areas of diol component in Sample solution S2A are less than the corresponding peak areas of Reference solution (q).

B.3.4] Amides and Stearates

Use sample solution as sample solution S2C as described in Non-phenolic Antioxidants.

Reference solution (r). A 0.2% of Stearic *Acid RS* prepared in *methylene chloride*.

Reference solution (s). A 0.2% of Plastic *Additive 12 RS* prepared in *methylene chloride.*

Reference solution (t) A 0.2% of *Plastic Additive 13 RS* prepared in *methylene chloride*.

Test A

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*

Mobile phase. a mixture of 75 volume of *trimethylpantane* and 25 volumes of *alcohol*

Apply to the plate 10µL of sample solution S2C, reference solution (r). Develop the plates over a path of 10 cm with Mobile phase. After development, dry the plate in air and examine by spray with 2% 2,6-dichlorophenol-indophenol sodium in dehydrated alcohol heat in an oven at 120°C for a few minutes to intensify the spots. Any spot corresponding to additive stearic acid in the chromatogram obtained with sample solution S2C (R_f = about 0.5) is not more intense than the spot in the same position in the chromatogram of reference solution (r).

Test B

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*

Mobile phase A. Hexane

Mobile phase B. A mixture of 95 volumes of *methylene chloride* and 5.0 volumes of *methanol.*

Apply to the plate 10µL of sample solution S2C, reference solution (s) and reference solution (t). Develop the plates Over a path of 13cm with Mobile phase A and Over a path of 10cm with Mobile phase B respectively. After development, dry the plate in air and examine by spray with 40% *phosphomolybdic acid* in *alcohol* heat in an oven at 120°C for a few minutes to intensify the spots. Any spot corresponding to additive oleamide or erucamide in the chromatogram obtained with sample solution S2C (R_f = about 0.2) is not more intense than the spot in the same position in the chromatogram of reference solution (s) and reference solution (t).

B.4] Total Organic Carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the Total Organic Carbon analyses should have a limit of detection of 0.2mg/L (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20mg/L (which encompasses the TOC limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank total organic carbon concentrations is not more than 5mg/L.

B.5] Extractable Metals

Solution S3 is used for extracting acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A)

Aluminium: Solution S3 contains not more than 0.4mg/L (ppm), corresponding to 1µg/g.

Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium: Report the measured value in Solution S3 at values above 0.01mg/L (ppm), corresponding to 0.025µg/g. If the measured values are below these values, report the result as less than 0.01mg/L (ppm), corresponding to less than 0.025µg/g.

Titanium: Solution S3 contains not more than 0.4mg/L (ppm), corresponding to 1µg/g.

Zinc: Solution S3 contains not more than 0.4mg/L (ppm), corresponding to 1µg/g.

6.2.1.2.7. Poly (Ethylene-vinyl Acetate)

A] Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800cm^{-1} to 600cm^{-1} (2.6–15 µm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of *Poly(ethylene-vinyl acetate) RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and RS spectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

The thermogram of the specimen is similar to the thermogram of *Poly(ethylene-vinyl acetate) RS*, and the melting point temperature obtained from the thermogram of the specimen does not differ from that of the RS by more than 6.0°.

B] Chemical Tests

Preparation of Special Solutions for subsequent tests on Poly(ethylene-vinyl acetate)

Solution S1 (Water extraction)

Place 25g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500mL of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500mL volumetric flask and dilute with purified water to volume; the diluted solution is *Solution S1*.

Use *Solution S1* within 4 hours of preparation.

Solution S2 (Toluene extraction)

Place 2.0g of the test material in a 250-mL borosilicate glass flask with a ground-glass neck. Add 80mL of toluene and boil under a reflux condenser for 1.5 hours, stirring constantly. Allow to cool to 60°C and add 120 mL of methanol with continued stirring. Pass the resulting solution through a sintered-glass filter. Rinse the flask and the filter with 25mL of a mixture of 40 volumes of toluene and 60 volumes of methanol add the rinsing to the filtrate, and dilute to 250mL with the same mixture of solvents to produce *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5g in a borosilicate glass flask with a ground-glass neck. Add 100mL of *0.1M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100mL volumetric flask, and dilute to volume with *0.1 M hydrochloric acid*; the diluted solution is *Solution S3.*

Tests Using Special Solutions

B.1] Absorbance (2.4.7)

Determine the spectrum between 220 and 340nm in Solution S1.

Absorbance should be not more than 0.2.

B.2] Acidity or alkalinity

To 100mL of Solution S1 add 0.15mL of *BRP indicator solution*. Determine the titration volume of *0.01M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100mL portion of Solution S, add 0.2mL of *Methyl orange solution*. Determine the titration volume of *0.01M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not More than 1.0mL of *0.01N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3] Plastic Additives

These tests should be carried out in whole or in part as required due to the stated composition of the material.

B.3.1] Phenolic Antioxidants

Solvent mixture: A mixture of equal volumes of *acetonitrile* and *tetrahydrofuran.*

Sample solution S2E. Evaporate 50mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the resulting residue with 5.0 mL of the Solvent mixture. Prepare a blank solution from the blank solution corresponding to Solution S2.

Sample solution S2F. Evaporate 50mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the residue with 5.0mL of *methylene chloride*. Prepare a blank solution from the blank solution corresponding to Solution S2.

Reference solution (k). A 0.01% of *Butylated Hydroxytoluene RS,* 0.016% of *Plastic Additive 02 RS*, 0.016% of *Plastic Additive 03 RS,* and 0.016% of *Plastic Additive 04 RS* in the solvent mixture.

Reference solution (l). A 0.016% of *Plastic Additive 04 RS* and *0.016% of Plastic Additive 05 RS* in *methylene chloride*

Note: Of the following reference solutions, prepare only those that are necessary for the analysis of the phenolic antioxidants stated in the composition of the substance to be examined

Test A

Determine by liquid chromatography (2.4.14).

