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SYNTHESIS OF SILVER NANOPARTICALS FROM AEGLE MARMELOS LEAF EXTRACT BY GREEN SYNTHESIS APPROACH AND PREPARATION AND EVALUATION OF ANTIMICROBIAL CREAM. – A REVIEW

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ABSTRACT

Nanoparticles are novel drug delivery systems. They have tremendous advantages over the conventional drug delivery system. Hence, these days researchers been working on finding out optimal usage of silver nanoparticles in various fields including medicine. Silver nanoparticles are one of the nanoparticles, which have significant therapeutic applications such as antimicrobial, treat burns, anti inflammatory and immunomodulatory effects. But they have many side effects due to usage of synthetic excipients. To avoid this problem green synthesis approach for synthesis of silver nanoparticles is making a good impact on drug delivery and it's improved safety. The synthesized nanoparticles are characterized for checking it's physical and chemical properties by techniques like spectroscopy, transmission electron microscopy, chromatography etc. As well for ease of application of silver nanoparticles for its Antimicrobial properties on skin, topical cream is convenient option. This cream is evaluated by different evaluation tests like morphology, pH, Viscosity, spreadability and it's antimicrobial activity against different pathogens.

KEYWORDS: Nanotechnology, Nanoparticles, Green synthesis, Silver nanoparticles, Algae Marmelos, Antimicrobial cream.

INTRODUCTION

NANOTECHNOLOGY

Nanotechnology deals with the research and development at the atomic, molecular or macromolecular scale.[1] The science deals with the design and manipulation of materials at the atomic and the molecular scale to produce nano-sized materials that can be measured in nanometers. Hence, they have earned the nick name tiny science.

Nanotechnology, that speaks of manipulating matter in terms of atomic or molecular dimensions, has evolved significantly from where Richard Feynman envisioned it in his path-breaking lecture back in 1959, when he first proposed the concept of controlling individual atoms. During the 1981 discovery of the scanning tunneling microscope, scientists were able to visualize and manipulate matter at a level never before seen; in 1991, carbon nanotubes were discovered, and in 1999, the National Nanotechnology Initiative was formed, breaking all barriers in place for research and development. Over the years, nanotechnology has been applied in medical drugs delivery systems, as well as used in electronics to produce advanced materials. Currently, scientists have expedited their research on how nanotechnology can be applied in further research keeping in mind safety and ethical concerns with regard to its usage.[1]

CLASSIFICATION OF NANOMATERIALS

Natural Nanomaterials

Definition: Nanomaterials which can be found in nature.

Examples: Volcanic ash, Smoke particle, Biological molecules (e.g., hemoglobin) Structural colors in nature (e.g., peacock feathers)

Artificial Nanomaterials

Definition: Nanomaterials originating from human work or designed for some special application.

Types

1. Unintentionally Produced: Result from processes not specifically aimed at creating nanomaterials (eg, vehicle exhaust, pollution).
2. Intentionally Produced: Deliberately engineered for applications in various fields (eg, nanocomposites in manufacturing, nanoparticles in medicine.[1][2][22]

NANOPARTICLES

Nanoparticles are particulate dispersions or solid particles with sizes between 10 to 1000 nm. They exist naturally and have been used since ancient times, leading to various applications in medicine, electronics, and materials science.

Nanoparticles are minute particles or particulate matters below 100 Nm in diameter which can be categorized into liposomes, metallic nanoparticles, polymeric nanoparticles, and albumin bound nanoparticles.[2]

Types of Nanoparticles

Micelles

Micelles are spherical aggregates of amphiphilic surfactant molecules of the size 10- 100 nm in diameter. They enhance the solubility of hydrophobic drugs and are used as Nano carriers in drug delivery, imaging, and contrast agents.

Liposomes

Liposomes are lipid vesicles with bilayered structures ranging from 30 nm to several microns in size. They can encapsulate both hydrophilic and hydrophobic drugs and can be engineered for targeted release. An example of a PEGylated liposomal doxorubicin is used in breast cancer treatment.

Dendrimers

These are highly branched macromolecules containing a central core and functional groups. They can encapsulate or carry therapeutic agents, which in turn improves their bioavailability. They have more promise in gene delivery and drug efficacy.

