Available online on 15.06.2026 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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Review Article

Tin Oxide (SnO_2) Nanoparticles in Modern Medicine: Development, Standardization, and Therapeutic Applications

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A B S T R A C T

Tin dioxide nanoparticles (SnO_2) represent an extremely versatile class of metal oxide nanomaterials with vast potential in a broad spectrum of modern medical applications. The key characteristics of tin dioxide nanoparticles include high optical bandgap energy (~3.6 eV), rutile crystal phase structure, elevated surface area to volume ratio, remarkable chemical stability, and controllable surface chemistry. Thus, tin dioxide nanoparticles display an excellent array of optical, electrical, and biological properties enabling their exploitation for numerous medical purposes. The current review article offers a systematic investigation of physicochemical properties, synthesis techniques, characterization procedures, standardization criteria, and various biomedical applications of tin dioxide nanoparticles with particular focus on advancements published from 2020 to 2026. Different synthesis techniques (physical processes, such as laser ablation and vapor deposition; chemical synthesis, namely sol-gel process, hydrothermal treatment, co-precipitation, microemulsion; and green synthesis using plants and microorganisms) are analyzed in terms of the underlying mechanism, particle size, shape, and scalability. The mechanisms responsible for the interaction of tin dioxide nanoparticles with biological entities (cellular uptake, protein corona, reactive oxygen species, and apoptosis) are presented in detail. The range of therapeutic applications includes antitumor activity, antibacterial effect, controlled drug delivery, biosensor applications, and anti-inflammatory and antioxidant activities. Toxicology data, which includes in vitro toxicity studies, genotoxicity studies, and in vivo organ toxicity data, is carefully evaluated to demarcate the therapeutic window and determine safety limits. Advances in the field such as functionalized nanoparticles, graphene-SnO_2 nanocomposites, doping techniques, and stimuli-responsive drug delivery systems have been mentioned. In conclusion, the paper identifies the critical issues that hamper the clinical application of SnO_2-based nanoparticles and discusses future research directions, particularly related to artificial intelligence, personalized nanomedicines, and GMP-based manufacture.

Keywords: Tin oxide nanoparticles; Nanomedicine; Drug delivery; Anticancer activity; Green synthesis

A R T I C L E I N F O: Received 28 Dec.2025; Review Complete 25 Feb, 2026; Accepted 22 March. 2026; Available online 15 June. 2026

Cite this article as:

Chavan OD, Deepak D. Sonawane, Mayuri P. Pol, Tin Oxide (SnO_2) Nanoparticles in Modern Medicine:Development, Standardization, and Therapeutic Applications, Asian Journal of Pharmaceutical Research and Development. 2026; 14(3):226-241,
DOI: **http://dx.doi.org/10.22270/ajprd.v14i3.1785**

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INTRODUCTION

Nanotechnology, usually defined as the design of structures or machines with at least one dimension measuring between 1 and 100 nanometers, has undergone explosive growth since it was conceptualized by Richard Feynman in 1959 and named by Norio Taniguchi in 1974." The integration of nanotechnology and biomedical sciences leads to the emergence of the domain known as nanomedicine, where the physicochemical properties of nanoparticles are exploited to solve problems related to the diagnoses and therapy of various diseases. Nanostructured materials exhibit unique properties because of quantum effects, enormous surface area-to-volume ratios, unique electron structure, and optical behavior. The uniqueness of nanostructured materials results in numerous advantages, including improved bioavailability, enhanced pharmacodynamics, site-specific delivery of drugs, and evasion from biological defense mechanisms.(1,2)

The development of nanomedicine technology has gone through several generational levels. First-generation nanomedicines such as Doxil® (approved by the FDA in 1995), for instance, were an indication that drugs can be encapsulated in nanocarriers, which resulted in lowering their toxicity level as well as increasing their ability to enter tumors via EPR effect. Future generations of nanomedicine incorporated other elements such as targeting ligands, delivery triggers, and diagnostics into one system for diagnosis and therapy, resulting in theranostics. In the current generation of nanomedicines, there is use of inorganic nanoparticles such as metal oxide nanoparticles due to their unique physical and chemical properties as well as ease of functionalization on their surface.(3,4)

Metal Oxide Nanoparticles in Biomedical Science

Nanoparticles, which stand out among other particles used in nanomedicine, include metal oxide nanoparticles (MONPs) owing to the diversity of their properties that differ depending on the composition, crystalline phase, imperfections, and morphology. The most investigated MONPs consist of TiO_2, ZnO, Fe_3O_4, γ-Fe_2O_3, CeO_2, and SnO_2. Each metal oxide nanoparticle has individual properties; thus, iron oxides are highly valued owing to their application possibilities in magnetic resonance imaging and targeted drug delivery, TiO_2 and ZnO are used in photo-catalytic destruction of bacteria in photo-catalysis, CeO_2 exhibits antioxidant enzyme mimicry, and SnO_2 is used as a photocatalyst in photodynamic therapy of cancer.(5,6)

The antibacterial activity of MONPs can primarily be ascribed to the capability of these nanoparticles to generate reactive oxygen species (ROS), including superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($^{\cdot}OH$). With regard to cancer treatment, MONPs have been utilized in the direct killing of cancer cells as well as in drug delivery to target cancer sites using MONPs as nanocarriers of anti-cancer medications. Regarding the regulation of nanomedicine products containing MONPs, while the regulatory system is still evolving, several guidelines have been published by the US FDA and European Medicines Agency (EMA).(7)

Overview of SnO_2 Nanoparticles

Tin dioxide, often referred to as SnO_2, represents an n-type wide gap semiconductor that adopts the rutile (cassiterite) structure with a tetragonal crystal system and space group $P4_2/mnm$, characterized by lattice constants a = b ≈ 4.74 Å and c ≈ 3.19 Å. The tin atoms are six-coordinated by oxygen atoms, and oxygen atoms are three-fold coordinated by tin atoms within the same plane. These properties make this semiconductor very thermally stable (m.p. ~1630°C), chemically inert in oxidizing conditions, and a direct-gap semiconductor with optical band gap of about 3.6 eV, which makes it transparent for visible light but absorbs ultraviolet light. At the nanoscale level, the properties of SnO_2 become strongly affected by quantum confinement effect, increase in surface defect concentration, and enhanced surface activity, becoming vital to its biomedical applications.(8, 9)

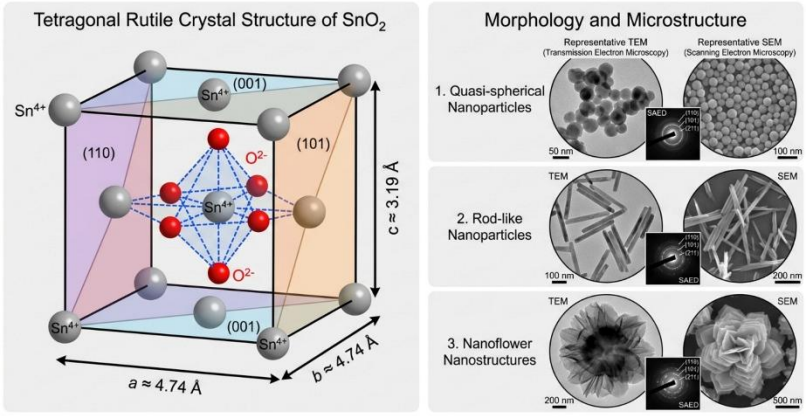

Figure 1: Structure of SnO_2 nanoparticles

SnO_2, known as tin oxide, is an n-type wide-gap semiconductor having rutile (or cassiterite) structure in the form of tetragonal crystal system with a space group symmetry of $P4_2/mnm$, where the lattice parameters a = b ~ 4.74 Å and c ~ 3.19 Å. The coordination number of tin with oxygen is six, and likewise that of oxygen with tin is three along the same plane. This leads the semiconductor to have high thermal stability (melting point of ~1630°C), chemical inertness under oxidizing conditions, direct band-gap semiconductor with optical band gap energy of ~3.6 eV, which makes it invisible to visible light, but absorbing in ultraviolet range. At the nanometer scale, the material becomes highly sensitive to effects like quantum confinement, increase in surface defects, and increased surface reactivity, making it critical for medical purposes.(10,11)

Scope, Research Gaps, and Objectives

Despite numerous advancements in the synthesis and initial biological assessment of SnO_2 nanoparticles, substantial research limitations still exist. Understanding the molecular mechanism underlying their targeted anticancer effect as opposed to cytotoxicity toward healthy cells is far from complete. Methods for ensuring consistency in nanoparticle synthesis, interbatch uniformity, and colloidal stability in physiological solutions have not been established. There are

very few data available on the pharmacokinetics and distribution of these nanoparticles in living organisms, and no clinical trials have been conducted. Moreover, the process of regulating inorganic nanoparticles is quite complicated and requires its own quality control criteria.(12,13,14)

This review paper seeks to tackle all these knowledge gaps by presenting an all-inclusive account of the chemistry of SnO_2 nanoparticles, the synthesis and characterization of SnO_2 nanoparticles, the standardization of SnO_2 nanoparticles, the biological interactions of SnO_2 nanoparticles, the medical uses of SnO_2 nanoparticles, the toxicity of SnO_2 nanoparticles, the current research and advances in SnO_2 nanoparticles, and future trends in SnO_2 nanoparticles.

