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# Fine bubble technology — General principles for usage and measurement of fine bubbles —

## Part 5: Shelled bubble vocabulary

*Technologie des fines bulles — Principes généraux pour l'utilisation et le mesurage des fines bulles —*

*Partie 5: Vocabulaire des bulles enveloppées*



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# Contents

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This document was prepared by Technical Committee ISO/TC 281, *Fine bubble technology*.

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# Introduction

Fine bubbles are the bubbles of a size typically less than 100 µm. Fine bubbles without a shell have recently seen growth in their applications in both industrial and biomedical fields, especially wastewater treatment, food processing, ultrasound imaging and medicine.

This document recognizes general principles of the definition of fine bubbles. However, it is to define the fine bubbles with shell materials encapsulation at the gas-liquid interface, resulting longer stability and controllability when application.

The shelled gas bubbles have shown extraordinary potential when used in the biomedical and food industries, especially in the applications of drug delivery and ultrasonic imaging. Shelled bubbles combine the unique responsiveness of bubbles to ultrasound and the specific functionalization of shells.

Bubbles have a strong acoustic impedance, which allows them to reflect sound waves far more efficiently than the surrounding fluid and biological tissue. Therefore, the use of bubbles in ultrasound imaging can effectively enhance the reflection of ultrasound, so as to obtain a higher image resolution. Contrast-enhanced ultrasound can be used to observe blood perfusion in an organ, to measure the flow rate of blood in the heart or other organs, and for a number of other purposes.

Different types of materials can also be chosen to endow bubbles with different functions, such as specific targeting, and carriers for drugs, genes and other contrast agents for multimodal imaging. Besides, bioactive gases such as oxygen gas, nitric oxide, hydrogen can be stored in the shelled bubble. Bubbles coated with nutritional ingredients or drugs can help to improve the nutrition or act as a medicinal aid in food.

When a gaseous core is encapsulated with shell materials encapsulated at the gas-liquid interface, it will result in longer stability and increased controllability when applied. With the shell, the size distribution of fine bubbles can be further controlled. The bioactive gasses (e.g. oxygen, hydrogen, nitric oxide) and/or soluble gases (e.g. carbon dioxide, sulfur dioxide, hydrogen sulfide, ozone) bubbles can be obtained in the solution for a longer duration time. Other functions of fine bubbles can be also tuned for specific applications. There is no document for distinction between a shelled bubble and nanoparticle or a fine bubble without a shell.

This document specifies terms, definitions and categories of a shelled bubble. Shelled bubbles accelerate further applications in the biomedical field, and also initiate new applications in other fields, such as energy storage, the food industry, environmental technology, agriculture and separation technologies. Development of appropriate general principles for usage, measurement and vocabulary for shelled bubbles is therefore critical to business trade or product acceptance by hospitals and consumers.

# Fine bubble technology — General principles for usage and measurement of fine bubbles —

# Part 5:
# Shelled bubble vocabulary

## 1 Scope

This document specifies the general principles of the definition of bubbles with shells, including the gas-filled structures/particles dispersed in liquids. The shell cited in this document is one created deliberately in manufacturing. Shells created by naturally occurring layers created on the surface of bubbles due to adhesion of bubbles are out of the scope of this document.

## 2 Normative references

There are no normative references in this document.

## 3 Terms and definitions

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

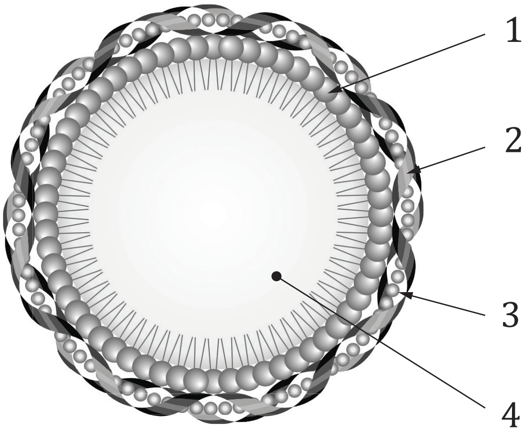
— ISO Online browsing platform: available at https://www.iso.org/obp

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

### 3.1 Terms related to shelled bubble

**3.1.1**
**shelled bubble**
gas in a liquid/solid medium (hollow particles), completely covered by an appropriate process with a shell made of biocompatible materials (proteins, polysaccharides, or lipids) or inorganic/organic particles at an interface

Note 1 to entry: Figure 1 shows an example of the schematic diagram of a gas core completely encapsulated with shell materials. Gas bubbles trapped in gaps and cavities of nanoparticles are out of the scope of this document.




**Key**

1 phospholipids
2 polymers
3 inorganic nanoparticles
4 gas core

**Figure 1 — Example of a shell diagram of bubble**

**3.1.2**
**shelled fine bubble**
*shelled bubble* (3.1.1) with a volume equivalent diameter of less than 100 µm

Note 1 to entry: 100 µm is also represented as $1 \times 10^{-4}$ m.

**3.1.3**
**shelled ultrafine bubble**
*shelled bubble* (3.1.1) with a volume equivalent diameter of less than 1 µm

**3.1.4**
**shelled microbubble**
*shelled bubble* (3.1.1) with a volume equivalent diameter of from 1 to 100 µm

**3.1.5**
**organic shell**
shell materials composed of organic materials

Note 1 to entry: For example, organic materials are phospholipids, polymers, proteins, surfactant, etc.