Carbon Nanotubes

These are cylindrical structures consisting of rolled-up carbon sheets; they have a very large surface area and load drugs significantly. Their unique properties make them useful as imaging agents and biological sensors.

Metallic Nanoparticles

These include iron oxide and gold nanoparticles, vary in size, and also can be functionalized for targeted delivery. The application area includes imaging, laser treatments, and as drug delivery carriers.

Quantum Dots

Quantum dots are the fluorescent semiconductor nanocrystals, sized between 1-100 nm. They are recognized by their optical property along with an application in drug delivery and cellular imaging.[2][3]

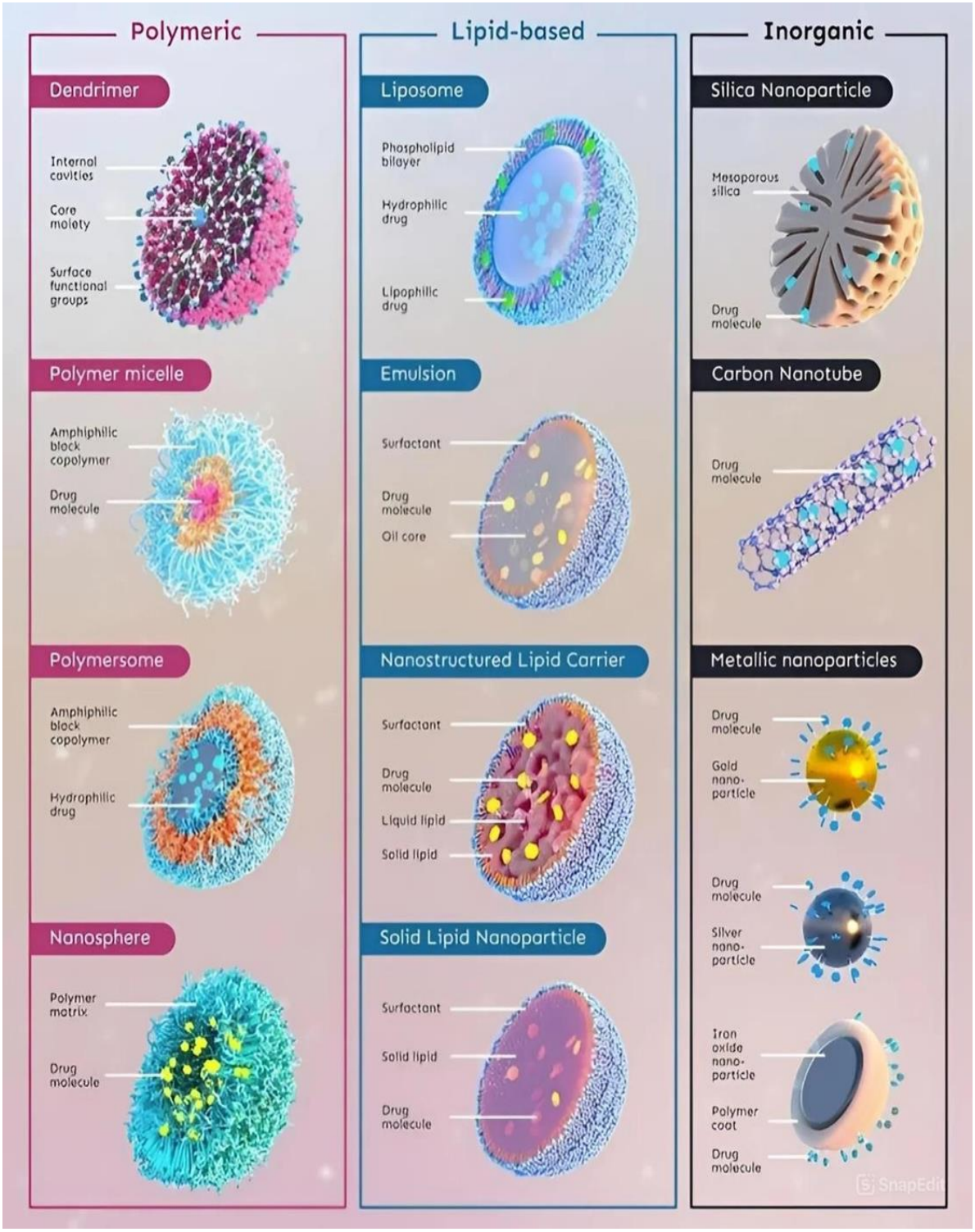

Fig. 1: Types Of Nanoparticles.