Physicochemical Properties of SnO_2 Nanoparticles

Structural Characteristics

At ambient conditions, the principal crystalline form of SnO_2 is the tetragonal rutile-type phase with a space group $D^4{}_1{}^4h$ ($P4_2/mnm$) that contains two Sn^{4+} ions and four O^{2-} ions in the unit cell. The Sn^{4+} ions reside in the interstitial positions of the octahedral coordination geometry, surrounded by six equivalent O^{2-} ions with distorted octahedra sharing their edges along the c-direction and corners in the ab-plane. Such a chemical environment leads to a crystal with significant anisotropy in terms of its physical properties and distinct surface chemistry at the (110), (101), (100), and (001) facets. The most energetically favorable (110) facet has bridging oxygen and tin atom chains as the terminating species, which are common in equiaxed nanoparticles prepared by chemical synthesis.(15,16)

There are several morphological forms that have been identified for nanosized SnO_2, based on the synthesis process used. This includes spherical-shaped nanoparticles (5–50 nm), nanorods (diameter 10–40 nm, length 100–500 nm), nanobelts, nanosheets, and nanoflowers. Morphology determines surface area, defects, and the biological activity. Specific surface area measured through BET for SnO_2 nanoparticles generally falls between 20 and 150 m^2/g depending on particle size and synthesis method. The crystallite size, calculated using the Debye-Scherrer formula from X-ray diffraction data, is usually within the range 4–30 nm, depending on the lower calcination temperature and high precursor concentration.(17,18)

Surface Properties and Functionalization

The surface of SnO_2 nanoparticles consists of hydroxyls (Sn–OH), bridges (Sn–O–Sn), and oxygen vacancies. The isoelectric point (IEP) of bare SnO_2 nanoparticles lies between pH 4.0 and 5.5; below that, the surface gets positively charged due to the protonation of the surface hydroxyl groups, whereas the surface becomes negatively charged when the pH rises above 5.5. Zeta potential is an important parameter for the colloidal stability of a nanoparticle. Typically, for bare SnO_2 nanoparticles, zeta potential lies between −15 and −40 mV in alkaline biological environments, where pH values lie between 7.0 and 7.4. Zeta potential values lower than −25 mV indicate electrostatic repulsion responsible for colloidal stability.(19,20)

Surface functionalization of SnO_2 nanoparticles can be performed using various approaches. Silane-based coupling agents, such as 3-aminopropyltriethoxysilane (APTES), enable the incorporation of amino functionalities to the surface, allowing for further attachment of targeting ligands, drug molecules, and fluorescent probes. PEG coating prevents protein adsorption, increases blood half-life and reduces nanoparticle opsonization by the mononuclear phagocyte system. Surface modification with carboxyl groups allows carbodiimide chemistry (EDC/NHS) to take place.(21) This strategy allows for immobilization of biological molecules on SnO_2 surface through conjugation with antibodies, peptides, aptamers and other biomolecules. Positive charge provided by chitosan surface coating enables electrostatic interaction with cell membrane leading to increased cellular uptake.(22,23)

Optical and Electronic Properties

The optical direct bandgap of SnO_2 at room temperature is around 3.6-3.8 eV based on the estimation from Tauc plots of UV-vis diffuse reflectance spectra. The large bandgap value makes bulk SnO_2 an optically transparent material in the visible range but can absorb photons in the near-UV region ($\lambda < 345$ nm). Quantum size effect is reflected in the blue shift of the absorption edge for nanoparticles smaller than about 10 nm due to the confinement of the electron-hole pairs when the particle size is close to the exciton Bohr radius (2.7 nm in the case of SnO_2).(24)

The photoluminescent (PL) spectra of SnO_2 nanoparticles generally show broad emission bands at visible wavelengths (450–650 nm), which result from the radiative recombination process of electrons on the surface defects. This involves oxygen vacancy and tin interstitial defects in particular, both of which are biologically important because they act as active sites for redox reactions and hydrogen peroxide production as well as catalysis in the peroxidase-like reaction. The intrinsic n-type conductivity of SnO_2, which is due to donor defects, lends electrical properties to SnO_2 that have been useful for developing biosensors through electrical resistance changes due to analytes.(25,26)

Thermal and Chemical Stability in Biological Systems

The SnO_2 material is characterized by high chemical stability for a wide range of pH values and temperatures applicable to biological processes. In contrast with ZnO that dissolves below pH 6 resulting in release of highly toxic Zn^{2+} ions, the SnO_2 material preserves its structure under physiological conditions (4.5-7.4 pH) without releasing any ions in physiological media during 72 hours incubation in the temperature of 37° C. Another important property of SnO_2 is the high thermal stability up to 600° C in air; the rutile crystal form is stable even at temperatures above 700° C.On account of their surface properties, in biologically relevant protein-rich fluids, such as blood plasma and cell culture media, SnO_2 nanoparticles experience fast protein adsorption, leading to a protein corona, which is a complex coating of albumins, immunoglobulins, fibrinogens, complements, and apolipoproteins, affecting the colloid's stability, interaction with cells, and biodistribution. The nature of the protein corona is determined by the nature of the surface chemistry of nanoparticles, their surface charge, and the type of biological medium.(26,27)

Methods of Synthesis

Physical Methods

Physical methods to synthesize SnO_2 nanoparticles include ablation by lasers and physical vapor deposition approaches. For example, in pulsed laser ablation in liquids (PLAL), a highly focused laser beam (Nd:YAG laser, wavelength 532 nm or 1064 nm, nanosecond pulse length, energy of pulses between 10 and 30 mJ) is directed toward a metal or SnO_2 target placed in an aqueous solution. Upon exposure to the laser beam, target materials are vaporized, generating a hot plume of plasma that rapidly cools in a liquid solvent, producing SnO_2 nanoparticles unaltered by chemicals. These nanoparticles are pure with small size distribution (5-40 nm). Lack of any ligand or reductant in this method makes such nanoparticles ideal for biomedicine. Disadvantages are low yield and expensive machinery making them impractical for use in pharmaceutical industry.(28,29,30)

The CVD and PVD techniques utilize the gaseous forms of tin-based precursors, including tin(IV) chloride ($SnCl_4$) or tin(II) acetylacetonate, which decompose and oxidize at elevated temperatures (600-900°C). The CVD and PVD techniques are effective approaches for depositing SnO_2 films and have been used in gas sensor technology, but their application for forming colloidal suspensions is limited owing to difficulties associated with recovering and redispersing the particles.(3)

