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determine the approximate concentrations of sodium oxide (and potassium oxide and calcium oxide, if present) by reference to calibration graphs produced from the reference solutions of suitable concentration.

FINAL DETERMINATION

If dilution is unnecessary add to each container a volume of the spectrochemical buffer solution equivalent to 5 per cent of the filling volume, mix well and determine sodium oxide, calcium oxide and potassium oxide, if present, by reference to calibration graphs. For the determination of the calcium oxide concentration by flame atomic spectrometry, the nitrous oxide/acetylene flame shall be used.

If dilution is necessary, determine sodium oxide, calcium oxide and potassium oxide, if present, following the procedures as described above. The measuring solutions shall contain 5 per cent *V/V* of the spectrochemical buffer solution. Concentration values less than 1.0 µg/ml are expressed to 2 decimal places, values greater than or equal to 1.0 µg/ml to 1 decimal place. Correct the result for the buffer addition and for dilution, if any.

CALCULATION

Calculate the mean value of the concentration of individual oxides found in each of the samples tested, in micrograms of the oxide per millilitre of the extraction solution and calculate the sum of the individual oxides, expressed as micrograms of sodium oxide per millilitre of the extraction solution using the following mass conversion factors:

- 1 µg of potassium oxide corresponds to 0.658 µg of sodium oxide,
- 1 µg of calcium oxide corresponds to 1.105 µg of sodium oxide.

Limits. For each container tested, the result is not greater than the value given in Table 3.2.1-7.

Table 3.2.1-7. – *Limit values in the test for surface hydrolytic resistance by flame atomic absorption spectrometry*

Filling volume (ml)	Maximum values for the concentration of oxides, expressed as sodium oxide (µg/ml)
	Glass containers Types I and II
Up to 1	5.00
Above 1 and up to 2	4.50
Above 2 and up to 5	3.20
Above 5 and up to 10	2.50
Above 10 and up to 20	2.00
Above 20 and up to 50	1.50
Above 50 and up to 100	1.20
Above 100 and up to 200	1.00
Above 200 and up to 500	0.75
Above 500	0.50

3.2.2. PLASTIC CONTAINERS AND CLOSURES FOR PHARMACEUTICAL USE

A plastic container for pharmaceutical use is a plastic article which contains or is intended to contain a pharmaceutical product and is, or may be, in direct contact with it. The closure is a part of the container.

Plastic containers and closures for pharmaceutical use are made of materials in which may be included certain additives; these materials do not include in their composition any substance that can be extracted by the contents in such quantities as to alter the efficacy or the stability of the product or to present a risk of toxicity.

The most commonly used polymers are polyethylene (with and without additives), polypropylene, poly(vinyl chloride), poly(ethylene terephthalate) and poly(ethylene-vinyl acetate).

The nature and amount of the additives are determined by the type of the polymer, the process used to convert the polymer into the container and the intended purpose of the container. Additives may consist of antioxidants, stabilisers, plasticisers, lubricants, colouring matter and impact modifiers. Antistatic agents and mould-release agents may be used only for containers for preparations for oral use or for external use for which they are authorised. Acceptable additives are indicated in the type specification for each material described in the Pharmacopoeia. Other additives may be used provided they are approved in each case by the competent authority responsible for the licensing for sale of the preparation.

For selection of a suitable plastic container, it is necessary to know the full manufacturing formula of the plastic, including all materials added during formation of the container so that the potential hazards can be assessed. The plastic container chosen for any particular preparation should be such that:

- the ingredients of the preparation in contact with the plastic material are not significantly adsorbed on its surface and do not significantly migrate into or through the plastic,
- the plastic material does not release substances in quantities sufficient to affect the stability of the preparation or to present a risk of toxicity.

Using material or materials selected to satisfy these criteria, a number of identical type samples of the container are made by a well-defined procedure and submitted to practical testing in conditions that reproduce those of the intended use, including, where appropriate, sterilisation. In order to confirm the compatibility of the container and the contents and to ensure that there are no changes detrimental to the quality of the preparation, various tests are carried out such as verification of the absence of changes in physical characteristics, assessment of any loss or gain through permeation, detection of pH changes, assessment of changes caused by light, chemical tests and, where appropriate, biological tests.