**3.1.6**
**inorganic shell**
shell materials composed of colloidal particles or nanoparticles such as colloidosomes, colloidal crystals, iron oxide nanoparticles and silicon nanoparticles

**3.1.7**
**hybrid shell**
shell materials composed of the combination of organic and inorganic materials

**3.1.8**
**monolayer shell**
shell consisting of a single continuous layer one molecule or particle thick

**3.1.9**
**double layer shell**
shell made up of two continuous layers consisting of two *monolayer shells* (3.1.8)

**3.1.10**
**multilayer shell**
shell made up of three or more continuous layers consisting of three or more *monolayer shells* (3.1.8)

**3.1.11**
**shell interface**
boundary of shell material molecules existing on the outermost surface of the liquid phase in contact with the gas phase

**3.1.12**
**shell thickness**
length of the shell boundary from gas interface to liquid interface

Note 1 to entry: Shell thickness is usually measured by transmission electronic microscopy (TEM) and/or scanning electronic microscopy (SEM).

**3.1.13**
**shell shape**
stable geometric contours of the shell such as spherical or irregular

Note 1 to entry: Shell shape is usually observed by dark field microscopy, transmission electronic microscopy (TEM) and scanning electronic microscopy (SEM).

**3.1.14**
**insoluble gases in a shelled bubble**
gas that has generally non-affinity with water

EXAMPLE Oxygen, hydrogen, sulfur hexafluoride, carbon monoxide or perfluorocarbons.

**3.1.15**
**soluble gases in a shelled bubble**
gas that has affinity with water

EXAMPLE Nitric oxide, carbon dioxide, sulfur dioxide, hydrogen sulfide and ozone.

**3.1.16**
**zeta potential of shell**
outer surface of the gas shelled bubble in the core when dispersed in a liquid/solid medium

Note 1 to entry: Zeta potential is often determined by dynamic light scattering (DLS).

**3.1.17**
**shelled bubble size half-life stability**
duration time for a volume of a *shelled bubble* (3.1.1) to shrink to half under a given temperature and pressure conditions

Note 1 to entry: Shelled bubble size half-life stability is usually characterized by dynamic light scattering (DLS).

**3.1.18**
**shelled bubble number half-life stability**
duration for the number of *shelled bubbles* (3.1.1) to shrink to half under a given temperature and pressure conditions

Note 1 to entry: Shelled bubble number half-life stability is usually determined by particle tracking analysis.

**3.1.19**
**lipid shell**
shell components composed of the phospholipids

Note 1 to entry: For example, the lipid molecules are phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidic acid (PA) and lysophosphatidic acid (LPA), phosphatidylglycerol (PG). The lipid components also consist of a glycerol molecule, two fatty acids and a phosphate group that is covalently linked with molecules (cholamine, amino acid, etc.) or polymers i.e. polyethylene glycol, etc.

**3.1.20**
**polymer shell**
shell components composed of synthetic polymers or functionalized natural polymers

Note 1 to entry: For example, the synthetic polymers are polystyrene (PS), polypropylene (PP), polyvinyl chloride (PVC), polyvinyl alcohol (PVA), polyethylene (PE), polyurethane (PU), polycarbonate (PC), polyethylene terephthalate (PET), polyetheretherketone (PEEK), poly-(lactic-co-glycolic acid) (PLGA), polylactic-co-glycolic acid, poly(ε-caprolactone) (PCL), polyLactic Acid (PLA), polyacrylic acid, poly(3- hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), poly(butyl cyanoacrylate) (PBCA), poly(n-butyl cyanoacrylate), Pluronic F-68, etc.

Note 2 to entry: For example, the natural polymers are dextran, hyaluronic acid, chitosan and cellulose, etc.

**3.1.21**
**protein shell**
shell components composed of proteins (albumin, lysozyme, hydrophobin, etc.) or functionalized proteins

**3.1.22**
**surfactant shell**
shell components composed of span-type surfactants (sorbitan fatty acid esters), and tween-type surfactants (sorbitan polyoxyethylene fatty acid esters)

**3.1.23**
**gas-filled structures/particles dispersed in liquids**
preformed structures/particles with removable cores (templates or water) filled with gases and re-dispersed in liquids to form the gas-filled fine colloidal dispersions

**3.1.24**
**bioinert gases**
gases which do not initiate a response or interact when introduced to biological tissue

EXAMPLE Air, sulfur hexafluoride or perfluorocarbons.

**3.1.25**
**bioactive gases**
gases having an effect upon a living organism, tissue or cell

Note 1 to entry: Nitric oxide, oxygen, hydrogen, carbon dioxide, carbon monoxide.

## 3.2 Terms related to shelled bubble categorization

**3.2.1**
**soft shell**
bubble shell materials that are more permeable to the entrapped gas and can be re-stabilization at the gas-liquid interface when the volume diameter of a *shelled bubble* (3.1.1) doubles or halves

EXAMPLE The lipid, surfactant and protein.



**3.2.2**
**hard shell**
bubble shell materials that less permeable to the entrapped gas can re-stabilization at the gas-liquid interface when the volume diameter of a *shelled bubble* (3.1.1) doubles or halves

Note 1 to entry: Polymeric or nanoparticles.

**3.2.3**
**cross-linked shell**
shell materials connected by covalent bonds

**3.2.4**
**noncross-linked shell**
shell materials not connected by covalent bonds

## 3.3 Terms related to generation and characterization of shelled bubbles

**3.3.1**
**dispersion method**
method by which fine bubbles with a shell of biocompatible materials are produced by sonication or high-speed agitation to disperse the shell materials with the gas interface

**3.3.2**
**condensation method**
method by which hollow fine structures (capsules and particles) are often preformed and filled with gases to form shell fine bubbles

**3.3.3**
**microfluidic system method**
method by which fine bubbles with a shell of biocompatible materials are produced by an injection device that consists of three components: microsyringe, micropipette and pipette.

**3.3.4**
**sonication-microfluidics method**
method which consists of two components: a microfluidic device to generate gas-in-liquid slug flow and a sonication device to realize cavitation and the coating of the bubbles