If the substance to be examined contains additive butylated hydroxytoluene and/or additive ethylene bis[3,3-bis[3-(1,1dimethylethyl)-4-hydroxyphenyl]butanoate

Chromatographic system

- a stainless steel column 25cm x 4.6mm, packed with octadecylsilane bonded to porous silica microparticles (5 µm)
- mobile phase: a mixture of 70 volumes of *tetrahydrofuran,* 60 volumes of *acetronitrile*, and 10 volumes of *water*
- flow rate: 1.5 mL/minute
- spectrophotometer set at 280nm
- injection volume: 20µL

Inject reference solution (k).The test is not valid unless the resolution between the peaks due to *Plastic Additive 02 RS* and *Plastic Additive 03 RS* peaks is not less than 2.0 and the column efficiency is not less than 2500 theoretical plates calculated for *Butylated Hydroxytoluene RS.*

Inject Sample solution 12 corresponding blank solution, Reference solution (k), Run the chromatogram for about 30 minutes. The peak areas of Sample solution 12 are less than the corresponding peak areas of reference solution (k).

Note: Sample solution S2E shows only peaks caused by antioxidants stated in the reference solution (k) and minor peaks that also correspond to the blank solution.

Test B

If the chromatogram obtained via Test A for Test solution S2E shows a peak with the same retention time as the last antioxidant eluted from Reference solution K.

Determine by liquid chromatography (2.4.14).

Chromatographic system

Carry out the test as described in Test A with the following modifications

- mobile phase: a mixture of 45 volumes *of 2 propanol* 50 volumes of *methanol* and 5.0 volumes of *water*
- flow rate: 1.5mL/minute
- spectrophotometer set at 280nm
- injection volume: 20µL

Inject reference solution (l). The test is not valid unless the resolution between the peaks due to *Plastic Additive 04 RS* and *Plastic Additive 05 RS* peaks is not less than 2.0.

Inject Sample solution S2F corresponding blank solution, Reference solution (l). The peak areas of Sample solution S2F are less than the corresponding peak areas of Reference solution (l).

Note: Sample solution 13 shows only peaks caused by antioxidants stated in the reference solution (l) and minor peaks that also correspond to the blank solution.

B.3.2] Amides and Stearic Acid

Sample solution S2G: Evaporate 100mL of Solution S2 to dryness under vacuum at 45°C. Dissolve the resulting residue with 2.0mL of acidified *methylene chloride*.

Reference solution (r) A 0.2% of *Stearic Acid RS* prepared in *methylene*

Reference solution (s) A 0.08% of *Plastic Additive 12 RS* prepared in *methylene chloride*

Reference solution (t) A 0.08% of *Plastic Additive 13 RS* prepared in *methylene chloride.*

Test A

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254.*

Mobile phase. a mixture of 75 volume of *trimethylpantane* and 25 volumes of *ethanol.*

Apply to the plate 10µL of sample solution S2G, reference solution (r). Develop the plates over a path of 10 cm with mobile phase. After development, dry the plate in air and examine by spray with 2.0 % w/v 2, 6-dichlorophenol-indophenol sodium in dehydrated alcohol and heat in an oven at 120°C for a few minutes to intensify the spots. Any spot corresponding to additive stearic acid in the chromatogram obtained with sample solution S2G is not more intense than the spot in the same position in the chromatogram of the corresponding reference solution (r).

Test B

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*

Mobile phase A. Hexane

Mobile phase B. A mixture of 95 volumes of *methylene chloride* and 5.0 volumes of *methanol.*

Apply to the plate 10µL of sample solution S2G, reference solution (s) and reference solution (t). Develop the plates Over a path of 13cm with Mobile phase A and Over a path of 10cm with Mobile phase B respectively. After development, dry the plate in air and examine by spray with 40% *phosphomolybdic acid* in *alcohol* heat in an oven at 120°C for a few minutes to intensify the spots. Any spot corresponding to additive oleamide or erucamide in the chromatogram obtained with sample solution S2G is not more intense than the spot in the same position in the chromatogram of reference solution (s) and reference solution (t).

B.4] Related Substances (Residual Monomers / Residual Solvents)

B.4.1] Vinyl Acetate

Test solution: Place 0.25 to1.0g of the test material into a 300mL conical flask containing a magnetic stirrer. Prepare an extraction blank starting with an otherwise empty 300mL conical flask. Add 40mL of *xylene* and boil under a reflux condenser with stirring for 4 hours. After heating, continue stirring, allowing the solution to cool to the point that precipitation starts. Slowly add 25mL of alcoholic *potassium hydroxide*. Boil again under a reflux condenser for 3 hours with continued stirring. While stirring, allow the solution to cool, rinse the condenser with 50mL of water and add 30 mL of *0.05M sulphuric acid* to the flask. Transfer the contents of the flask to a 400-mL beaker, rinsing the flask with the following:

2.0 quantities, 50mL each, of a 200gram/ /L solution of anhydrous sodium sulphate

3.0 quantities, 20mL each, of water

Add the rinsings to the flask.

Titrate the excess sulphuric acid in Test solution with *0.1M sodium hydroxide*, determining the endpoint potentiometrically (2.4.25). Carry out a titration of the extraction blank.

Determine the amount of titrant (mL) required by subtracting the titrant volume used for the extraction blank (mL) from the titrant volume used for the extract (mL). Determine the amount of vinyl acetate by multiplying the volume of titrant required by the quantity 8.609mg/mL. The content of vinyl acetate is calculated as:

Content of vinyl acetate (weight%) = [amount of vinyl acetate (mg)/weight of material extracted (g)]/10.

