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Innovative Analytical Method for Quality Control of Nanomedicine

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ABSTRACT
Nanotechnology (NTc) offers transformative solutions for societal challenges through innovative therapeutic products and materials. However, the rapid evolution of NTc outpaces existing regulatory frameworks. Silver nanoparticles (1-100 nm) are widely used across various industries, including electronics and catalysis, due to their unique optical, electrical, and magnetic properties. These nanoparticles serve diverse applications such as antimicrobial agents, biosensors, and food preservation. Various production methods, including chemical reduction and electrochemical processes, have been employed to create and stabilize silver nanoparticles. As Nano medicine progresses, advancements in manufacturing technologies are crucial for scalable and quality-assured production. This review discusses the significance of characterization techniques like electron microscopy and infrared spectroscopy in understanding nanomaterial's, alongside exploring green synthesis approaches and the challenges in Nano medicine's transition from research to clinical practice.

KEYWORDS –Nanoparticles, Nanotech, Gravimetric method, microscopic method, Analysis.

I. INTRODUCTION

Nanotechnology-enabled health products, known as nanomedicines, are at the forefront of innovative pharmaceutical solutions, providing new avenues for diagnostics, therapy, and personalized medicine. The Global Summit on Regulatory Science workshops held in 2015 and 2016 (GSRS15 and GSRS16) highlighted key priorities for the nanomedical sector, including the need for reference materials (RMs) for drug delivery systems such as liposomes(2).

Currently, two projects funded by the Horizon 2020 Research and Innovation program are advancing the regulatory science of nanomedicines. The European Nanomedicine Characterization Laboratory (EUNCL) and the Regulatory Science Framework for Nano (bio) material-based Medical Products and Devices (REFINE) are focused on developing appropriate testing methods for characterizing these products. (2)

The EUNCL (www.euncl.eu) is a research infrastructure dedicated to establishing a pre-clinical characterization cascade. This initiative aims to investigate the physical and chemical properties of nanomedicines that significantly impact their safety and efficacy. (2) It proposes integrated testing strategies based on scientific principles, utilizing novel physicochemical and biological characterization methods to evaluate next-generation nanomedicines. Nanomedicines have the potential to address limitations associated with traditional medicinal products. They encompass a wide range of drugs with varying complexities. For instance, nanocrystals have been developed to address solubility challenges for BCS class II drugs— those that are highly permeable but have low solubility in the biopharmaceutical classification system. More complex forms of nanomedicines utilize nanomaterials to navigate tissue barriers and enhance targeting to specific body sites, improving both efficacy and safety. (25) Additionally, nanotoxicology has developed into a well-established field, contributing to the systematic understanding of risks associated with nanomaterials (NMs) and supporting the development of safer, nano-enabled products. This knowledge is crucial for the successful clinical translation of nanomedicines.

The advancement of nanomedicine can be traced back to the pharmaceutical industry's progress in the 1960s, leading to the creation of nanomaterial-based systems for controlled drug release. Despite the long history of nanomedicine,

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as of 2016, there were only about 50 FDAapproved nanomedicines and 77 in clinical trials, primarily involving liposomes and protein complexes. While definitions may vary, both nanotoxicology and nanomedicine share a fundamental focus on the dose-response relationship of nanomaterials. The goal of nanomedicine is to enhance the specificity and efficacy of drugs and diagnostic agents while minimizing the required doses. This is based on the concept that engineered nanoparticles can be utilized to combat biological entities, such as corona viruses, leveraging the expertise of nanotoxicology and practical strategies from nanomedicine. (17)

Targeted delivery methods allow for lower therapeutic doses, reducing unwanted off-target toxicities and enhancing the overall safety of treatment strategies. Mitochondria play vital roles in cellular metabolism, function, and regulation, influencing processes such as redox status, cell growth, signaling, and ion homeostasis. (16) The term "nano" has gained traction across various scientific fields over the past decade. Derived from the ancient Greek word "nanos" through Latin, it essentially means "tiny." The nanoscale is typically measured in nanometers (1 nm = 10^{-9} m), encompassing systems larger than molecular dimensions but smaller than macroscopic scales (generally between 1 nm and 100 nm). (13)

