PD ISO/TS 19807-2:2021



BSI Standards Publication

Nanotechnologies — Magnetic nanomaterials

Part 2: Specification of characteristics and measurement methods for nanostructured magnetic beads for nucleic acid extraction

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National foreword

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The UK participation in its preparation was entrusted to Technical Committee NTI/1, Nanotechnologies.

A list of organizations represented on this committee can be obtained on request to its committee manager.

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Published by BSI Standards Limited 2021

ISBN 978 0 539 02606 1

ICS 07.120

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This Published Document was published under the authority of the Standards Policy and Strategy Committee on 31 October 2021.

Amendments/corrigenda issued since publication

Date	Text affected

PD ISO/TS 19807-2:2021

TECHNICAL SPECIFICATION

ISO/TS 19807-2

First edition
2021-10-25

Nanotechnologies — Magnetic nanomaterials —

Part 2: Specification of characteristics and measurement methods for nanostructured magnetic beads for nucleic acid extraction

Nanotechnologies — Nanomatériaux magnétiques —

Partie 2: Spécification des caractéristiques et des méthodes de mesure pour les billes magnétiques nanostructurées pour l'extraction d'acide nucléïque

Reference number
ISO/TS 19807-2:2021(E)

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Foreword

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This document was prepared by Technical Committee ISO/TC 229, *Nanotechnologies*.

A list of all parts in the ISO/TS 19807 series can be found on the ISO website.

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Introduction

Magnetic beads are composed of a large number of magnetic nanoparticles immobilized within a nonmagnetic matrix with a size range between tens of nanometres and hundreds of micrometres (see Annex A). The immobilization matrix is typically based on silica or organic polymers. The beads are commonly supplied while dispersed in a liquid suspension, for example, ethanol, isopropanol, sodium azide solutions, pure water. Magnetic beads in liquid suspension have become one of the most widely used nanomaterials in the biological and chemical fields, due to their unique magnetic properties and interactions with applied magnetic fields.

When the size of a magnetic object is small enough, it will form a single magnetic domain, behaving as a single large macrospin. At yet smaller sizes (for iron oxide, typically less than 30nm[1]), the thermal energy of the object can be sufficient to result in frequent reorientations of the magnetization direction of the object. If the timescale of these reorientations is shorter than the timescale of the measurement, the term 'superparamagnetism' is used to describe this behaviour and the magnetic nano-objects are said to be superparamagnetic. In large non-interacting ensembles of such particles, the thermally induced switching events will result in the average magnetization of the ensembles being zero in the absence of an applied magnetic field. In the presence of an applied large field, the ensemble of magnetic nano-objects is observed to acquire a large net magnetization, as the magnetic field overcomes the thermal fluctuations and aligns the macrospins of the individual magnetic nano-objects within the ensemble. Beads, if incorporating a large fraction of magnetic nano-objects which exhibit this behaviour, are often referred to as "superparamagnetic beads". However, as the beads may not themselves be superparamagnetic, they are referred to as "magnetic beads" herein.

Magnetic beads have been applied in many fields, especially in biosensing applications[2] such as *in vitro* diagnostics, targeted drug delivery[3]-[5], magnetic resonance imaging[6], bioseparation[7], and genetic engineering[8], among others. For example, nucleic acids, which carry genetic information, can be extracted or isolated from blood, saliva, faeces, urine, leaves, viral lysates, using suitably functionalized magnetic beads.

The nucleic acids (DNA) and ribonucleic acid (RNA) carry the key information that organisms use to build or maintain their biostructures. Correctly identifying DNA offers immensely valuable information on health. In recent years, in the human blood stream, scientists have not only found circulating cell free DNA (cfDNA), but also circulating tumour DNA (ctDNA). Now ctDNA extraction is one of the most widely used liquid-biopsy methods to determine cancer or track cancer development. However, the content of ctDNA is only 1 % or less of the total cfDNA amount. The concentration of cfDNA is very low, generally 5 ng/ml blood to 30 ng/ml blood. Therefore, the development of reliable methods for extracting the ctDNA is critical. The proper description of physicochemical characteristics of magnetic beads for DNA extraction is both valuable for developers of extraction kits and for users applying them for DNA analysis.

Nucleic acid binding to magnetic beads relies on electrostatic interactions, hydrophobic interactions, hydrogen bonding or specific binding mechanisms to the bead surface. Once DNA or RNA from cell or tissue lysate is released into the solution, then nucleic acids can bind to surface-modified magnetic beads to form a "nucleic acid-magnetic bead complex".[9]-[19]

Then, the complex can be separated under a proper combination of magnetic field and magnetic field gradient. The eluate can wash away the residual impurities. Finally, the nucleic acids to be extracted can be obtained from the beads after desalination and purification.[9]-[19]

The different forms of magnetic beads and dispersing media for the extraction of nucleic acid will have different physicochemical characteristics such as specific surface area, bead concentration etc. All these characteristics will affect their performance to extract nucleic acid to varying extents. [9]-[19]

In common with other nanostructured materials, the manufacturing and material specification of composite magnetic beads are complex. Small variations in the synthesis conditions during bead manufacturing and functionalization can lead into dramatic shifts in the properties and binding capacities of the manufactured beads. This requires these products to have high manufacturing consistency. Currently, different manufacturers provide different characteristics and most of them

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never provide the measurement methods, so it is difficult for consumers or regulators to compare different products or to verify the characteristics, which increases the difficulty of further development of the application. Universally accepted material specification and test reports for magnetic beads are a requirement in order to ensure customer confidence and the quality of the nucleic acid extraction products.

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TECHNICAL SPECIFICATION **ISO/TS 19807-2:2021**

Nanotechnologies — Magnetic nanomaterials —

Part 2: Specification of characteristics and measurement methods for nanostructured magnetic beads for nucleic acid extraction

1 Scope

This document specifies characteristics to be measured of magnetic beads in suspension and powder forms for nucleic acid extraction applications. This document deals with magnetic beads that contain a substantial amount of magnetic nanoparticles (which can be superparamagnetic). Potential applicable measurement methods are listed for the individual characteristics. Specifically, this document lists critical characteristics of magnetic beads and suspensions, and additional characteristics to describe the magnetic beads and the suspension for nucleic acid extraction.

Health, safety and environmental aspects of magnetic beads are not within the scope of this document.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO/TS 80004-1, *Nanotechnologies — Vocabulary — Part 1: Core terms*

ISO/TS 80004-6, *Nanotechnologies — Vocabulary — Part 6: Nano-object characterization*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO/TS 80004-1, ISO/TS 80004-6 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
bead mass concentration
ratio of the mass of *magnetic beads* (3.6) to the total volume of a magnetic beads sample in suspension or powder form

3.2
bead size
effective outer diameter of a *magnetic bead* (3.6) determined by using the specified measurement method

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