Content of vinyl acetate

For containers: Not more than 25% by weight

For tubing: Not more than 30% by weight

B.5] Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.31).

The method used to perform the Total Organic Carbon analyses should have a limit of detection of 0.2mg/L (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20mg/L (which encompasses the TOC limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank Total Organic Carbon concentrations is not more than 5mg/L.

B.6] Extractable Metals

Solution S3 is used for extracting acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A).

All metals: Report the measured value in Solution S3 at values above 0.01mg/L (ppm), corresponding to 0.025µg/g. If the measured values are below these values, report the result as less than 0.01mg/L (ppm), corresponding to less than 0.025µg/g.

6.2.1.2.8. Polycarbonate

A] Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800 cm^{-1} to 600 cm^{-1} (2.6–16 µm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of the *Polycarbonate RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and RS spectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

The thermogram of the specimen is similar to the thermogram of *Polycarbonate RS*, and the melting peak temperature obtained from the thermogram of the specimen does not differ from that of the RS by more than 8.0°. Note that the results of the DSC analysis are strongly dependent on the amount of plasticizer in the test article.

B] Chemical Tests

Preparation of Special Solutions for subsequent tests on Polycarbonate

Solution S1 (Water extraction)

Place 25g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500mL of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500mL volumetric flask and dilute with purified water to volume; the diluted solution is *Solution S1*.

Use *Solution S1* within 4 hours of preparation.

Solution S2 (Acid extraction)

Place 5g in a borosilicate glass flask with a ground-glass neck. Add 100mL of *0.1M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100mL volumetric flask, and dilute to volume with *0.1M hydrochloric acid*; the diluted solution is *Solution S2.*

Tests Using Special Solutions

B.1] Absorbance (2.4.7)

Determine the spectrum between 220 and 340nm in Solution S1

Absorbance should be not more than 0.20

B.2] Acidity or alkalinity

To 100mL of Solution S1 add 0.15mL of *BRP indicator solution*. Determine the titration volume of *0.01M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100mL portion of Solution S, add 0.2mL of *Methyl orange solution*. Determine the titration volume of *0.01M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5mL of *0.01M hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3] Related Substances (Residual Monomers / Residual Solvents)

B.3.1] Residual Solvents

By Head Space Gas Chromatography (2.4.13):

Test solution. Weigh 1.0g of the test material and place it in a 20-mL headspace vial. Add 10mL of *N, N,-dimethylformamide*, cap the vial closed, and sonicate for 4 hours. Cool to room temperature. Prepare a sample blank in a similar fashion.

Residual solvents primary solution. Weigh 500mg each of *dichloromethane*, *toluene,* and e*thylbenzene* and 1250mg of *chlorobenzene* into a 50mL volumetric flask; dissolve and adjust with *N,N,-dimethylformamide* to volume.

Residual solvents stock solution. Transfer 5mL of the Residual solvents primary solution into a 100mL volumetric flask; adjust with *N, N-dimethylformamide* to volume.

Reference solutions. Pipet 0, 2, 3, 4, 5, and 6mL of the Residual solvents stock solution into individual 100mL volumetric flasks, dilute with *N-N-dimethylformamide* to volume and mix well. The six reference standards thus obtained (Reference solution blank and WS1 through WS5) contain, respectively, 0, 10, 15, 20, 25, and 30mg / /L of *dichloromethane, toluene*, and *ethylbenzene* and 0, 37.5, 50, 62.5, and 75mg/ /L of *chlorobenzene.*

Chromatographic system

- a capillary column 30m × 0.32mm, packed with 100% bonded and cross linked polyethylene glycol (5µm)
- temperature:
  - column: Start at 50°C, hold for 20 min. Heat to 165°C at 6°C/min, hold for 20 min
  - inlet port.140 °C
  - detector 250°C
- flame ionization detector
- flow rate. adjust to provide a constant pressure of 10 psi, using Helium as carrier gas
- Injection volume: 1µL, split

Head space conditions

Temperatures

- Thermostating: 115°C
- Needle: 110°C
- Transfer: 120°C
- Thermostating, 60 min
- Pressurization, 0.5 min
- Injection, 0.1 min
- Withdrawal, 0.2 min
- Carrier gas pressure, 20 psi

Conditioning. Inject the reference solution blank three times into the chromatographic system.

Inject reference solution WS3 five times into the chromatographic system. The test is not valid unless, the relative standard deviation of the peak areas in the chromatogram obtained with reference solution WS3 for is not less than 5.0%. The symmetry factor for the caprolactam peak obtained for the third injection must be between 0.8 and 1.3.

Rinsing. Inject the Reference solution blank once.

Calibration, front of bracket. Inject each of the five Reference solutions once. Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their analyte concentrations for each analyte. The correlation coefficient (r2) obtained for the best-fit linear regression line must be not less than 0.99.

Rinsing. Inject the Reference solution blank once.

Sample. Inject each test solution once, including the blank. Inject not more than six test solutions.

Rinsing: Inject Reference solution blank once.

Calibration, back of bracket: Inject each of the five Reference solutions once.

Calculations: Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their analyte concentrations (using the front and back of the bracket). The correlation coefficient (r2) obtained for the best-fit linear regression line must be not more than 0.99. Calculate the amount of each analyte in the test solution by putting the peak area obtained for the test solution into the calibration curve.

Calculate the amount of each in the test material by multiplying this result by a factor of 10 and dividing the product by the weight of the test material in g, producing a result in µg/g.

Analyte (µg/g) = (Analyte in Sample solution (mg/L) × 10) ÷ weight of test material, g.

B.3.1] Bisphenol A

[NOTE—*Bisphenol A is monitored although it is a residual monomer and not an additive*.]