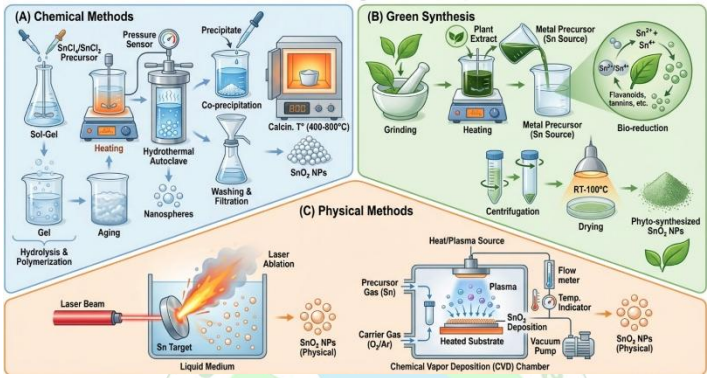

Figure 2: Synthesis methods flowchart

Chemical Methods

Chemical synthesis stands out as the primary strategy for obtaining SnO_2 nanoparticles on a large scale for applications in biomedical science. In the sol-gel process, there is hydrolysis of tin alkoxide sources like tin(IV) ethoxide and tin(IV) isopropoxide or inorganic tin salts such as $SnCl_4$ and $SnCl_2$ in aqueous/alcoholic medium, whereby a tin oxide hydroxide sol is generated, which undergoes condensation, gelation, drying, and calcinations at 400-600 °C to produce crystalline SnO_2 nanoparticles. The major advantages of using the sol-gel technique include the possibility of compositional control, uniform distribution of the particles, and synthesis of porous nanostructured materials with large surface areas (maximum 150 m^2/g).(33,34)

This process utilizes the increased chemical reactivity and solubility of reagents at high temperatures and pressures (150–220°C, 12–24 h) in stainless steel autoclaves coated with Teflon. By undergoing dissolution-recrystallization reactions through hydrothermal conditions, aqueous alkaline or acidic precursors give rise to SnO_2 nanocrystals in rod, wire, tube, and flower forms, which may vary based on the concentration, pH, temperature, reaction time, and surfactants. This technique is beneficial for synthesizing nanocrystals with better crystallinity and cleaner surface, but it is difficult due to the requirement of pressure-resistant apparatus.(36)

In co-precipitation, the alkaline precipitants such as ammonium hydroxide, sodium hydroxide, or urea are directly mixed with aqueous solutions of either $SnCl_4$ or $SnCl_2$, causing immediate nucleation and growth of the tin hydroxides, which can then be filtered, washed, dried, and heated to produce tin oxide nanoparticles. The co-precipitation technique is simple to use, fast (within an hour), and inexpensive, yet has relatively wide particle size distributions and poor morphological control. Microemulsion techniques make use of the water-in-oil or bicontinuousmicroemulsion system, where the aqueous precursors are contained within a surfactant shell, allowing better control over nucleation and growth, producing extremely small particles with very narrow size distributions (3-20 nm).(37,38)

Green Synthesis

Recently, the concept of green synthetic methods has gained immense popularity due to their eco-friendly nature and biological compatibility. In plant-mediated synthesis, the aqueous extract from different parts of the plants, such as leaves, roots, seeds, and flowers, is used as a source of the reducing and capping agent. Polyphenols, flavonoids, terpenoids, and alkaloids, which are present in the plant extract, reduce the ions of Sn^{4+} or Sn^{2+} into SnO_2 nanocrystals while simultaneously providing a bioactive coating for the nanoparticles formed. Various plants reported for this purpose are Moringaoleifera, Azadirachtaindica, Justiciaadhatoda, Solanumnigrum, Rheum turkestanicum, among many others. The size of the particles prepared by plant-mediated synthesis varies from 10 to 50 nm, while the zeta potential value lies between −15 to −35 mV.(39,40).

The microbial synthesis of SnO_2 nanoparticles using bacteria such as Bacillus subtilis and Pseudomonas fluorescens and fungi like Aspergillus niger and Trichodermaviride has been successfully achieved. Cell-free filtrates of microorganisms or complete cells act as the bioreactor where enzymes,

organic acids, and reducing agents facilitate the reduction of soluble tin ions to SnO_2 nanoparticles under normal temperatures. Despite being an environment-friendly approach, microbial-mediated synthesis suffers from considerable drawbacks because of the intrinsic batch-to-batch variability of biological systems, potential contamination issues, and biological input standardization problems.(41,42)

Factors Affecting Synthesis

Physicochemical properties of SnO2 nanoparticles are highly sensitive to process variables like precursor concentration, pH, temperature, time, surfactants, and capping agents. For example, higher concentrations of precursors result in rapid nucleation, generating a large number of nuclei. Consequently, the size of the resulting nanoparticles would be low because there is no sufficient room for growth of the nanoparticles. Lower concentrations would result in the production of only few nuclei, which can be used to form nanoparticles with high sizes. The hydrolysis of precursors and charge of the nanoparticles would vary greatly based on the pH value. Hydrothermal temperatures can be used to induce high crystallinity and control the particle size of the product. Higher reaction time would give rise to growth and ripening of the particles leading to large nanoparticle size and monodispersity. The identity of the surfactant and capping agents affects the formation of the desired shapes through selective crystal face passivation. (43,44).

Table 1: Summary of SnO_2 Nanoparticle Synthesis Methods, Conditions, and Characteristics

Method	Conditions	Particle Size	Advantages	Limitations
Sol-gel	pH 7–9, 60–80°C, calcination at 400–600°C	5–30 nm	High purity, homogeneous distribution, scalable	Time-consuming, solvent waste
Hydrothermal	180–220°C, 12–24 h, autoclave, alkaline pH	10–50 nm	Crystalline, good morphology control, eco-friendly	High-pressure equipment required
Co-precipitation	RT–80°C, NH3 or NaOH precipitant, rapid mixing	15–60 nm	Simple, fast, low cost, scalable	Poor size distribution control
Microemulsion	RT, surfactant-mediated, controlled water pools	3–20 nm	Narrow size distribution, controlled morphology	High surfactant cost, complex purification
Green (Plant)	Leaf extract reducing agents, 25–80°C	10–50 nm	Eco-friendly, no toxic reagents, biocompatible	Batch variability, extract standardization issues
Green (Microbial)	Bacterial/fungal culture filtrates, RT–37°C	15–70 nm	Sustainable, low energy input	Slow process, contamination risk
Laser Ablation	Pulsed laser, target in liquid, nanosecond pulses	5–40 nm	High purity, no chemical contamination	Low yield, expensive equipment
Chemical Vapor Dep.	600–900°C, SnCl4 precursor, O2 atmosphere	10–100 nm	Thin film production, good crystallinity	High temperature, specialized reactor needed

Characterization Techniques

Electron Microscopy (TEM and SEM)

The transmission electron microscope (TEM) represents the ultimate method for examining the size, morphology, and structural details of nanoparticles at the atomic scale. TEM utilizes a beam of energetic electrons (80–300 keV) that passes through a thin section of material (usually <100 nm), whereby contrast is generated by electron scattering caused by the differences between the sample and the surrounding vacuum. With HRTEM imaging, individual lattice planes and spacings (interplanar d-spacing) may be measured and associated with specific lattice planes (d_{110} = 3.35 Å, d_{101} = 2.64 Å) to determine that the particle is of rutile SnO_2. The SAED patterns produced with the TEM also provide phase identification and data on crystallinity and preferred orientation. EDX, used in combination with TEM, provides elemental mapping at the nanoscale level.(45,46)

Scanning Electron Microscopy (SEM) works on the basis of a scanning electron beam which moves across the specimen surface to detect either secondary or back-scattered electrons and create three-dimensional topographic images with nanometer resolution in modern field emission microscopes. SEM is a technique that complements TEM in that it can reveal information about morphology (aggregation state, shape of particles, surface texture), but not internal structure like in TEM. Elemental Analysis using SEM is done by EDX and is semi-quantitative, helpful in determining dopant and surface functionalization information. Cryo-electron microscopy is a new method with growing importance in studies of SnO_2 nanoparticles, especially in their hydrated native condition.(47,48)

X-ray Diffraction (XRD)

XRD is therefore a key analytical method for the determination of phases as well as structural characterization of tin oxide nanoparticles. By employing the principles of Bragg's equation ($n\lambda = 2d \sin\theta$) on a crystalline material, using monochromatic X-radiation (Cu Kα line, λ = 1.5406 Å) in XRD of powdered samples, a diffraction pattern

representing diffracted intensity as a function of the 2θ angle results which when compared to the JCPDS reference data (card no. 41-1445 for SnO_2) allows phase determination. The characteristic diffraction peaks of rutile SnO_2 occur at the following 2θ positions, among others: 26.6° (110), 33.9° (101), 37.9° (200), 51.8° (211), and 65.9° (301). Broadening of diffraction peaks due to crystallite size and lattice strain can be analyzed with the help of the Williamson-Hall approach to determine both the crystallite size and root mean square lattice strain independently. For crystallite size estimation, the Scherrer equation ($D = K\lambda/\beta\cos\theta$, where $K = 0.94$ for spherical nanoparticles, β is the full-width-at-half-maximum of the peak intensity in radians) may be used to obtain size information in the approximate range of 5-30 nm.(49,50)