APPLICATION OF NANOPARTICLES

1. Nanoparticles for Antimicrobial Therapy: Nanoparticles, especially silver, copper, and zinc oxide, have in stronger antimicrobial properties. These can be used to kill bacteria, viruses, and fungi, hence, they may offer a solution to the antibiotic-resistant infections.
2. Nanoparticles for Gene Delivery: The nanoparticles can be engineered such that they deliver genetic material, DNA or RNA, inside the cells. Such a technique has turned out to be very important in gene therapy for the treatment of genetic disorders or enhancement of the immune response against cancer.
3. Immunotherapy Nanoparticles: Results have demonstrated that functionalized nanoparticles can be employed to enhance the immune response of the human body. For example, it would enhance the outcome of cancer immunotherapy if nanoparticles are used to deliver antigens or agents with an immunomodulatory action to stimulate the body's immune cells against the tumor.
4. Nano-particles in Wound Healing: Nano-particles, either lipid-based or polymer- based are employed in wound-dressing for quick healing. They can provide growth factors or antimicrobial agents directly to the wound site for the speedy recovery process, even preventing infection as well.
5. Nanoparticles for brain drug delivery: With size-smallness and the ability to penetrate through the blood-brain barrier, nanoparticles are currently under development for direct drug delivery directly to the brain. They can easily target the brain for diseases like Alzheimer's and Parkinson's or brain cancers.
6. Vaccine delivery nanoparticles: Nanoparticles are engineered to house and deliver vaccine antigens with high efficiency and stability, thereby being used for targeting specific cells in order to elicit the best possible immune responses in controlling disease.
7. Diagnostic Imaging Using Nanoparticles (Nano-biosensors): Nanoparticles are being utilized for advanced diagnostic methods as biosensors. Due to the high interaction with biomolecules, it is capable of detecting early markers of disease, therefore, advanced early diagnostics of conditions such as cancer, diabetes, or infections.
8. Nanoparticles in Tissue Engineering Nanoparticles can also be used in tissue engineering scaffolds. Similar to the extracellular matrix, these particles promote cellular growth and differentiation, which assist in tissue and organ regeneration.
9. Nanoparticles for Photothermal Therapy Against Cancer: Gold or carbon-based nanomaterials may absorb the light energy and transform it into heat. Activated by a

beam of light at the tumor sites, these nanoparticles can selectively kill cancer cells by heating them up, referred to as photothermal therapy.

10. MRI and CT Imaging Nanoparticles Iron or gold-based nanoparticles are being developed to be used as contrast agents in MRI and CT scans, which will enhance the resolution and precision for better detection of abnormalities or diseases.[6][2]

ADVANTAGES OF NANOPARTICLES

1. Enhanced Solubility: Nanoparticles can enhance the solubility of poorly soluble drugs.
2. Targeted Release: Nanoparticles can be designed to deliver the drug to a specific tissue or cell, reducing the systemic side effects.
3. Controlled Release: The release of drug can be planned to sustain for a longer period, thereby reducing the frequency of dosing.
4. Protection: Protects the drug from in vivo degradation.
5. Improved Bioavailability: Can increase the amount of drug that ultimately reaches its site of action.

DISADVANTAGES OF NANOPARTICLES

1. Toxicity: Some nanoparticles may have toxicity problems due to the materials used or their size.
2. Scaling up Manufacturing: Methods of preparing nanoparticles might pose some problems when scaled up for large-scale productions.
3. Stability: Nanoparticles may aggregate or degrade in storage where their performance is compromised.
4. Price: It is also more costly to synthesize and validate nanoparticles compared to the more commonly available drug formulation.[2][8]

SILVER NANOPARTICLES

Silver nanoparticles (AgNPs) are one of the most explored categories of nanomaterials for new and improved biomaterials and biotechnologies, with impressive use in the pharmaceutical and cosmetic industry, anti-infective therapy and wound care, food and the textile industry.