Test solution. Weigh 1.0g of the test material and place it in a 250mL round-bottom flask. Add 50mL of *methylene chloride* and heat at 50°C for 1.0 hours under a reflux condenser to dissolve the test material. Cool the solution to room temperature and slowly add 75mL of *methanol* to the room-temperature solution, with continuous stirring. Place in a refrigerator for 2 hours to cool the resulting solution. Filter the cooled solution through a sintered-glass filter. Wash the round-bottom flask and the filter twice with 15mL of *methanol*. Evaporate the filtrate to dryness under vacuum at 45°C. Dissolve the residue in 5mL of *methylene chloride*. Add 0.5mL of this solution and 0.5mL of N,O-bis(trimethylsilyl)trifluoroacetamide to a 1.5-mL vial and close the vial immediately. Heat the closed vial at 40°C for 2 hours and then cool to room temperature. Prepare a sample blank in a similar fashion.

Bisphenol A primary solution. Weigh 20mg of *Bisphenol A RS* in a 200mL volumetric flask; dissolve and dilute with *methylene chloride* to volume.

Reference solutions. Pipet 0, 5, 10, 20, 30, and 40mL of the Bisphenol A primary solution into six 100mL volumetric flasks. Dilute with *methylene chloride* to volume and mix well. The six reference standards thus obtained (Reference solution blank and WS1 through WS5) contain, respectively, 0, 5, 10, 20, 30, and 40 mg/ /L of Bisphenol A.

Add 0.5mL each of the Reference solutions and 0.5mL of N,O-bis(trimethylsilyl)trifluoroacetamide to separate 1.5-mL vials and close the vials immediately. Heat the closed vials at 40°C for 2 hours and then cool to room temperature.

Chromatographic system

- a capillary column 25m × 0.25mm, packed with 100% dimethylpolysilxane (0.25µm)
- temperature:
  - column: 250°C
  - inlet port
  - detector 300 °C
- flame ionization detector
- flow rate: adjust to provide a constant pressure of 13 psi, using Helium as carrier gas
- Injection volume: 2µL, split

Head space conditions

Temperatures

- Thermostating: 115°C
- Needle: 110°C
- Transfer: 120°C
- Thermostating, 60 min
- Pressurization, 0.5 min
- Injection, 0.1 min
- Withdrawal, 0.2 min
- Carrier gas pressure, 20 psi

Conditioning. Inject the reference solution blank three times into the chromatographic system.

Inject reference solution WS3 five times into the chromatographic system. The test is not valid unless, the relative standard deviation of the peak areas in the chromatogram obtained with reference solution WS3 for is not less than 5.0%.

Rinsing: Inject the Reference solution blank twice.

Calibration, front of bracket: Inject each of the five Reference solutions once. Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their bisphenol A concentrations. The correlation coefficient (r2) obtained for the best-fit linear regression line must be not less than 0.98.

Rinsing: Inject the Reference solution blank once.

Sample: Inject each test solution once, including the Sample blank. Inject not more than six test solutions.

Rinsing: Inject the Reference solution blank once

Calibration, back of bracket: Inject each of the five Reference solutions once.

Calculations: Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their bisphenol A concentrations (front and back of bracket). The correlation coefficient (r2) obtained for the best-fit linear regression line must be not less than 0.98. Calculate the amount of bisphenol A in the Sample solution by putting the peak area obtained for the Sample solution into the calibration curve.

Calculate the amount of bisphenol A in the test material by multiplying this result by a factor of five and dividing the product by the weight of the test material in g, producing a result in µg/ /g,

Bisphenol A (µg/ /g) = (Bisphenol A in test solution (mg/ /L) × 5) ÷ weight of test material

Not more than 100µg/g.

B.4] Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the TOC analyses should have a limit of detection of 0.2mg/L (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20mg/L (which encompasses the TOC limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank Total Organic Carbon concentrations is not more than 5 mg/L.

B.5] Extractable Metals

Solution S2 is used for extracting acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A)**.**

Arsenic, lead, cadmium, mercury, cobalt, nickel, and vanadium: Report the measured value in Solution S3 at values above 0.01mg/L (ppm), corresponding to 0.025µg/g. If the measured values are below these values, report the result as less than 0.01mg/L (ppm), corresponding to less than 0.025µg/g. Additional acceptance criteria for certain metals are provided as follows.

6.2.1.2.9. Polyamide 6

A] Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800cm^{-1} to 600cm^{-1} (2.6–16µm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of the *Polyamide 6 RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and RS spectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

The thermogram of the specimen is similar to the thermogram of *Polyamide 6 RS*, and the melting peak temperature obtained from the thermogram of the specimen does not differ from that of the RS by more than 8.0°. Note that the results of the DSC analysis are strongly dependent on the amount of plasticizer in the test article.

B] Chemical Tests

<u>Preparation of Special Solutions for subsequent tests on Polyamide 6</u>

Solution S1 (Water extraction)

Place 25g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500mL of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500mL volumetric flask and dilute

with purified water to volume; the diluted solution is *Solution S1*. Use *Solution S1* within 4 hours of preparation.

Solution S2 (Acid extraction)

Place 5 g in a borosilicate glass flask with a ground-glass neck. Add 100mL of *0.1M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100mL volumetric flask, and dilute to volume with *0.1M hydrochloric acid*; the diluted solution is *Solution S2*.

Solution S3 (Phenol extraction)

Dissolve 1.0g of the test material in 50mL of phenol by heating at 50°C for 4 hours with constant stirring. This process produces *Solution S3*. Prepare a blank solution.

Tests Using Special Solutions

B.1] Absorbance (2.4.7)

Determine the spectrum between 220 and 340 nm in Solution S1.