4.3 Fourier Transform Infrared Spectroscopy (FTIR) and X-ray Photoelectron Spectroscopy (XPS)

The FTIR technique allows for the determination of vibrational modes in the chemical bonds found in or on the SnO_2 nanoparticles. This is useful in the identification of functional groups on the surface, as well as any surface modification performed. The characteristic vibrations for Sn-O stretch appear between 540 and 680 cm^{-1}, while those for O-Sn-O bending occur near 477 cm^{-1}. The functional groups on the surface will include hydroxyl groups that exhibit a wide band for O-H stretching, centered around 3400 cm^{-1}, and H-O-H bending at ~1620 cm^{-1}. After functionalization of the surface, FTIR will show additional bands corresponding to the functional layer. These include C-H stretch near 2900 cm^{-1}, C=O stretch at ~1720 cm^{-1}, N-H bending near 1550 cm^{-1}, and amide I/II bands at ~1650/1550 cm^{-1}.(51)

X-ray photoelectron spectroscopy is an analytical technique based on probing the surfaces with monochromated x-ray radiation (such as Al Kα, 1486.6 eV) and measuring the kinetic energy of the ejected photoelectrons. It is a relatively surface-sensitive analysis method (probing depth is about 5-10 nm). Because the binding energies of core-level electrons depend on both the element and its oxidation state, XPS enables the determination of elements and their oxidation states in the sample surface. In case of SnO_2 nanoparticles, the XPS analysis of the Sn 3d spectrum allows detecting the doublet consisting of two peaks centered at 486.7 eV for Sn^{4+} and 485.0 eV for Sn^{2+} ions. The quantification of the relative intensity of the peaks makes it possible to evaluate the surface ratio of Sn^{4+}/Sn^{2+} species. Oxygen 1s photoelectron spectra are usually deconvoluted to separate signals coming from lattice oxygen (~530.5 eV), oxygen vacancies (~531.5 eV), and hydroxyl surface oxygen (~532.5 eV).(52)

Dynamic Light Scattering (DLS) and Zeta Potential

Dynamic light scattering (DLS), alternatively known as photon correlation spectroscopy, involves detecting the fluctuations in intensity of light scattered through Brownian movement of nanoparticles in solution. Through auto-correlation of the detected fluctuating intensities of scattered light, DLS can determine the translational diffusion coefficient, and subsequently the hydrodynamic diameter using Stokes-Einstein Equation: $D_h = k_BT/(3\pi\eta D_t)$, where kB represents the Boltzmann constant, T is the absolute temperature, η represents solvent viscosity, while Dt stands for the diffusion coefficient. It is important to note that hydrodynamic diameter determined by DLS is the total size of nanoparticle, taking into account both the nanoparticle core, surface coating, and hydration layer, and therefore will always be higher than the TEM core diameter. Polydispersity Index (PDI), calculated through cumulants analysis of the auto-correlation function, describes the width of the size distribution; PDI less than 0.2 implies monodisperse particles suitable for use in medicine.(53,54)

The zeta potential is measured using laser Doppler microelectrophoresis (LDV) technique, which determines the electrophoretic mobility of the charged particle in an applied electric field. The magnitude and polarity of the zeta potential indicate the effective charge present on the surface of the solid-particle/liquid medium interface at the point of slip. In case of SnO_2 nanoparticles dispersed in biological buffer solutions, the zeta potentials usually vary between -10 mV to -40 mV (negative) for uncoated particles at physiological pH. It is well known that the value of $|\zeta| \geq 25$-30 mV is taken as the critical limit for the electrostatic stabilization of colloidal suspensions. However, due to the contribution of sterically stabilizing polymer coating, colloidal suspensions can remain stable even below this critical limit.(55)

UV-Visible Spectroscopy and Photoluminescence

UV-Vis spectrometry of SnO_2 nanoparticle suspensions or compressed powders yields insight into the nature of optical transitions, bandgap energy, and light absorption properties. Absorption onset resulting from interband transitions occurs in the UV regime (~300–350 nm) in the case of SnO_2 nanoparticles. Optical bandgap energy of SnO_2 nanoparticles is calculated according to the Tauc plot of $(\alpha h\nu)^2$ vs. photon energy hν for direct allowed optical transitions, and the bandgap energy value lies within 3.6-3.8 eV. Bandgap energy size dependent blue shifts have been noted for nanoparticles smaller than ~10 nm because of quantum confinement effects. The UV-Vis spectrum of functionalized SnO_2 nanoparticles may exhibit additional bands originating from conjugated organic ligands, drugs, and other fluorophores bound to the nanomaterial surface, which might also be used for determination of the amount of drug or fluorescent probe immobilized onto the surface. Photoluminescence spectroscopy upon excitation with UV radiation (300–350 nm) leads to the identification of photoluminescent bands attributed to surface defect states.(56,57).

Table 2: Characterization Techniques for SnO_2 Nanoparticles – Principles and Applications

Technique	Principle	Parameters Determined	Significance in SnO2 NP Characterization
TEM	Transmission of electrons through ultrathin sample	Particle size, morphology, lattice spacing, crystal planes	Reveals core-shell structure, crystal defects, and interlayer d-spacing
SEM/EDX	Secondary electrons from surface bombardment	Surface morphology, elemental composition	Confirms surface topology and elemental purity of synthesized NPs
XRD	Bragg diffraction of X-rays from crystal planes	Crystal structure, phase purity, crystallite size (Scherrer equation)	Confirms rutile tetragonal phase; Scherrer size typically 5–30 nm
FTIR	Absorption of IR radiation by molecular bonds	Surface functional groups, ligand binding, coating confirmation	Confirms Sn–O stretching (~620 cm-1), surface modification
XPS	Photoelectron emission from X-ray irradiation	Elemental composition, oxidation states (Sn2+/Sn4+), surface chemistry	Determines Sn 3d5/2 and 3d3/2 binding energies; identifies oxygen vacancies
DLS	Light scattering by diffusing particles (Stokes-Einstein)	Hydrodynamic diameter, polydispersity index (PDI)	Determines effective particle size in biological media; PDI <0.3 preferred
Zeta Potential	Electrophoretic mobility under electric field	Surface charge, colloidal stability	Values >±30 mV indicate stable suspension; predicts agglomeration tendency
UV-Vis	Electronic transitions, band gap absorption	Optical band gap (Tauc plot), surface plasmon resonance	Band gap ~3.6 eV; shift indicates quantum confinement in smaller NPs
BET Analysis	N2 adsorption-desorption isotherms	Surface area, pore size distribution, pore volume	High surface area (>50 m2/g) correlates with enhanced drug loading and catalytic activity

Standardization and Quality Control

Importance of Standardization in Nanomedicine

Standardization of nanoparticle synthesis and characterization techniques is critical for reliable biological testing, reproducibility among different laboratories, adherence to regulations, and ultimately translation into clinical practice. While chemical medicines are characterized by their known molecular composition, nanoparticles represent much more complicated structures whose biological performance is controlled by a number of physical and chemical parameters such as particle size, size distribution, shape, charge, chemistry, drug delivery, and stability, which could differ significantly depending on batch, origin of materials used, method of production, and storage conditions. Developing validated standard operating protocols (SOPs) for each stage of nanoparticle production (synthesis, purification, characterization, and formulation) is critical for ensuring that biological effects are due to nanoparticles and not batch-dependent differences in their characteristics.(59,60)

The problem of standardization is further complicated by the multidimensional nature of nanoparticle characterization, since there is no one analytical method that can capture all parameters of interest, and tests conducted in various media (pure water, physiological solution, cell culture medium, and serum) will produce significantly different results, due to the effect of proteins on the surface and ionic strength of media. The guidelines issued by the Nanotechnology Characterization Laboratory (NCL), the European Nanomedicine Characterization Laboratory (EUNCL), and the Technical Committee TC229 of ISO (nanotechnologies) define the basic requirements for characterization of nanoparticles intended for biomedical applications.(61)