In the 1990s, colloids, in fact silver nanoparticles, were introduced in ointments that could be applied on open wounds and killed the bacteria very effectively. Today, nanoscale silver-containing bandages and ointments and wound dressings are easily available.

The AgNPs now have applications in antiseptics, such as in one of its products in the form of bandages and ointments with excellent antibacterial activity. Most AgNPs in aqueous suspensions exist in a, +1 oxidation state, hence being more biologically active.

Silver nano-particles gather the most attention of all metallic nanoparticles. To begin with, their immense biological and medical applications-healing antibiotic, antifungal, and antiviral agent-have triggered a wide use, with over 100 million tons of silver used annually.[4][12]

SYNTHESIS METHODS Of SILVER NANOPARTICLES

The selection of the synthesis method is critical for nanoparticles processing. AgNPs are produced using physical, chemical, and biological approaches. The growth mechanism strongly affects the nanoparticle morphology and physicochemical properties.

- **Physical Method**

Some of the key physical methods used are evaporation-condensation and laser ablation. Here, solvent contamination is prevented, so that nanoparticles can be uniformly distributed within the product, and also increases the final product's purity.

- **Chemical Synthesis**

The most commonly used chemical synthesis for silver nanoparticles is reduction in the presence of various organic and inorganic reducing agents. Other common chemical methods include microemulsion, sonochemical processes, electrochemical methods, and solvothermal decomposition. Each of these methods has its own benefits regarding yield, size control, and scalability.

- **Green Synthesis Approach**

Green synthesis depends upon the utilization of biological systems such as bacteria, fungi, and extracts from plants for synthesizing nanoparticles. This method has gained wide acceptability in recent times due to cost effectiveness and lesser levels of toxicity in comparison to conventional methods. In recent times, research on this method has been increasingly reported because it is believed to offer a promising future in the synthesis of nano-materials that are ecofriendly.

This is achieved through sustainable nanoparticle synthesis using microorganisms, plant extracts, or templates incorporating membranes and DNA.[5]

BENEFITS OF GREEN SYNTHESIS APPROACH

- Environment-Friendly and Non-Toxic: The green synthesis of silver nanoparticles uses plant extracts which come directly from natural resources, thereby reducing the dependency on harmful chemicals and resulting environmental impact.
- Low Cost: Using easily available low-cost plant materials not only reduces the cost but also is quite simple. Thus, the green approach is economically sound for mass productions.
- Biocompatibility: Silver nanoparticles obtained from greener routes were more biocompatible and thereby safer for medical and environmental applications.
- Scalable: This green synthesis method is relatively simple and easy to scale up with no complicated equipment or conditions required for large-scale production.
- Low toxicity: Silver nanoparticles produced by green synthesis tend to have low toxicity compared to their chemical synthesis counterparts, making them safe for biological purposes.[28][29]

MATERIAL AND METHODOLOGY

AEGLE MARMELOS

The use of Aegle marmelos for the synthesis of silver nanoparticles:

Aegle marmelos is widely known as Bael. This medicinal plant has been in use for a long time in traditional medicine, having antimicrobial and antioxidant properties. In this paper, the green synthesis of AgNPs using the extract of Aegle marmelos shall be emphasized with potential applications in topical cream formulations for enhancing the antibacterial activity used in treating dermatological disorders. The biological synthesis of silver nanoparticles using Aegle marmelos leaf extract holds much promise. Moreover, silver nanoparticles synthesized from the methanolic extract of Aegle marmelos fruit exhibit high antimicrobial activity against the host of pathogens.

It's at unprecedentedly Increasing interest in green nanotechnology, as the research attention is currently being steered more and more toward the therapeutic applicability and the environmental advantages of silver nanoparticles mediated by plants. This trend patently outlines commitment towards sustainability in innovation in materials science.[7][10]

Fig. 2: Aegle Marmeloes.

Table 1: Morphology of Aegle marmeloes.