Absorbance should be not more than 0.25

B.2] Acidity or alkalinity

To 100 mL of Solution S1 add 0.15 mL of BRP indicator solution. Determine the titration volume of *0.01 M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100mL portion of Solution S, add 0.2mL of *Methyl orange solution*. Determine the titration volume of *0.01M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5mL of *0.01N sodium hydroxide* is required to change the colour of the indicator to blue.

Not more than 4.0mL *of 0.01N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3] Free Base Functions

Perchloric acid in 70% phenol. Dissolve approximately 0.72g (target 0.710–0.7250g) of *perchloric acid* in 50mL of phenol.

Titrate 50mL of solution S3 with Perchloric acid in 70% *phenol*, determining the end-point potentiometrically (2.4.25). Carry out a blank titration using phenol as extraction blank.

The difference between the titration volumes, extract versus extraction blank, is not more than 0.4mL.

B.4] Related Substances (Residual Monomers / Residual Solvents)

B.4.1] Caprolactam.

Determine by gas chromatography (2.4.13).

Test Solution. Dissolve 1.0g of the test substance in sufficient quantity of *formic acid*. Dilute to 10mL with same solvent.

Caprolactam primary solution. Dissolve 125mg of *Caprolactam RS* in *formic acid* and dilute to 50mL with same solvent.

Reference solutions. Pipet 0, 2, 4, 6, 8, and 10mL of the Caprolactam primary solution into six 20mL volumetric flasks. Dilute with anhydrous formic acid to volume. The six reference standards thus obtained

(blank and WS1 through WS5) contain, respectively, 0, 250, 500, 750, 1000, and 1250 mg/ /L of caprolactam.

Chromatographic system

- a capillary column 2m × 4mm, packed with silanized diatomaceous earth for gas chromatography impregnated with 10% m/m of polyethylene glycol 20000
- temperature:
  - column. 170 °C
  - inlet port.
  - detector 250 °C
- flame ionization detector
- flow rate 25mL/min. using Helium as carrier gas

Conditioning. Inject 1µL of the Reference solution blank three times into the chromatographic system.

Inject Reference solution WS4 five times into the chromatographic system. The test is not valid unless, the relative standard deviation of the peak areas in the chromatogram obtained with reference solution WS4 for is not less than 5%. The symmetry factor for the caprolactam peak obtained for the third injection must be between 0.8 and 1.3.

Rinsing. Inject 1µL Reference solution blank once.

Calibration, front of bracket: Inject each of the five Reference solutions once. Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their caprolactam concentrations. The correlation coefficient (r2) obtained for the best-fit linear regression line must be not less than 0.98.

Rinsing. Inject 1µL the Reference solution blank once.

Sample. Inject 1µL each test solution once. Inject not more than six test solutions.

Rinsing. Inject 1µL Reference solution blank once.

Calibration, back of bracket. Inject 1µLeach of the five Reference solutions once.

Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their caprolactam concentrations (both front and back of bracket). The correlation coefficient (r2) obtained for the best-fit linear regression line must be not less than 0.98. Calculate the amount of caprolactam in the test solution by putting the peak area obtained for the test solution into the calibration curve. Calculate the amount of caprolactam in the test material by multiplying this result by a factor of 10 and dividing the product by the weight of the test material in g, producing a result in weight %.

Not more than1%.

B.5] Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.31).

The method used to perform the Total Organic Carbon analyses should have a limit of detection of 0.2mg/L (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20mg/L (which encompasses the Total Organic Carbon limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank Total Organic Carbon concentrations is not more than 5mg/L.

B.6] Extractable Metals

Solution S2 is used for extracting acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A)

Arsenic, lead, cadmium, mercury, cobalt, nickel, and vanadium: Report the measured value in *Solution S3* at values above 0.01mg/L (ppm), corresponding to 0.025µg/g. If the measured values are below these values, report the result as less than 0.01mg/L (ppm), corresponding to less than 0.025µg/g. Additional acceptance criteria for certain metals are provided as follows**.**

6.2.1.3. Plastic Containers for Ophthalmic Preparations

Plastic containers for ophthalmic preparations are made from plastic composed of a mixture of homologous compounds having a range of molecular weights. Such plastics frequently contain other substances such as residues from the polymerisation process, plasticisers, stabilisers, antioxidants, lubricants and pigments. For deciding the suitability of a plastic for use as a container for opthalmic preparations, factors such as the composition of the plastic, processing and cleaning procedures, contacting media, adhesives, adsorption and permeability of preservatives, conditions of storage, etc. should be evaluated by appropriate additional specific tests.

Plastic containers for ophthalmic preparations comply with the following tests.

Leakage test; Collapsibility test. Comply with the tests described under Plastic Containers for Parenteral Preparations (6.2.1.1).

Clarity of aqueous extract; Non-volatile residue. Comply with the tests described under Plastic Containers for Non- Parenteral Preparations (6.2.1.2.).

Eye irritation test. This test is designed to evaluate responses to the instillation of extracts of material under examination in the eye of a rabbit.

Extracting media– *(a) Sodium Chloride Injection (b) Vegetable Oil*.

Test animals. Select healthy, albino rabbits having no visible eye irritation and not previously used for an eye irritation test. The animal house should be designed and maintained so as to exclude sawdust, wood chips, or other extraneous materials that might produce eye irritation. Examine both eyes of the animals before testing and use only those animals without eye defects or eye irritations.

To test the suitability of the rabbit ocular system in use for a given set of samples, select one test animal and proceed as shown under procedure using 100µL of a blank prepared as directed under Systemic injection test in one eye and 100µL of sterile water for injection in the other eye. The rabbit ocular system is suitable if no significant differences are found between the two eyes.