5.2 Physicochemical Standardization Parameters

A thorough physicochemical characterization suite for SnO_2 nanoparticles that are to be used in biomedical applications would involve: (i) determination of size and shape of primary particles using TEM with statistical analysis based on a minimum of 200 particles; (ii) determination of crystallite size and crystal structure using XRD, including Rietveld analysis where necessary; (iii) determination of hydrodynamic size and PDI using DLS in ultrapure water as well as biological fluids (PBS, DMEM + 10% FBS); (iv) zeta potential measurement using LDV as a function of pH and in biological fluids; (v) determination of specific surface area and porosity using nitrogen adsorption analysis (BET method); (vi) determination of surface chemistry and functional groups using FTIR and XPS; (vii) elemental analysis using ICP-OES or ICP-MS; (viii) determination of endotoxin levels using LAL test (less than 1 EU/mL in injectable formulations); and (ix) sterility testing for parenteral formulations.(62,63)

Long-term stability testing at storage and use conditions, such as accelerated stability testing at increased temperatures (40°C/75% relative humidity) and real-time stability testing at 4°C and 25°C, should be performed to evaluate variations in particle size, polydispersity index, zeta potential, drug loading, and biological activity throughout the desired shelf life period. Colloidal stability testing in simulated physiological media (SGF, SIF, PBS, and DMEM with serum) under conditions that mimic the mode of administration is necessary for formulation development. The efficiency of drug encapsulation, loading capacity, and

in vitro drug release profiles (dialysis or non-dialysis membrane methods) under sink conditions are critical for drug delivery applications.(64,65)

Biological Evaluation

The biological standardization involves cytotoxicity analysis, hemocompatibility, immunotoxicity profile, and genotoxicity study before proceeding to in vivo investigations. Cytotoxicity can be carried out using the MTT or WST-1 method on selected cells, measuring IC_{50} concentrations for 24, 48, and 72 hours in the presence of a proper positive control (known cytotoxin) and blank. Any interference with SnO_2 nanoparticle in colorimetric or fluorometric assays must be determined and eliminated. Hemocompatibility tests involve hemolysis test with human erythrocytes and plasma recalcification time as well as platelet aggregation since the product would be delivered intravenously. Immunotoxicity screening comprises the study on cytokines (IL-1β, IL-6, TNF-α, IFN-γ with THP-1 and peripheral blood mononuclear cells) and complement activation. Genotoxicity study includes the Ames test (mutagenicity in S. typhimurium) and micronucleus as well as the comet test (for DNA strand breakage), according to OECD guidelines 471, 473, and 489, respectively.(66,67)

Regulatory Considerations

The regulatory framework for nanomaterial-containing pharmaceuticals is formed from a complex of international and national regulations, which are constantly being updated in accordance with the specific features of nanomedicine. FDA Guidance Documents concerning drug products that contain nanomaterials are focused on aspects associated with CMC studies, toxicity studies, and PK analysis (2022). The EMA Reflection Paper for Non-Clinical and Clinical Development of Medicinal Products Containing Nano-Materials is a guidance document based on a risk-assessment strategy for nanoparticles (2021); according to this document, each particular case should be studied individually considering different types of nanoparticles and their intended purposes. Although the guidance for pharmaceutical development (ICH Q8(R2)) does not specify any requirements for nanoparticle characterization, the quality by design principle described here can be used to characterize SnO_2 nanoparticles – identification of CQAs and CPPs, establishment of the design space and the application of PAT. There exist certain ISO standards for specific nanoparticles, such as standards for measuring biocompatibility (ISO 10993 series), determination of hydrodynamic diameter (ISO 22412), and particles' sizes (ISO 13321).(68,69)

Mechanisms of Biological Interaction

Cellular Uptake Pathways

The delivery of SnO_2 nanoparticles inside the cells is an important requirement for their use as anti-cancer agents, drug carriers, and bio-sensors, which occurs via energy-dependent processes called endocytosis. The specific pathway by which the nanoparticles enter the cell is influenced by factors such as particle size, surface charge, and functionalization of the surface. The clathrin-mediated endocytosis pathway (CME), which is best understood, occurs via invagination of clathrin-coated pits (pit diameter ~120 nm) after interaction with a receptor ligand or nonspecific binding at the plasma membrane, resulting in the formation of clathrin-coated vesicles. These clathrin-coated vesicles mature into early endosomes (pH ~6.5), late endosomes (pH ~5.5), and finally into lysosomes (pH ~4.5–5.0).(70,71)

The uptake of larger nanoparticles in groups (>500 nm) occurs via macropinocytosis, which is a non-specific process that involves actin-dependent uptake of large amounts of extracellular fluid. The positively charged nature of SnO_2 particles (such as those coated in chitosan) can result in the occurrence of electrostatic interaction with the negatively charged plasma membrane and thus contribute to the process of direct membrane permeation. The uptake process is also dependent on temperature, since it is inhibited at 4°C. Confocal laser scanning microscopy and transmission electron microscopy have revealed the intracellular pathway of SnO_2 nanoparticles, from plasma membrane via endosomes to lysosomes.(72)

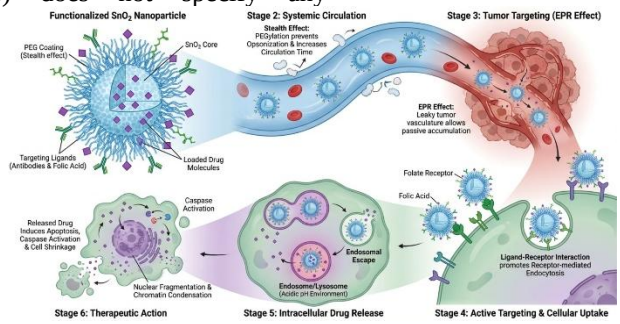

Figure 3: Drug delivery mechanism

Protein Corona Formation

Upon exposure to bodily fluids, SnO_2 nanoparticles rapidly bind to proteins within plasma to generate an ever-changing protein corona that essentially alters the nanoparticle-cell interaction process. Two distinct layers characterize the protein corona: a strong and tightly bound protein layer referred to as the "hard corona," which contains high-affinity proteins such as albumin, apolipoproteins, immunoglobulin, and complement protein and exchanges proteins at a rate much slower than the experimental time frame; and the soft corona comprising

low-affinity proteins that exchange rapidly with the environment. The composition of the hard corona depends on the nanoparticle's chemistry, charge, and curvature, and varies according to the Vroman effect, where the abundant first adsorbed proteins (albumin) are replaced by proteins of less abundance but higher affinity (fibronectin, vitronectin, complement protein C3). Formation of the protein corona could facilitate or impede nanoparticle internalization based on whether or not the bound proteins act as opsonins or dysopsonins.(73,74)

ROS Generation and Oxidative Stress

The process of ROS generation forms the core process involved in the anticancer and antimicrobial mechanisms as well as the toxicological risks of SnO_2 nanoparticles. The ROS generation process for SnO_2 nanoparticles takes place via several processes including: (1) Fenton-type reactions via surface interactions involving oxygen vacancies and Sn^{2+}/Sn^{4+} surface redox pairs leading to the formation of $^{\cdot}OH$ from the disproportionation of H_2O_2; (2) excitation of the near-UV light producing e^{-}–h^{+} pairs that interact with O_2 and H_2O to produce $O_2^{\cdot-}$, hydrogen peroxide, and hydroxyl radicals; (3) inhibition of the mitochondrial electron transport chain complex through internalization of nanoparticles, leading to increased superoxide generation within mitochondria; and (4) inhibition of cellular antioxidant protection mechanisms via surface adsorption.(75,76)

Cellular oxidative stress caused by the action of SnO_2 nanoparticles leads to several downstream signaling events, where Nrf2 pathway activation along with other downstream genes like HO-1, NQO1, and GPx is part of a defensive mechanism against oxidative stress, while severe oxidative stress results in DNA damage, lipid peroxidation, and protein oxidation which lead to apoptosis or necrosis. Oxidative stress is concentration dependent; thus, low levels can lead to antioxidants and anti-inflammatories, whereas higher levels cause cytotoxicity.(77)