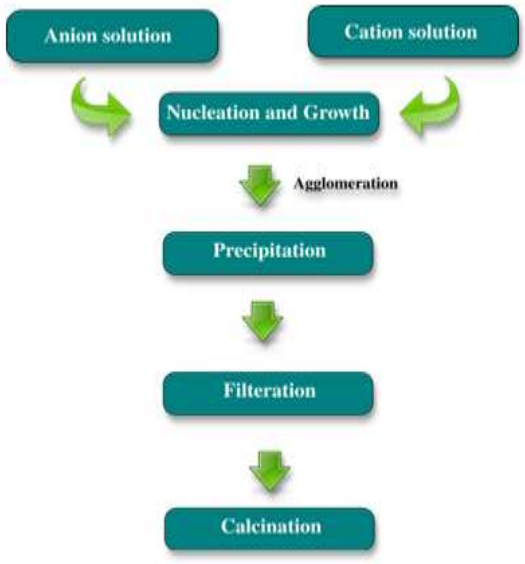
In recent years, research in biotechnology and nanoscience has surged across diverse commercial sectors, enabling the production of materials, particularly for medical applications, where traditional methods may fall short. Nanoscale properties are increasingly incorporated into bulk materials and larger surfaces. Over the last few decades, research in nanotechnology the intentional design, characterization, production, and application of materials, structures, devices, and systems by controlling their size and shape at the nanoscale (1-100 nanometers) has flourished globally. (3)

II. METHODS

Gravimetric Method:

the quantitative approaches that rarely on figuring out the mass of a pure substance that the analyte is chemically connected .The gravimetric method is the predominant technique employed for measuring particulate matter suspended in the air.Gravimetric analysis is utilized in various applications, including the chemical examination of ores and other industrial materials, the calibration of equipment, and the elemental analysis of inorganic compounds.

Precipitation gravimetry : Analyte is extracted as a precipitate from sample solution and transformed into a weighted, known-composition chemical. precipitation technique for creating nano- and microparticles. After mixing the cation and anion solutions continuously to precipitate hydroxide, they are dried to create oxide. Gravimetric precipitation analysis separates ions from solution using a precipitation process a reaction resulting from the reaction of two soluble solid products with an insoluble solid product). The chemical substance that forms sediment in a sedimentation reaction is called sedimentation.



Volatilization gravimetry: The substance is isolated from. transforming a sample into a gas to analyze different components Chemical composition that is identified and can be measured in terms of weight . Evaporation gravimetry separates the components of our mixture by heating or chemically manipulating the sample. Heat and chemical reactions separate inorganic compounds, causing a mass change that we can measure. The analytical method of thermal evaporation separates masses using thermal or chemical energy to determine mass. In this method, solid reactant molecules are converted to gas molecules using heat or chemical energy. Various volatile gases such as carbon dioxide, chlorine etc. can be separated using evaporation gravimetry.

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Electro gravimetry: Discharge analysis is divided into electrical and electronic circuits The electrogravimetric method is used to separate the ions of a substance, usually a metal. In this method, the filter solution is electrolyzed. As a result of the electric discharge, the filter is sent to the cathode. In electrogravimetry, the analyte is subjected to an electrode under controlled conditions. The weight gain is an accurate measure of the amount of analyte in the sample

Microscopic Method: The scanning tunneling microscope (STM) is one of several tools that enable researchers to observe and manipulate nanoscale particles, atoms, and small molecules. The invention of this instrument led to Gerd Binnig and Heinrich Rohrer being awarded the Nobel Prize in Physics in 1986. The scanning electron microscopy (SEM) technique offers insights into the morphology of nanocarriers by utilizing a focused beam of electrons to scan the surface. This method also reveals information regarding the chemical composition, crystalline structure, and orientation of the materials constituting the specimen, while significantly reducing. Microscopy is essential in the field of nanoscience, as it enables the direct observation, characterization, and manipulation of materials at the nanoscale. The fundamental procedure for preparing a microscope slide involves positioning the specimen on the slide, adding a drop of water or oil for a wet mount slide, and subsequently lowering a coverslip gently over the specimen.

Fig no.1 scanning tunneling microscope

Optical microscopy: The optical characteristics of nanomaterials hold significant importance in numerous aspects. These materials can confine their electrical properties, leading to quantum effects, with variations in shape, size, or type influencing the colors they emit. Using a high-quality optical microscope, we are able to observe and distinguish structures as small as approximately 250 nanometers. However, this still leaves numerous nanoscale objects and features that remain invisible to this type of microscopy. To visualize these smaller entities, an electron microscope is required.