Procedure. Use three albino rabbits for each extract to be examined. Restrain the animals firmly but gently until quiet. Gently pull the lower lid away from the eyeball to form a cup, and instil about 100µL of *sterile water for injection*. Hold the lid together for about 30 seconds. Instil in to the other eye 100µL of the sample extract prepared as directed underSystemicinjection test. Examine the eyes 24, 48 and 72 hours after instillation. The requirements of the test are met if the sample extract shows no significant irritant response during the observation period over that with the blank extract and the rabbit ocular system is suitable. If irritation is observed in the control eyes treated with sterile water for injection or if the rabbit ocular system is shown not to be suitable, repeat the test using three additional rabbits. In the repeat test, all the rabbits meet the test requirement.

Biological Tests. Perform the test for Biological Reactivity, *In Vitro* (2.2.23). Materials that meet the requirements of this test are not required to undergo testing as described in test for Biological Reactivity, *In Vivo* (2.2.24).

6.2.2. Glass Containers

Glass containers may be colourless or coloured.

Neutral glass is a borosilicate glass containing significant amounts of boric oxide, aluminium oxide, alkali and/or alkaline earth oxides. It has a high hydrolytic resistance and a high thermal shock resistance.

Soda-lime-silica glass is a silica glass containing alkali metal oxides, mainly sodium oxide and alkaline earth oxides, mainly calcium oxide. It has only a moderate hydrolytic resistance.

According to their hydrolytic resistance, glass containers are classified as:

- Type I glass containers which are of neutral glass, with a high hydrolytic resistance, suitable for most preparations whether or not for parenteral use,
- Type II glass containers which are usually of soda-lime-silica glass with high hydrolytic resistance resulting from suitable treatment of the surface. They are suitable for most acidic and neutral, aqueous preparations whether or not for parenteral use,
- Type III glass containers which are usually of soda-lime-silica glass with only moderate hydrolytic resistance. They are generally suitable for non-aqueous preparations for parenteral use, for powders for parenteral use (except for freeze-dried preparations) and for preparations not for parenteral use.

Glass containers intended for parenteral preparations may be ampoules, vials or bottles. The glass used in the manufacture of such containers complies with one of the requirements for hydrolytic resistance given below.

Containers of Type II or Type III glass should be used once only. Containers for human blood and blood components must not be re-used. Glass containers with a hydrolytic resistance higher than that recommended for a particular type of preparation may generally also be used.

Containers for parenteral preparations are made from uncoloured glass except that coloured glass may be used for substances known to be light - sensitive; in such cases, the containers should be sufficiently transparent to permit visual inspection of the contents.

Hydrolytic resistance

The tests to be done for defining the type of glass are given in Table 2.

Table 2

Type of container	**Test to be done**
Type I and Type II glass containers to distinguish from Type III glass containers	Test 1 (surface test)
Type I and Type II glass containers where it is necessary to determine whether the high hydrolytic resistance is due to the chemical composition or the surface treatment	Tests 1 and 2

Test 1. Carry out the determination on the unused containers. The number of containers to be examined and the volumes of test solution to be used are given in Table 3.

Table 3

Nominal capacity of container (mL)	Number of containers to be used	Volume of test solution to be used for titration (mL)
Up to 3	At least 20	25.0
5 or less	At least 10	50.0
6 to 30	At least 5	50.0
More than 30	At least 3	100.0

Remove any debris or dust from the containers. Rinse each container at least twice with *water* at room temperature. Just before the test rinse each container with freshly prepared *distilled water* and allow to drain. Complete the cleaning procedure from the first rinsing in not less than 20 minutes and not more than 25 minutes. Fill the containers to the brim with freshly prepared distilled water, empty them and determine the average overflow volume.

Heat closed ampoules on a water-bath or in an air-oven at about 50°C.Fill the ampoules with freshly prepared *distilled water* to the maximum volume compatible with sealing them by fusion of the glass and seal them. Fill bottles or vials to 90% of their calculated overflow volume and cover them with borosilicate glass dishes or aluminium foil previously rinsed with freshly prepared *distilled water*. Place the containers in an autoclave containing water so that they remain clear of the water. Close the autoclave, displace the air by passage of steam for 10 minutes, raise the temperature from 100°C to 121°C over 20 minutes, maintain a temperature of 121°C for 60 minutes and reduce the temperature from 121°C to 100°C over 40 minutes, venting to prevent vacuum.

Remove the containers from the autoclave and cool them in a bath of running tap water. Carry out the following titration within 1 hour of removing the containers from the autoclave. Combine the liquids from the containers under examination, measure the volume of test solution specified in Table 2 into a conical flask and add 0.15mL of *methyl red solution* for each 50mL of liquid. Titrate with *0.01M hydrochloric acid* taking as the end-point the colour obtained by repeating the operation using the same volume of freshly prepared *distilled water*. The difference between the preparations represents the volume of *0.01M hydrochloric acid* required by the test solution. Calculate the volume of *0.01M hydrochloric acid* required for each 100mL of test solution, if necessary. The result is not greater than the value stated in Table 4.

Table 4

Capacity of container [corresponding to 90% average overflow volume (mL)]	Volume of 0.01M hydrochloric acid /100mL of test solution	
	Type I or II glass (mL)	Type III glass (mL)
Not more than 1	2.0	20.0
More than 1 but not more than 2	1.8	17.6
More than 2 but not more than 5	1.3	13.2
More than 5 but not more than 10	1.0	10.2
More than 10 but not more than 20	0.80	8.1
More than 20 but not more than 50	0.60	6.1
More than 50 but not more than 100	0.50	4.8
More than 100 but not more than 200	0.40	3.8
More than 200 but not more than 500	0.30	2.9
More than 500	0.20	2.2

Test 2. Examine the number of containers indicated in Table 2. Rinse the containers twice with water and then fill completely with a 4% v/v solution of *hydrofluoric acid* and allow to stand at room temperature for 10 minutes. Empty the containers and rinse carefully five times with water. Carry out the procedure described under Hydrolytic resistance. Compare the results with the limiting values given in Table 3. For Type I glass the values obtained with the hydrofluoric acid-treated containers are closely similar to those stated in the Table for Type I or Type II glass. For Type II glass the values obtained with the hydrofluoric acid-treated containers greatly exceed those given in the Table for Type I or Type II glass and are similar to those given for Type III glass.