Apoptosis and Cytotoxic Mechanisms

Cancer cell apoptosis induced by SnO_2 nanoparticles occurs mostly through the intrinsic or mitochondrial pathway that includes the generation of ROS causing depolarization of mitochondrial membrane potential ($\Delta\Psi m$), releasing cytochrome c in the cytoplasm to activate the apoptosome (cytochrome c/Apaf-1/caspase-9), triggering the activation of executioner caspases-3, -6, and -7 that will cleave PARP, lamins A/C, cytoskeleton, and other cellular substrates to complete apoptotic morphology (nuclear fragmentation, cell shrinkage, membrane blebbing, formation of apoptotic bodies). The upregulation of pro-apoptotic (Bax and Bak) and downregulation of anti-apoptotic (Bcl-2, Bcl-xL) Bcl-2 family members due to ROS produced from SnO_2 nanoparticles and p53 protein causes MOMP. Activation of extrinsic or death receptor-mediated apoptosis through death receptors such as TRAIL, FasL is also observed in surface-functionalized SnO_2 nanoparticles against certain cancers.(78)

Biodegradation and Clearance

The disposition of SnO_2 nanoparticles after intravenous injection depends on their physical properties, namely size, surface chemistry, and protein corona. For nanoparticles with sizes of 8–80 nm, blood circulation followed by accumulation in tumors due to the EPR effect prevails, whereas for smaller particles (<8 nm), renal clearance through urine elimination occurs. Nanoparticles larger than 200 nm get captured by the MPS system, with primary accumulation in the Kupffer cells of the liver and macrophages of the spleen. In contrast to biodegradable polymer nanoparticles, which tend to degrade to biologically active forms, SnO_2 nanoparticles remain chemically stable within a biological matrix and will not disintegrate into soluble forms. The potential for toxicity caused by accumulation in organs such as the liver and spleen necessitates further research focusing on modifications of the particle surface.(79)

Therapeutic Applications

Anticancer Activity

The anticancer properties of SnO_2 nanoparticles have been well established for a broad range of human cancer cell lines such as breast (MCF-7, MDA-MB-231), lung (A549), liver (HepG2), cervical (HeLa), colorectal (HCT116), and prostate (PC-3). Cytotoxicity resulting from generation of ROS is considered the primary mode of action in direct anticancer effects, whereby IC_{50} levels generally vary between 10 and 100 µg/mL, depending on the characteristics of the particles. Flow cytometry has shown that the treatment with SnO_2 nanoparticles caused a dose-dependent increase in the sub-G1 phase (i.e., apoptosis) and the disruption of cell cycle arrest in G2/M phase due to DNA damage response.(80)

The Western blot and immunofluorescence results indicated that cleaved caspase-3, cleaved PARP, Bax, and p53 were upregulated and Bcl-2 and cyclin B1 were downregulated.One clinically significant feature of the nanoparticles under consideration is their selective action on cancerous cells against normal ones, which is due to high endogenous ROS concentrations and low antioxidant capacity in cancer cells, making them highly vulnerable to further oxidation. The selectivity index, defined as the ratio of IC_{50} value in normal cells to IC_{50} in cancer cells, is one of the essential factors in assessing the therapeutic efficacy of a compound. In green-synthesized SnO_2 nanoparticles, a promising selectivity index was observed in several studies, and it can be explained by the role of plant components in protecting SnO_2 nanoparticles and creating a synergy effect. The synergy effect was also noted when using SnO_2 nanoparticles along with common chemotherapeutics such as doxorubicin, cisplatin, and 5-fluorouracil, which could prove valuable in combination chemotherapy schemes.(81,82)

Antimicrobial Activity

SnO_2 nanoparticles have shown broad-spectrum antibacterial efficacy against Gram-positive bacteria (S. aureus, S. mutans, E. faecalis) and Gram-negative bacteria (E. coli, P. aeruginosa, K. pneumoniae) with minimum inhibitory concentration (MIC) values in the range of 32-256 µg/mL, dependent on the type of bacteria, nanoparticle size, and functionalization. The antibacterial mechanism includes: (1) generation of reactive oxygen species (ROS)

for oxidative damage to the cell membrane, resulting in a reduction in cell membrane stability and leakage of the intracellular material; (2) damage to the electron transport chain in the bacterial membrane, leading to an inability to produce ATP; (3) inhibition of enzyme activity by coordination between Sn^{4+} ions and enzyme-active sites via sulfur-containing compounds; (4) blocking of DNA replication and transcription processes by damaging the DNA through oxidation; and (5) physical disruption of the cell membrane due to adsorption and penetration by the nanoparticles into the cell wall.(83)

The efficacy of SnO2 nanoparticles against multidrug-resistant (MDR) bacterial strains, such as MRSA (methicillin-resistant S. aureus) and ESBL-producing E. coli strains, has been established in numerous studies, thus making these nanomaterials strong candidates to serve as substitutes or supplements for existing antibiotics in combating the worldwide phenomenon of antibiotic resistance. The antibiofilm activity is another important characteristic that may prove beneficial in overcoming the increasing levels of antibiotic resistance by targeting the mechanism of drug tolerance. The antifungal activity of SnO2 nanoparticles has also been proven, along with the potential modes of action against various fungi, such as Candida albicans, Aspergillus niger, and Fusariumoxysporum.(84)

Drug Delivery Systems

There are various features associated with SnO_2 nanoparticles that have rendered them promising candidates for the development of nanocarriers for drug delivery. The features include a high surface area suitable for drug loading, the ability to decorate the surfaces of SnO_2 nanoparticles with targeting molecules, pH-triggered release of the drugs in an acidic environment, and theranostics capability. Electrostatic or hydrogen bond interaction is used to absorb hydrophilic drugs on the nanoparticle surface, while hydrophobic drugs are loaded into SnO_2 nanoparticles coated with polymer materials.(85,86)

Release in response to changes in pH has been designed using pH-sensitive surface coatings, such as hydrazone linkages, acetyl hydrazone linkages, and polyanion coatings, which respond to increased acidity of tumor tissue (pH 6.5-6.8) and lysosomes (pH 4.5-5.0) compared to normal blood pH (7.4). The development of sustained release over a period of 24-72 hours, rather than burst release exhibited by nanoparticles without surface coatings, has been accomplished through careful manipulation of parameters including coating thickness, cross-linking density, and interaction between drug and matrix. Tumor specificity has been attained through conjugation of ligands such as folic acid, targeting folate receptors on cancer cells; transferrin, targeting transferrin receptors; hyaluronic acid, targeting CD44 receptors; and RGD peptides, targeting $\alpha v\beta_3$ integrins, to the surface of SnO_2 nanoparticles, thereby increasing tumor-specific accumulation in xenograft animals 2-5 times compared to control nanoparticles without surface coatings.(88,87)

Biosensing Applications

The inherent electrochemical activity of SnO_2 nanoparticles, which is due to their n-type semiconductor characteristics and surface peroxidase-mimic activity, makes them excellent candidates for sensor applications. Biosensors utilizing glucose oxidase (GOx) on the modified surface of glassy carbon electrodes with SnO_2 nanoparticles provide electrochemical signals in response to glucose concentration that are detectable at a limit of detection as low as 0.1 µM. Fluorescent probes utilizing SnO_2 quantum dots have been used as labels in immunoassays for cancer biomarkers, including carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), and CA-125, with detection limits reaching the pg/mL level. Sensors based on surface acoustic wave (SAW) and quartz crystal microbalance (QCM) systems with SnO_2 nanoparticle layers as sensing components have been developed for VOCs associated with diseases' breath biomarkers.(89)

Anti-inflammatory and Antioxidant Effects

Besides being pro-oxidants, which exhibit their effects through anticancer and antimicrobial mechanisms, the nanoparticles of tin dioxide have been found to exhibit both anti-inflammatory and antioxidant properties depending on concentration and cell-type specific conditions. Sub-cytotoxic concentrations of the nanoparticles of SnO_2 have been observed to inhibit pro-inflammatory cytokine production (such as TNF-α, IL-1β, IL-6) and expression of iNOS and COX-2 by blocking the nuclear translocation and subsequent activation of NF-κB in LPS-stimulated macrophages (RAW 264.7, THP-1). The observed radical scavenging activity via the DPPH and ABTS assays has been associated with the donating ability of the surface oxygen vacancies. Anti-inflammatory and antioxidant effects might be valuable for therapeutic purposes against inflammatory and neurodegenerative disorders and in oncology to counteract inflammation induced by cancer therapy.(90)