Category	Detail
Common Name	Bael, Bengal quince, Wood apple
Biological Name	Aegle marmelos
Source	Native to the Indian subcontinent found in India, Bangladesh, Nepal, and Sri Lanka
Parts used	Leave, fruit, bark, seeds
Chemical Constituents	Flavonoids(quercetin and rutin)
Traditional Use	Antimicrobial, Anti-inflammatory, Digestive Health, Antioxidant

INTRODUCTION TO CREAMS

Creams are topical dosage forms intended to deliver therapeutic effects at specific targets in the skin with minimal side effects. Such preparations contain easy administration and transport, making them good drugs for dermatologic treatment of various skin diseases. There is recent research which has indicated that creams formulations containing silver nanoparticles possess a considerably enhanced level of antibacterial activity when compared with conventional ointments. Such efficacy levels put these formulations at the forefront of potential applications in dermatological preparations.[11]

METHODOLOGY

Collection of Plant Material

Fresh plant material of Aegle marmelos will be collected from the botanical garden of Arvind Gavali College of Pharmacy in Jaitapur, Satara.

Preparation of Plant Extract

- Fresh leaves of A. Marmelos will be plucked from a tree, washed three times with deionized water, and dried in a hot air oven at 40–45 °C for 48 hours till they attain

approximately 6% moisture content that has been analyzed through the Sartorius MA-150 moisture analyzer. Powdering of dry leaves will be done. The highly concentrated brown leaf extract will be prepared by dissolving 1 g of the leaf powder in ultrapure water at 5%, w/v, and heating it using a hot water bath at 100 °C for about 10 minutes. The residue will then be filtered using Whatman filter paper.

- Fresh leaves of Aegle marmelos shall be used in order to draw out the extract. The leaves shall be washed thrice in distilled water, and then cut into fine pieces after which they shall be placed in a 500 mL Erlenmeyer flask. Thereafter, distilled water shall be added in the amount of 100 mL, and the mixture shall be heated for a period of 10 minutes. The extract shall be filtered using Whatman no. 1 filter paper after cooling it to room temperature.[17][21][23]

Synthesis of Silver Nanoparticles

- Silver nitrate, AgNO3 is being used as a precursor for synthesizing silver nanoparticles. We will prepare an aqueous solution at a 0.1 mM concentration of silver nitrate. Silver nanoparticles were synthesized by mixing 25 mL of plant extracts in 75 mL of silver nitrate to get a final concentration of 0.1 mM at room temperature. At 2 minutes, a color change is observed. The color of the solution changes from colorless to dark yellow, manifesting silver nanoparticles synthesis. The color darkens and turns into dark brown after 5 minutes.
- 15 mL of 1 mM silver nitrate solution will be taken in 50 mL conical flask and 1 mL of A. marmelos leaf extract will be added dropwise. The color of the reaction mixture turns from colorless to yellowish-brown showing formation of silver nanoparticles.
- The reduction of Ag+ ions has been confirmed by viewing the UV-Vis spectrum of the solution. A mixture of synthesized nanoparticles and the remaining constituents will be centrifuged at 10,000 rpm for 20 minutes. Centrifugation will be performed 3 to 4 times. Further, organic material present in the leaf extract will be removed by suspending the pellets in distilled water. The pellets from the bottom of the centrifuge tube will then be dried at 60°C in a hot air oven.[11][22][24][25]

PREPARATION OF CREAM

- Oil phase-the waxes should be melted at 75°C and ingredients mixed well. Aqueous phase: Deionised water soluble ingredients should be dissolved in deionised water. The water phase should be warmed at 75–80°C until all the ingredients are dissolved. If the

temperatures of both water and oil phases are the same, add slowly, with moderate agitation, the aqueous phase to the oil phase. Stir until temperature is reduced to 40 °C.