Arsenic. Glass containers for aqueous parenteral preparations should comply with the following test. Carry out the test on ampoules the inner and outer surfaces of which are washed five times with freshly distilled *water*.

Prepare a test solution as described in the test for Hydrolytic resistance for an adequate number of containers to produce 50mL. Pipette 10mL of the test solution from the combined contents of all the containers into a flask, add 10mL of *nitric acid* and evaporate to dryness on a water-bath. Dry the residue in an oven at 130°C for 30 minutes. Cool, add to the residue10.0mL of *hydrazine-molybdate reagent*, swirl to dissolve and heat under reflux on a water-bath for 20 minutes. Cool to room temperature. Determine the absorbance of the resulting solution at the maximum at about 840nm (2.4.7), using 10.0mL of *hydrazine-molybdate reagent* as the blank. The absorbance of the test solution does not exceed the absorbance obtained by repeating the determination using 0.1mL of *arsenic standard solution (10ppm As)* in place of the test solution (0.1ppm).

6.2.3. Metal Containers

Collapsible Metal Tubes for Ophthalmic Ointments-Metal collapsible tubes comply with the following test for metal particles.

Select a sample of 50 tubes from the lot to be tested and clean each tube by vibration and/or "blowing". (A lot may be either the tube manufacturer's day's production or a consignment delivered to the tube user). Fill the tubes with a suitable molten eye ointment base, close the open end of each tube by a double fold and allow the filled tubes to cool overnight at a temperature of 15°C to 20°C.

Assemble a metal bacteriological filter with a 4.25-cm filter paper of suitable porosity supported on suitable perforated plate in place of the standard sintered carbon disc and heat it in a suitable manner to a temperature above the melting range of the base. Remove the caps from the cooled tubes and apply uniform pressure to the closed end of each tube in turn, in such a manner that the time taken to express as much of the base as possible through each nozzle is not less than 20 seconds. Collect the extruded base from the 50 tubes in the heated filter, applying suction to the stem of the filter in order to draw the molten base through the filter paper. When the entire melted base has been removed, wash the walls of the filter and the filter paper with three successive quantities, each of 30mL, of chloroform, allow the filter paper to dry and immediately mount it between glasses for examination.

Examine the filter paper under oblique lighting with the aid of magnifying glass with a graticule of 1mm squares, one of which is sub-divided into 0.2mm squares and note (a) the number of all metal particles 1mm in length and longer, (b) the number in the range 0.5mm to less than 1mm and (c) the number in the range 0.2mm to less than 0.5 mm.

Carry out two further examinations with the filter paper in two different positions so that the lighting comes from different directions and calculate the average number of metal particles counted in each of the three ranges specified. Give each metal particle detected on the filter paper a score as follows and add the scores together.

Particles 1 mm and above	50
Particles 0.5 mm but less than 1 mm	10
Particles 0.2 mm but less than 0.5 mm	2
Particles less than 0.2 mm	Nil

The lot of tubes passes the test if the total score is less than 100 points; if the total score is more than 150 points, the lot fails the test. If the total score is between 100 and 150 (inclusive), the test is repeated on a further sample of 50 tubes and the lot passes the test if the sum of total scores in the two tests is less than 150 points.

6.3. CLOSURES FOR CONTAINERS

A closure for a container for an aqueous parenteral preparation or for a sterile powder is a packaging component which is in direct contact with the drug. A rubber closure is made of materials obtained by vulcanisation (cross-linking) of elastomers with appropriate additives. The elastomers are produced from natural or synthetic substances by polymerization - polyaddition or polycondensation. The nature of the principal components and of the various additives such as vulcanisers, accelerators, stabilising agents, pigments, etc. depends on the properties required for the finished closure. The requirements of this chapter do not apply to closures made from silicone elastomer, to laminated closures or to lacquered closures.

Rubber closures are used in a number of formulations and consequently different closures possess different properties.

NOTE 9: Closures made from plastics will be governed by all requirements covered in 6.2.1. and its subsections.

The closures chosen for use with a particular preparation should be such that the components of the preparation in contact with the closure are not adsorbed onto the surface of the closure to an extent sufficient to affect the product adversely. The closure should not yield to the product substances in quantities sufficient to affect its stability or to present a risk of toxicity. The closures should be compatible with the preparation for which they are used throughout the shelf-life of the product.

It shall be the responsibility of the user/manufacturer to ensure the compatibility of the pharmaceutical products and stability of the product in the package system. Towards this the user / manufacturer shall have in place a system of quality assurance with the supplier / convertor to ensure compliance of the components of the package with the requirement stated in this chapter at all times. The user should take the "risk-based approach" to determine the testing and its frequency required to ensure this.

The following test procedures apply to rubber closures which comprise wads (flat rubber discs), plugs (with or without skirt or flange) and caps (rubber covers held in position on the outsides of the containers by the tension of the rubber) so as to form with their appropriate seals an effective barrier against micro-organisms after sterilisation.

Identification of the type of rubber used for closures is not covered in the following tests. The tests given distinguish elastomer and non-elastomer closures but do not differentiate the various types of rubber.

Description. Rubber closures are elastic and either translucent or opaque; the colour depends on the additives used. They are homogeneous and practically free from flash and adventitious materials such as fibres, foreign particles and adhering rubber pieces.