The method of manufacture is such as to ensure reproducibility for subsequent bulk manufacture and the conditions of manufacture are chosen so as to preclude the possibility of contamination with other plastic materials or their ingredients. The manufacturer of the product must ensure that containers made in production are similar in every respect to the type samples.

For the results of the testing on type samples to remain valid, it is important that:

- there is no change in the composition of the material as defined for the type samples,
- there is no change in the manufacturing process as defined for the type samples, especially as regards the temperatures to which the plastic material is exposed during conversion or subsequent procedures such as sterilisation,
- scrap material is not used.

Recycling of excess material of well-defined nature and proportions may be permitted after appropriate validation.

Subject to satisfactory testing for compatibility of each different combination of container and contents, the materials described in the Pharmacopoeia are recognised as being suitable for the specific purposes indicated, as defined above.

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corrected 6.0

3.2.2.1. PLASTIC CONTAINERS FOR AQUEOUS SOLUTIONS FOR INFUSION

DEFINITION

Plastic containers for aqueous solutions for infusion are manufactured from one or more polymers, if necessary with additives. The containers described in this section are not necessarily suitable for emulsions. The polymers most commonly used are polyethylene, polypropylene and poly(vinyl chloride). The specifications of this text are to be read in conjunction with section 3.2.2. *Plastic containers and closures for pharmaceutical use.*

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 suspended and which will withstand the tension occurring during use. 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 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.

The empty containers display no defects that may lead to leakage and the filled and closed containers show no leakage.

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

TESTS

Solution S. Use solution S within 4 h of preparation. Fill a container to its nominal capacity with *water R* and close it, if possible using the usual means of closure; otherwise close using a sheet of pure aluminium. Heat in an autoclave so that a temperature of 121 ± 2 °C is reached within 20 min

to 30 min and maintain at this temperature for 30 min. If heating at 121 °C leads to deterioration of the container, heat at 100 °C for 2 h.

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

Appearance of solution S. Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity. To a volume of solution S corresponding to 4 per cent of the nominal capacity of the container add 0.1 ml of *phenolphthalein solution R*. The solution is colourless. Add 0.4 ml of 0.01 M sodium hydroxide. The solution is pink. Add 0.8 ml of 0.01 M hydrochloric acid and 0.1 ml of *methyl red solution R*. The solution is orange-red or red.

Absorbance (2.2.25). Measure the absorbance of solution S from 230 nm to 360 nm, using the blank (see solution S) as the compensation liquid. At these wavelengths, the absorbance is not greater than 0.20.

Reducing substances. To 20.0 ml of solution S add 1 ml of dilute sulphuric acid *R* and 20.0 ml of 0.002 M potassium permanganate. Boil for 3 min. Cool immediately. Add 1 g of potassium iodide *R* and titrate immediately with 0.01 M sodium thiosulphate, using 0.25 ml of starch solution *R* as indicator. Carry out a titration using 20.0 ml of the blank. The difference between the titration volumes is not greater than 1.5 ml.

Transparency. Fill a container previously used for the preparation of solution S with a volume equal to the nominal capacity of the primary opalescent suspension (2.2.1) diluted 1 in 200 for a container made from polyethylene or polypropylene and 1 in 400 for other containers. The cloudiness of the suspension is perceptible when viewed through the container and compared with a similar container filled with *water R*.

LABELLING

The label accompanying a batch of empty containers includes a statement of:

- the name and address of the manufacturer,
- a batch number which enables the history of the container and of the plastic material of which it is manufactured to be traced.

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3.2.3. STERILE PLASTIC CONTAINERS FOR HUMAN 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 of manufacture of the containers are 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 correspond to the appropriate specifications, their quality is controlled by the methods indicated in those specifications (see 3.1. *Materials used for the manufacture of containers* and subsections).