- Beeswax and liquid paraffin will be mixed up in a water bath at 90 °C to prepare the oil phase. For the aqueous phase, distillated water is mixed up with borax at 50 °C in the solution of silver nanoparticles and it should be added slowly to the oil phase while stirring at a constant rate for forming the cold cream containing silver nanoparticles.[11][19]

CHARACTERIZATION OF NANOPARTICLES

Characterization of nanoparticles is an important component of nano metrology and involves measurement of the physical and chemical properties of the nanoparticles. This characterization process defines size, shape, surface area, and morphology. Such factors determine behavior and applications, including catalysis, electronics, and drug delivery. Such a characterization ensures quality, consistency, and safety as it helps in assessment of environment and toxicity.

Key techniques include electron microscopy for the assessment of particle size and morphology, for example scanning, transmission electron microscopy, and atomic force microscopy. Elemental analysis techniques measure the bulk chemical composition, with crystal structure determined by X-ray diffraction or electron diffraction.

For instance, methods to measure solubility include atomic absorption spectroscopy and inductively coupled plasma mass spectroscopy. The BET, dynamic light scattering (DLS), SEM, and TEM methods have to ascertain surface area.[9][23][24]

UV Visible spectroscopy

UV-Vis spectroscopy is a very simple and sensitive technique to characterize and confirm the existence of silver nanoparticles in a material. In other words, it measures the absorbance of a substance in the ultraviolet and visible ranges of the electromagnetic spectrum.

Some of the characterizations related to silver nanoparticles by UV-Vis spectroscopy as follows

- **Wavelength**: The general range of the wavelength for the absorbance measurements is between 200 and 700 nanometers.
- **Preparation of sample:** The colloidal solution with silver nanoparticles is concentrated and determined with a UV-Vis spectrophotometer. Normally, the blank is deionized water.

- **Change in color:** The color of the sample is also recorded, as the excitation of electrons in transition metals influences the absorption within the ultraviolet region. For instance, the solution might shift from light yellow to dark brown during the synthesis of silver nanoparticles.
- **Peak Identification:** The UV-Vis spectrum can have peaks that correspond to the absorption of silver nanoparticles.[24][25]

FTIR spectroscopy

- An FTIR (Fourier Transform Infrared) spectroscopy has been an efficient characterization tool for silver nanoparticles, especially in terms of their surface chemistry and interaction.
- **Wavelength range:** FTIR spectroscopy measures absorbance in the range of infrared, typically 4000 to 400 cm^{-1}. This wavelength interval falls within a variety of molecular vibrations.

- **Sample preparation:** Samples containing silver nanoparticles may be prepared as follows:
- Solid films: Nanoparticles can be suspended in a solution, then dried and pressed into a pellet with KBr.
- Liquid samples: Solutions can be analyzed with a proper cell or by merely dropping the solution onto a substrate compatible with FTIR.

- **Functional groups identification:** FTIR is suited for the identification of functional groups present on the surface of silver nanoparticles. Peaks in the spectrum represent specific molecular vibrations, such as C=O, N-H, and O-H.
- The existence of stabilizing agents or capping agents involved in nanoparticle synthesis may be confirmed through characteristic absorption bands.

- **Peak assignment:** Peaks in the FTIR spectrum characterize the chemical bonds. For silver nanoparticles, peaks can be formed from the following:
- The silver-oxygen interaction
- Organic ligands and capping agents that are bound on the nanoparticle surface.
- Qualitative changes in peak intensities and positions would indicate any interactions or transformation resulting from environmental conditions or synthesis protocols.

- **Characterization of Surface Chemistry:** It can be useful in providing insight to the surface chemistry and functionality of the silver nanoparticle, especially for catalysis, sensing, and medicine.
- This can be used to interpret the level of functionalization and the presence of contaminants.[24][25]

Transmission Electron Microscopy: Transmission Electron Microscopy (TEM) is one of the most powerful characterization techniques to characterize the silver nanoparticle at nanoscale and provides invaluable insight into structural and morphological properties. High resolution is achieved with TEM, and thus detailed visualization down to atomic levels must be realized for an understanding of the structure of such a crystal. Such a technique will directly enable measurement of size and shape, which happens to be critical factors influencing the physical and chemical properties of these nanoparticles, such as catalytic activity and stability. This complete characterization is significant for the optimization of synthesis and application of silver nanoparticles in the fields of medicine, electronics, and remediation of environment.