Toxicological Profile and Safety

In Vitro Toxicity

SnO_2 nanoparticles have been comprehensively tested in terms of their cytotoxic effects on both normal and cancerous human cell lines. Experiments involving IC_{50} evaluation of various normal human cells including human embryonic kidney (HEK-293), human umbilical vein endothelial cells (HUVEC), peripheral blood mononuclear cells (PBMC), and L929 cells show consistently higher IC_{50} values (>150–200 µg/mL) for the SnO_2 nanoparticles than for malignant cells of equal exposure, indicating an exploitable differential toxicity effect. While the MTT test is commonly used for such purposes, its ability to detect cytotoxic effects by SnO_2 nanoparticles could be biased due to interference of nanoparticles with formazan absorbance, thus requiring independent validation through orthogonal approaches (release of LDH, trypan blue staining, Annexin V/PI analysis).(91,92)

Genotoxic evaluation using the alkaline comet assay technique has shown concentration-dependent increased occurrence of DNA double-strand breaks within Chinese Hamster Ovary and human lymphocytes following exposure to the SnO_2 nanomaterials at concentrations higher than 100 – 200 µg/mL, due to free radical induced oxidative damage to the genetic material. In the micronucleus tests conducted in various laboratories, positive results have been reported at high concentrations (>400 µg/mL), whereas negative results at low therapeutic concentrations indicate a critical value below which there would be no genotoxic hazard. For hemocompatibility assessment performed on human erythrocytes, the level of hemolysis is found to be less than 5% at a concentration of 200 µg/mL.(93,94)

In Vivo Toxicity

The in vivo acute toxicity experiments conducted in rodents (BALB/c mice and Wistar rats) through oral, intraperitoneal, and intravenous dosing suggest relative resistance with the oral LD_{50} > 2000 mg/kg in almost all available reports and have placed SnO_2 nanoparticles in the low-toxicity category based on the GHS Classification Scheme. The histopathological assessment of major organ systems (liver, kidney, spleen, lungs, heart) in sub-acute (14 days) and sub-chronic (28 days) dosing with concentrations from 100–500 mg/kg/day showed mild inflammatory responses with deposition in the liver and kidneys, associated with slight increases in the levels of liver enzymes (AST, ALT) and creatinine in serum, which could be reversed with discontinuation of dosing.(95)

The pulmonary effects associated with intratracheal administration in relation to occupational inhalation exposure studies have shown dose-dependent acute lung inflammation (neutrophils and cytokines in bronchoalveolar fluid) in doses ranging from 2–5 mg/kg with fibrotic alterations being seen temporarily at the highest concentrations. The physiochemical characteristics of tin dioxide (nano-sized, bulk, state of surface functionalization, agglomeration status), in particular, are critical in determining the extent of toxicity in animal models of exposure and therefore highlight the importance of characterization of nanomaterials in toxicology studies. In zebrafish embryo developmental toxicity studies used to bridge in vitro and animal toxicity models, toxicity has been noted above 50 µg/mL with cardiac edema and axis bending observed as effects.(96)

Recent Advances and Innovations

Functionalized SnO_2 Nanoparticles

Functionalization of SnO_2 nanoparticles with targeting ligands, polymer coatings, and therapeutic drugs has been at the focus of intensive scientific investigations during 2020-2026, resulting in increasingly advanced multifunctional nanoplatforms. Folic acid-conjugated SnO_2 nanoparticles have proven to be able to undergo receptor-mediated endocytosis in cancer cells (KB, MCF-7) over-expressing folate receptors with a significantly elevated level of cellular uptake (2-4 times higher than that of non-targeted counterparts), along with an improved cytotoxic efficacy in animal models of xenograft tumors. Aptamer-functionalized SnO_2 nanoparticles have been successfully developed as a targeting vehicle for certain types of cancer cells that express biomarker molecules (EpCAM, HER2, PSMA) on their surface using the selectivity and specificity of aptamers produced by the SELEX methodology.(96,97)

Functionalized SnO_2 nanoparticles coated with chitosan have been widely explored for their use in oral drug delivery systems by virtue of the mucoadhesive, permeation enhancing, and pH-sensitive nature of chitosan. The development of alginate-SnO_2 nanocomposite beads for colon-specific drug delivery and hyaluronic acid-SnO_2 conjugates for CD44 targeting drug delivery are among the other forms of functionalized nanoparticles explored in literature between 2022 and 2025. Theranostic dual-functionalized nanoparticles having both drug targeting ligands and imaging moieties such as fluorescent dyes, gadolinium chelates, and radiolabels have also been fabricated.(95)

Hybrid Nanocomposites and Doped Systems

The synthesis of graphene oxide and SnO_2 hybrid nanocomposites is another area that holds great promise due to the unique ability to integrate multiple properties into a single material system. The GO-SnO_2 composite obtained by reducing GO in the presence of SnO_2 precursors through the hydrothermal method shows high surface area (>300 m^2/g), high electrical conductivity for biosensors, and an increased capacity for drug delivery (>40% w/w for doxorubicin) due to π-stacking interactions between drug molecules and the graphene basal plane. Reduced graphene oxide-SnO_2 nanocomposites also showed synergy between their antimicrobial and anticancer effects when exposed to visible light due to SnO_2 sensitization to visible light absorption by means of charge transfer from rGO.(98,97)

SnO_2 nanoparticles doped with metal ions like transition metals (Fe^{3+}, Co^{2+}, Mn^{2+}, Cu^{2+}, Ag^{+}) or rare earth metals (Ce^{3+}, La^{3+}) replacing Sn atoms in the Sn lattice show altered electronic structures, smaller bandgaps, and increased surface defects that increase their photocatalytic activity, anti-microbial activities, and biological applications. The photocatalytic activity of silver-doped SnO_2 nanoparticles has shown an exceptionally reduced MIC against multi-drug resistant bacteria such as MRSA (8-16 µg/mL against undoped SnO_2 64-128 µg/mL) where the contribution of Ag^+ ion release, along with the ability of SnO_2 nanoparticles to generate ROS, synergistically leads to antibacterial activity. SnO_2 nanoparticles doped with Ce^{3+} ions due to the Ce^{3+}/Ce^{4+} redox cycle have been studied as SOD and catalase mimics.(96,81)

Smart and Stimuli-Responsive Systems

Stimuli-sensitive SnO_2-based drug delivery systems, where drug molecules are released only when a certain physiological or external stimuli are detected, are another area of ongoing research. Among them, the most widely researched ones are the pH-sensitive systems, where there exist pH-sensitive bonds (hydrazone, acylhydrazone, boronate ester) between the drug molecules and nanoparticles which are relatively stable in normal physiological conditions (7.4 pH) but undergo rapid

hydrolysis under acidic conditions (pH 6.5–6.8) or even within the endosomes and lysosomes (pH 4.5–5.0). On the other hand, redox-sensitive systems take advantage of the increased intracellular glutathione (GSH) concentration (~10 mM) in cancer cells compared to the extracellular medium (10–100 times higher) for drug release through disulfide bond cleavage within the cancer cells. Moreover, pH and redox dual sensitive SnO_2-MOF nanocomposites have been synthesized between 2023–2025 that exhibit on-demand drug release behavior with low leakage rate and high drug loading efficiency (>30%).(50,51)

SnO_2 nanomaterials containing photosensitizers such as chlorin e6, protoporphyrin IX, or plasmonic Au nanoparticles have been demonstrated to produce cytotoxic singlet oxygen and heat when excited by near-infrared or UV-visible radiation, allowing selective and spatially-controlled tumor ablation with low systemic toxicity. The use of ultrasound-sensitive SnO_2 nanobubbles to induce mechanical damage to cell membranes, thus facilitating drug uptake and delivery under sonodynamic conditions is a novel approach to solid tumor therapy in the case where light penetration is difficult. In addition, the development of magnetic SnO_2 nanocomposites containing iron oxide Fe_3O_4 cores allows targeted delivery of drugs with MRI guidance.(52,67)