Fig No 2 Optical Microscopy

Electron microscopy: Electron microscopy is a costly and intricate technique, yet it is highly effective for examining nanoparticles. This method involves directing a focused electron beam onto the sample and systematically scanning a specified region. The resulting images are generated from the electrons emitted from the surface of the sample. Electron microscopes serve to examine the ultrastructure of various biological and inorganic specimens, encompassing microorganisms, cells, large molecules, biopsy samples, metals, and crystals. In industrial applications, these instruments are frequently employed for quality control and failure analysis. (10)

Fig No 3 Electron Microscopy

Scanning probe microscopy:SPM obtain Image examples provided by executing scans where the suggestion oscillates The movement across the sample is characterized by a repetitive oscillation a systematic line-by-line approach concurrently conducting a scan a perpendicular orientation across the. Designated image area the dimensions of the image area for a SPM can vary significantly ranging from approximately 100 micrometers to. Just Several nanometers. This methodology is particularly effective for characterizing epitaxial thin films achieving resolutions on the order of sub-angstrom scales the surface is examined in a raster pattern & ideally the engagement between the tip and the surface of the sample lead to the bendingThe deflection of the cantilever. A detector captures the cantilevers Deflection at the apex traverses the sample or alternatively as the sample moves beneath the tip. (10)

Field emission scanning electron microscopy (FESEM): The presence of field emission cathode segment in the electron gun of a SEM produces narrower probing beams, hence enhancing spatial resolution and reducing sample charge. These devices are known asfield emission scanning electron microscopes(FESEM). The FESEM resembles a cylinder column attached to a desk. The beam of electrons is supported by the column. The analysis of micellar surfaces with the help of scanning electronmicrographswas attempted, and it exhibited with lack of resolution issues because of earlier technologies with the need of metal layer over the sample . Recent exposure to a cold field-emission extreme high resolution scanning electron microscope(FESEM) helps to examine the surface features of caseinmicellesin deeper level than

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previously possible. In conventional SEM withthermionic emission, theelectron beamis generated by heating a filament, which is typically atungstenhairpin. The dimensions of the subsequent electron beam is therefore constrained by the filament geometry that in turn restricts pixel density and resolving power. A cold field emission source generates electrons by delivering a high voltage to a very narrow pointed tip and then retrieving the electrons straight from the point through a tunnels without heating. The FESEM module is illustrated in Fig. The FESEM is a microscope that utilizes negatively charged electrons as opposed to light. These electrons are able to scan the objects in the zig-zag pattern. Electrons are freed by an emission source and propelled by a strong electricfield gradient. Inside the section of high vacuum, these primary electrons are concentrated and diverted by electronic lenses to generate a tiny scan beam that assails the item. As a consequence, each area on the surface emitssecondaryelectrons. Angle and speed of these secondary electrons are related to the surface geometry of the substance. The secondary electrons are captured by a detector, which then generates an electrical signal. Finally, every signal is amplified and converted to a display or a digital picture that may be processed and stored. Organs and nucleus of cells, polymers, and coats are a few examples of items that are researched using a FESEM in practice.

Fig no 4-emission scanning electron microscopy (FESEM)

Dynamic light scattering (DLS):

Dynamic light scattering (DLS) methods have been chosen as the major approach for measuring the size distribution of nanoparticles in liquid solutions on the bench. DLS is a reasonably quick approach for determining the size of biomoleculesin solution, with measurements requiring only minutes. DLS can differentiate between a homogeneous monodisperse sample and an aggregation sample. It has achieved such market dominance that several nano-colloid researchers depend only on it for size characterization . The approach is employed for particle characterizationin dyes, paint, and, more significantly, biological diagnosis and medical intervention systems, as well as in several other sectors where the particle size is crucial. However, the approach has certain application limitations, such as in case of working capacity and data content. DLS is often used to measure the Brownian movementof discrete particles in liquids for particle size characterization. In contrast to different microscopy, the calibrated size is not only a feature of the element core size in air, as well as thehydrodynamicdiameter, along with the impacts of fluid stabilizing agents, wetting agents, and the electricaldouble layer thickness. In practice, DLS measures a greater size distribution than microscopy methods (TEM and SEM), which need nano-colloids to be transferred to a medium and dehydrated. DLS works on the theory of time-resolved monitoring ofcoherent lightdispersed by scattering objects such as bigmacromoleculesor tiny particles, which is shown in fig. The signals obtained after scattering are analysed based on the fluctuations that are obtained from different origins. DLS handles these oscillations, which are induced by the thermal motion of the dispersion particles and exist for extremely short time periods. DLS may, for instance, measure the vibrations in nanoparticle connections, allowing for the investigation of phase transformations in aggregates and the quantification of the elastic characteristics of gels. The most prevalent use of DLS is the measurement of submicron-sized particles.