As a whole, TEM is an important tool to further the understanding and application of silver nanoparticles in various technological applications.[25]

Antimicrobial activity

- Identified mechanisms of AgNPs as antibacterial have been summarized in the following points:
- Membrane Interaction: AgNPs penetrate bacterial membranes, accumulate within the inner membrane, and lead to membrane destabilization, increased membrane permeability, and leakage of cellular contents. Consequently, they cause cell death. They interact with the sulfur-containing proteins of the cell wall with enough force and thus are likely to demolish their structures.
- Cellular Impact. On reaching the cell, the AgNPs will interact with sulphur and phosphor groups in DNA and proteins, disrupting their structure and functions. Respiratory chain can be interfered with when AgNPs react with thiol groups in enzymes, which can give ROS and free radicals leading to breaking up of cellular machinery and apoptosis activation.
- Release of Silver Ions: AgNPs may release silver ions. Given that it is, in the majority of cases tiny and has a charge, it will be able to interact with components of the cell

- Differently through the alteration of metabolic pathways, membranes, genes and genetic material.[15][16]
- Silver nanoparticles kill microbes by their antimicrobial property. The agar well diffusion assay is applied for testing antimicrobial activity of silvernanoparticles. Preparations of microorganisms such as Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans and Aspergillus niger were applied uniformly in several spots using a sterile cotton swab on nutrient agar or Sabouraud dextrose agar plates. Five wells of 6-mm diameter were prepared in the agar plates. Solutions of silver nanoparticles prepared at four different concentrations namely 0.25, 0.50, 1.0, and 2.0 mM, were poured (20 µl each) into the corresponding wells. A control sample is added as BPE to test its antimicrobial activity.
- The test plates are kept at 37°C for 24 h and 48 h for the bacterial culture and yeast cultures, respectively. The diameters of inhibition zones are measured. After keeping at 37°C for 24 h, the zone of inhibition is measured and compared to that of levofloxacin as standard.[25][26][27]

EVALUATION PARAMETERS FOR AEGLE MARMELOS CREAM

1. Morphological evaluation

Morphological evaluation is a manual evaluation of cream's physical parameters like colour, odour and texture. This parameters are observed by naked eyes and other sensory organs and hence they are also called as organoleptic evaluation.

Aesthetic attributes like color and smell can significantly affect consumer preference and acceptance. Hence this test is performed.[11][12]

2. pH test

pH measures the concentration of hydrogen ions in a solution, quantifying how acidic or basic it is, with a scale of 0 to 14. A pH of 7 indicates neutrality while below 7 represents acidity and above 7, alkalinity.

This is because the pH in cream might pose instability, texture problems, and overall safety issues with the product. In so doing, adequate pH must be developed to ensure that the cream will come out with the proper qualities and not grow microbes. A pH meter is an instrument that can indicate a pH level in real time. 0.5 grams of cream would be dissolved in distilled water in the volume of 50 milliliters, and its pH would be measured.[11]

3. Viscosity

Viscosity is an important parameter in deciding the effectiveness by which the active agents of cream are allowed to distribute to the affected areas, thus affecting the overall therapeutic efficiency of it. The proper viscosity ensures that it is easily spreadable so that it can penetrate into the skin easily and ensure comfort to the user thereby effecting compliance. It also contributes to maintaining stability and uniform distribution so as to ensure the sustenance of ingredient activity during time. Well-balanced viscosity is highly critical to achieve quality control over every batch to ensure high-quality texture and performance. Another factor affecting packaging and dispensing, and hence, usability of the product is viscosity. It catches manufacturers' attention to ensure the dosing to be both effective and user-friendlySome of the widely accepted techniques of viscosity measurements are as follows: a.Viscometers, for example, Brookfield or rotational viscometer, measures the torque- force required to rotate the spindle inside the cream at controlled speed.

Capillary Viscometer: It measures the time taken to let a given volume of cream pass through a narrow tube under the influence of gravity.

Ball Falling Viscometers: It measures the time that the ball takes to fall through the cream, giving a viscosity scale.