Challenges and Limitations

Technical Challenges

Despite the considerable advances made in the study of SnO_2 nanoparticles, there still exist many technological obstacles that limit their applicability in medical science. The ability to produce such particles on an industrial scale by controlling their size, morphology, surface chemistry, and uniformity in batches is rather difficult, especially for environmentally friendly syntheses, in which the unpredictability of the composition of plant extracts leads to uncontrollable factors. The transition from laboratory-scale production of grams to large-scale production of kilograms in accordance with GMP regulations is a difficult task that still needs to be addressed.(10,99)

The ability of SnO_2 nanoparticles to remain colloidally stable over extended periods in physiologically-relevant media remains a challenging issue. Aggregation in media of high ionic strength and rich in proteins results in decreased surface area, altered uptake by cells, and modification of the dose-response relationship. This approach involves lyophilization (freezing and sublimation) with cryoprotectants such as trehalose, mannitol, and sucrose. This technique converts liquid formulations into stable dry nanoparticles that can be easily reconstituted at the time of use; however, optimizing the lyophilization process is needed to ensure minimal agglomeration of particles during freeze-drying and reconstitution. Chemical inertness, which allows stability of the material, prevents degradation and thus, increases the likelihood of bioaccumulation, warranting bioaccumulation tests for more than 90 days in rodents.(98,15)

Biological and Clinical Limitations

Challenges posed by biological factors for the use of SnO_2 nanoparticles in therapy appear to be quite significant. Dynamic remodeling of the nanoparticle-cell interface via formation of the protein corona in biological fluids can conceal targeting ligands on the nanoparticle surface and lead to the unpredictable cellular internalization mechanism that cannot be estimated using in vitro models with serum-free or low-serum growth media. The EPR effect, which forms the basis for the strategy of passive targeting, appears to be quite variable for different types of tumors, vascular density, and individual patients, resulting in poor reproducibility of nanoparticle accumulation in vivo. Two-dimensional cancer cell lines cannot represent the complexity of physiological conditions in human tumors, including their three-dimensional structure and composition, requiring further testing on other pre-clinical models.The lack of clinical trial evidence from SnO_2 nanoparticles is likely to be one of the biggest drawbacks. This is because the gap between successful preclinical results and actual clinical benefits has been known to be very wide in nanotechnology. Lack of standard guidelines on how to conduct preclinical trials that can be accepted by regulatory authorities, difficulties in verifying the manufacturing process, and expensive clinical trials are some of the challenges involved in translating the preclinical findings into clinical benefits. In addition, the absence of reliable animal models for specific diseases (such as drug-resistant bacteria and rare cancers) is a problem during preclinical trials.(56,91)

Regulatory and Economic Challenges

The process of regulation of SnO_2 nanomedicines involves an intricate process that is continuously evolving, but varies considerably among different regions. Unlike conventional drugs whose performance can be analyzed based on pharmacopeial standards, nanoparticle-based therapies must be assessed on a case-by-case basis because of the complex nature of their physicochemical properties and their high sensitivity to the conditions of manufacture. The absence of internationally accepted standards for characterizing nanomaterials and evaluating their safety makes the development of regulations around nanomedicine challenging, and consequently, discourages pharmaceutical companies from investing in the development of such products. The expenses incurred when producing clinically viable SnO_2 nanoparticles under good manufacturing practice (GMP) guidelines are significantly greater than those involved in laboratory-scale synthesis, and there is also the added difficulty of navigating through a complex intellectual property environment characterized by patent overlaps in synthesis processes, surface modification techniques, and applications.(100)

Future Perspectives

Clinical Translation

The clinical application of therapies utilizing nanoparticles based on SnO_2 particles is not only feasible, but also achievable within the foreseeable future based on the progress made to date. Some key highlights for the clinical development path of SnO_2 nanoparticles include: GMP-compliant development and characterization techniques that have undergone process validation with batch release criteria; completion of detailed preclinical pharmacokinetic, biodistribution, and ADME (absorption,

distribution, metabolism, excretion) testing in at least two animal models; completion of multiple dose repeat dose toxicity studies (at least 90 days) following relevant OECD guidelines (407, 408, 412), genotoxicity and carcinogenicity studies; and IND (Investigational New Drug) pre-submission with regulators to establish the drug development plan. The primary objective of clinical Phase I studies would involve evaluating safety and tolerability profiles, along with pharmacokinetic and pharmacodynamic assessments in small groups of patients.(98)

Personalized Nanomedicine

The use of SnO_2 nanoparticles in association with new trends in personalized medicine holds promising avenues for precise medical applications. Molecular profiling of cancer by identifying the unique gene mutation and receptor overexpression signatures of individual cancer patients' tumors allows the rational design of ligands and therapeutic drugs in nanoparticle fabrication tailored to each patient. Patient-specific organoid models and tumors on a chip could serve as platforms for predicting the efficacy of nanoparticles before clinical trials, allowing for personalized companion diagnostic tools. Biomarkers for identifying patient subpopulations responsive and non-responsive to nanoparticle therapy—similar to BRCA mutational analysis before using PARP inhibitors—is a novel research field.(67,68)

Artificial Intelligence and Advanced Technology Integration

The use of artificial intelligence (AI) and machine learning (ML) techniques has become prevalent for designing, optimizing, and translating nanomaterial-based therapeutics into clinics. With respect to SnO_2 nanoparticles, ML methods such as random forest, support vector machine, and deep learning neural network have been used for the prediction of the dependency between the conditions of synthesis (concentration of precursor, pH, temperature, and capping agent) and properties of synthesized nanoparticles (size, zeta potential, crystallinity, and biological effects) using available experimental data sets to optimize the synthesis process via simulations with significant reduction in experimental work. According to results published in 2024, the use of ML-assisted synthesis optimization decreases variation between batches (PDI <0.15, CV <5%) and expedites R&D cycle up to 60% compared to traditional one-factor-at-a-time (OFAT) optimizations.(98)

The adoption of advanced manufacturing techniques such as the use of microfluidic continuous flow synthesis, the development of additive manufacturing (3D printing) techniques for nanoparticle loaded drug delivery systems, and the incorporation of inline process analytical technology (PAT) and feedback control is increasingly making it possible to translate the synthesis of SnO_2 nanoparticles into large-scale reproducible and GMP-compliant manufacturing processes. The fusion of artificial intelligence with advanced manufacturing technologies can lead to the creation of completely automated nanoparticle production systems that can optimize the process parameters based on predefined product specifications.(99,100)

CONCLUSION

This exhaustive review has thoroughly analyzed the latest advancements in the biomedical application of SnO_2 nanoparticles, including their basic physicochemical characteristics, various fabrication strategies, necessary characterization processes, quality control considerations, biological interaction processes, and clinical applications. Based on the information obtained from this study, especially from the years 2020 to 2026, it is evident that SnO_2 nanoparticles have a high potential in medical therapy for cancer treatment, antimicrobial agents, drug delivery systems, biosensors, and anti-inflammation treatment owing to the diverse biological activities based mainly on ROS generation, pH-sensitive drug release, and cellular targeting through receptor binding.

The physicochemical adaptability of SnO_2, which involves the controllability of size and shape, easy modification of surface characteristics, outstanding stability in biological medium, and natural photo-catalytic and semiconductivity behavior of SnO_2, qualifies it as a highly adaptable nanostructure material in the design of biomedical multifunctional devices. The use of green synthesis approaches using plants and microorganisms has been significant in making SnO_2 nanoparticles more sustainable and biocompatible, while more advanced functionalization methods such as PEGylation and stimulation responsiveness have improved the selectivity, activity, and safety of SnO_2-based medicines. The incorporation of hybrid materials (GO-SnO_2), doping of SnO_2 (Ag-SnO_2, Ce-SnO_2), and stimuli responsive drug delivery systems mark the cutting edge of research in the field.

Despite the progress that has been made, a number of challenges persist on the road towards clinical application, such as the development of a GMP-compatible scalable synthesis process, thorough toxicological testing, adaptation to changing regulatory requirements, and clinical efficacy trials in humans. The use of artificial intelligence and cutting-edge manufacturing technologies is likely to expedite these processes. It is only through the concerted efforts of material scientists, pharmacologists, biologists, toxicologists, physicians, and regulatory authorities that the therapeutic potential of SnO_2 nanoparticles can be fully realized in medicine. The growing body of preclinical research examined here demonstrates the scientific and medical importance of SnO_2 nanoparticles, thereby providing a compelling case for further investigation in this area.

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