Identification

A. Heat 1g to 2g in a heat-resistant test-tube over an open flame to dry the sample and continue heating until the vapours formed are condensed near the top edge of the test-tube. Deposit a few drops of the condensate on a

potassium bromide disc and examine by infrared absorption spectrophotometry (2.4.6), comparing with the spectrum obtained with the type (standard) sample.

B. The total ash (2.3.19) is within ±10% of the value obtained with the type sample (specimen).

Preparation of samples. Wash the closures by agitation in a 0.2% w/v solution of an anionic surface-active agent for 5 minutes at room temperature. Rinse five times with *water*, place a number of the washed closures corresponding to a surface area of about 100cm^2, in a suitable container of borosilicate glass or inert material, and add 200mL of water/100 cm^2, surface area of the closures and weigh. Cover the mouth of the container with aluminium foil or a borosilicate glass beaker and heat in an autoclave so that a temperature of 119°C to 123°C is reached within 20 to 30 minutes and maintain at that temperature for 30 minutes. Cool to room temperature over about 30 minutes and make up to the original weight with *water for injection.* Shake and immediately separate the solution from the closures by decantation (Solution A).

Prepare a blank in the same manner using 200mL of *water for injection*.

Dry the treated closures at 64°C to 66°C at a pressure not exceeding 0.7 kPa for 24 hours.

Appearance of solution. Solution A is not more opalescent than opalescence standard OS3 (2.4.1), and not more intensely coloured than reference solution BYS6 (2.4.1).

Acidity or alkalinity. To 20mL of solution A add 0.1mL of *bromothymol blue solution*. Not more than 0.3mL of *0.01M sodium hydroxide* or 0.8mL of *0.01M hydrochloric acid* is required to change the colour of the solution to blue or yellow respectively.

Light absorption. Carry out the test within 4 hours of preparing solution A. Filter solution A through a membrane filter with a nominal pore size of 0.5µm and reject the first few mL of the filtrate. Measure the light absorption of the filtrate in the range 220 to 360nm (2.4.7), using as the blank a solution prepared in the same manner as solution A but using 200mL of *water* without the closures. The absorbance is not more than 2.0; if necessary, dilute the filtrate before measurement and correct the results for the dilution.

Reducing substances. Carry out the test within 4 hours of preparing solution A. To 20mL of solution A, add 1mL of *1M sulphuric acid* and 20mL of *0.002 M potassium permanganate* and boil for 3 minutes. Cool, add 1g of *potassium iodide* and titrate immediately with *0.01 M sodium thiosulphate* using 0.25mL of *starch solution,* added towards the end of the titration, as indicator. Repeat the operation using 20 mL of the blank prepared in the test for Light absorption. The difference between the titration volumes is not more than 7.0mL.

Heavy Metals (2.3.13). 20mL of solution A complies with the limit test for heavy metals, Method A.

Residue on evaporation. Evaporate 50mL of solution A to dryness on a water-bath and dry at 105°C. The residue weighs not more than 4.0mg.

Volatile sulphides. Place closures, cut if necessary, with a total surface area of 20±2cm^2 in a 100-mL conical flask and add 50mL of a 2% w/v solution of *citric acid*. Place a piece of *lead acetate paper* over the mouth of the flask and maintain the paper in position by placing over it an inverted weighing bottle. Heat in an autoclave at 121±2°C for 30 minutes. Any black stain on the paper is not more intense than that of a standard prepared at the same time in the same manner using 0.154mg of *sodium sulphide* and 50mL of a 2%w/v solution of *citric acid*.

Sterilisation test. The closures 'prepared' in the aforementioned manner shall not soften or become tacky and there shall be no visual change in the closure.

Fragmentation test. This test is applicable to closures intended to be pierced by a hypodermic needle. For closures that are intended to be used for aqueous preparations, place a volume of *water* corresponding to the nominal volume minus 4mL in each of 12 clean vials, close the vials with the 'prepared'closures, secure with a cap and allow to stand for 16 hours. For closures that are intended to be used for dry preparations, close 12 clean vials with the 'prepared' closures. Using a lubricated, long-bevel (bevel angle of 10°C to 14°C) hypodermic needle with an external diameter of 0.8mm (21 SWG) fitted to a clean syringe, inject 1mL of *water* into the vial and remove 1 mL of air; carry out this operation 4 times for each closure, piercing each time at a different site. Use a new needle for each closure and check that the needle is not blunted during the test. Pass the liquid in the vials through a filter with a nominal pore size of 0.5µm. Count the number of fragments visible to the naked eye. The total number of fragments is not more than 10 except in the case of butyl rubber closures where the total number of fragments is not more than 15.

Self-sealability. This test is applicable to closures intended to be used with multidose containers. Fill 10 suitable vials with *water* to the nominal volume, close the vials with the 'prepared' closures and secure with a cap. For each closure, use a new hypodermic needle with an external diameter of 0.8mm (21 SWG) and pierce the closure 10 times, piercing each time at a different site. Immerse the vials upright in a 0.1% w/v solution of *methylene blue* and reduce the external pressure by 27kPa for 10 minutes. Restore the atmospheric pressure and leave the vials immersed for 30 minutes. Rinse the outside of the vials. None of the vials contains any trace of coloured solution.

Biological Tests. Perform the test for Biological Reactivity, *In Vitro* (2.2.23). Materials that meet the requirements of this test are not required to undergo testing as described in test for Biological Reactivity, *In Vivo* (2.2.24).

6.4. LABELS ON CONTAINER

6.4.1. Basic Statutes Governing Labelling

Requirements on Labelling of the packages/container for pharmaceuticals shall be governed as/the following provisions:

- Labelling requirements as/the Drugs & Cosmetics Act, 1940 and the Drugs & Cosmetics Rules, 1945 as amended from time to time.

- Section on Labelling covered in General Notices in the applicable version of the Indian Pharmacopoeia.