Rheometers: It measures the flow and deformation behavior of the cream under varied stress and shear rates, providing detailed rheological data.[12]

4. Spreadability test

Checking for spreadability is important because if the cream spreads easily, this ensures that the product spreads evenly and that the action will achieve uniform coverage of the skin, which is critical for efficacy, especially when it comes to therapeutic products.

The creams with the best spreadability are most likely to be taken up, therefore enhancing the performance in general. The measurement of spreadability also assists the manufacturers in knowing how good or stable the formulation is, thereby whether it fulfills the required specifications. Checking spreadability ensures that the cream is functional and aesthetically acceptable to consumers.

The process which is commonly used for testing spreadability is known as "slide or sliding test" for spreadability. This method measures the time taken for two glass slides to separate after being loaded with a cream formulation, providing an indication of the cream's spreadability. The shorter the time for separation, the better the spreadability of the cream.

Formula for spreading testing is as follows

$$S = m * l/t155$$

Here,

M – weight tied on upper slide

L – length of glass slide

T – time in sec

On the other hand, we can also evaluate the spreadability of cream by applying it directly over human skin.[11][12]

5. Phase separation test

Phase separation test is important to check for the following reasons: it shows the stability of the formulation; phase separation indicates instability, which leads to the ineffective product. Active ingredients separation may compromise the therapeutic benefits of active ingredients, if it occurs. It is also useful for monitoring the separation of active ingredients to ensure uniformity in quality across batches-an essential aspect of consumer satisfaction and brand reputation. It may also affect the aesthetic appeal and texture negatively. Therefore, by detecting phase separation, the formulation and packaging of creams can be done better; hence, they would come to the consumer stable, effective, and not detrimental to their visual appeal, with higher consumer confidence.[11]

6. Irritancy testing

Irritancy testing of the cream is done to establish its safety and tolerability to the skin. As this test is based on negative reaction such as redness, swelling, or itching after application, the formulation must be safely established, even for sensitive skin or vulnerable populations such as children. It also ensures them of reaching the regulatory standards that are needed and an important step before marketing the product. In irritancy testing, the formulations can also be altered for improved safety as well as the effectiveness because the manufacturers judge their compatibility with the skin. Thus, with this result, irritancy testing benefits both the consumers as well as by upholding trust among them while using the product, hence moving towards success in the market. For this testing, cream is applied on dorsal surface of hand on about 1 sq. cm area, area and time should be noted. Irritancy, erythema, edema, is checked if any for regular intervals up to 24 hrs. and reported.[12][18]

7. The dye test

The dye test is performed on cream to determine its emulsion type i.e. water-in-oil or oil-in-water. To perform a dye test on cream, an amaranth solution is used. The dye is mixed with the cream, and a drop of the mixture is placed on a microscope slide and covered with a cover slip and after that it should be examined under a light microscope. If the drop appears red against a colorless background (the continuous phase), the type of formulated cream is identified as water-in-oil. Conversely, if the drop is colorless with a red background, the formulation is oil-in-water. This test helps detect and confirm the type of emulsion.[11]

8. Antimicrobial activity

Testing the antimicrobial activity of a cream is important for several reasons. It determines whether the cream has an inhibitory and lethal action toward pathogenic microorganisms, so it functions as it should be. Determining whether the cream can prevent infection, particularly in wound or skin applications, would have been quite essential. These results would also better formulate it to achieve maximum efficacy or at least reduce adverse effects. Beyond that, the potential to exhibit significant antimicrobial activity might improve consumer acceptance of the product. More broadly, any assessment of the cream's antimicrobial activity must take into consideration safety and efficacy for the intended use. At laboratory scale we can perform this test by conventional methods which include disk diffusion and agar dilution techniques.[15][13][18]

CONCLUSION

In conclusion, silver nanoparticles, especially those synthesized through eco-friendly green methods, offer significant advantages in drug delivery and therapeutic applications. Their unique properties, such as antimicrobial, anti-inflammatory, and immunomodulatory effects, make them highly effective in various medical treatments. Green synthesis enhances their safety and bicompatility, reducing the side effects associated with synthetic methods. With continued research and development, silver nanoparticles hold great potential for revolutionizing medicine, particularly in topical therapies, wound healing, and targeted drug delivery systems.

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