Fig no. 5 Dynamic light scattering (DLS):

Throughout its operation, samples are exposed to a coherence monochromatic polarizedlaser beamlight sourceand detector is placed at certain position (typically 173°) to receive the fluctuated light with different intensities. This scattered amplitude is dependent on particle diameter, solute molar mass, and the difference between the refractive indicesof solvent andsolute particles. DLS functions on the idea that thediffusion coefficient(D) of a particle is depending on its size, as described by the Stokes-Einstein equation:(1)$D=KBT6\pi RS$where K_B - Boltzmann constant, T-colloid temperature, η-viscosity of solvent, R_S – radius of sphere. This essentially describes how light reflects at varying rates based on size of particles. The DLS concept can be implemented in several instrumental configurations. Regarding optical setup, signal modification, signal processing, and sensor geometries, they differ. Conventional DLS devices have a scattered angle that is either sideward (90°) or rearward (at or near 180°). There are also devices with a small number of fixed scattering angles (3–5), allowing for the selection of the

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optimal angle θ for a specific sample. A small number of DLS sensors even permit the quasi-continuous modification of the scattering angle across a certain range. In addition toparticle size analysis, these multiangle dynamic light scattering (MA-DLS) systems are often used for other applications . Mani et al. utilized the DLS technique (HORIBA SZ-100 equipment) to analyse the synthesized particles size from Solanum surattense leaf for etherapeuticapplication and also analysed the nanoparticles dissolution in colloidal solution. The obtained mean particle size was 52.27 nm, andsilver nanoparticlesachieved azeta potentialof −20.4 mV. The size of the particles determined by DLS is slightly larger than the particle size obtained by SEM andTEMmicrographs, which is due to utilizationhydrodynamicradius technique for size calculations. The green synthesis ofiron oxidenanoparticles from the extracts of dried fruit (Ficus carica) utilized DLS technique for hydrodynamic diameter analysis in colloidal solutions. DLS analysis determined the amplitude mean diameter of nanoparticles as 475 nm, which is the diameter of a core and the materials surrounding it. The AgNPs extracted from Camellia sinensis through biogenic synthesis was subjected to DLS equipment with 173° angle and in an aqueous solution at 25 °C. The DLS tests observed that the mean hydrodynamic diameter size of AgNPs was 34.68 ± 4.95 nm, while the mean PDI value was 0.28 ± 0.01 and the mean zeta potential was −35.50 ± 3.50 mV . The DLS study was incorporated for the analysis of biosynthesized copper nanoparticles from C. halicacabum leaves extract forbiomedical application, and the mean particles size was in the range of 30–40 nm. These values are in good agreement withTEMand FESEM surface analysis results. The diverse size distribution of Cu NPs may be attributable to the varying reduction capacities of several ecofriendly natural compounds abundant in the aqueous CHL extracts . Another interesting work reported by Patil et al. also reveals the metallic nanoparticlesextracted from marinemicroorganismsshow larger particle size in DLS as compared to size observed in TEM equipment

III. CONCLUSION

Nanotechnology has revolutionized the field of medicine, offering novel solutions for diagnostics, therapeutics, and personalized healthcare. The development of nanomedicines, such as liposomes and nanocrystals, addresses limitations of traditional pharmaceuticals, improving solubility, bioavailability, and targeted drug delivery. Regulatory initiatives like EUNCL and REFINE are advancing the science of nanomedicine by establishing standardized characterization and testing protocols, which are critical for ensuring the safety, efficacy, and clinical translation of these complex products.

Despite decades of research, nanomedicine remains a rapidly evolving field with significant potential to reshape healthcare. By leveraging nanoscale properties, researchers aim to optimize drug delivery, reduce off-target toxicities, and enhance therapeutic outcomes. Furthermore, the integration of nanotoxicology into regulatory frameworks supports the development of safer nano-enabled products. As scientific understanding of nanomaterials deepens and regulatory pathways become more defined, nanotechnology-enabled health products are poised to make transformative contributions to modern medicine, ultimately improving patient care and health outcomes worldwide.

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