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Advanced Nanocarrier System - The Emergence of Nanoflowers

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ABSTRACT:

Recently, in nanoscience innovative and effective technologies have been increasing day by day to show the maximum efficiency in the delivery of drugs to a particular organ or tissue, the use of nanofibers, fullerenes, carbon nanotubes, nanorods, and nanowires are emerging based on the delivery of the material. Along with those recently developed nanoflowers for efficient delivery of the materials. These nanoflower structures have a higher surface-volume ratio, enhanced adsorption of materials, and unique morphologies when compared to other nanoparticles. These nanoflowers were classified into organic, inorganic, and hybrids. Hybrid nanoflowers include copper, calcium, gold, silver, and magnesium combined with the proteins and DNA for delivery. The application of the nanoflowers is based on structural features like size, shape, and the morphology of the nanoflowers generally. These nanoflowers were developed for biomedical applications and various fields like the biotechnology industry, medicine, sensing and diagnosing, and catalysis like electro, physical, and chemical processes.

An overview of the structure, manufacturing processes, kinds, and polymers of nanoflowers for their creation and use in a variety of domains, including biomedicine, sensing, cancer, hypertension, and microbiological research, is provided in ths article.

Keywords: Nanoflower, hydrothermal method, Polymers, gold nanoflowers, sensors, and biosensors.

INTRODUCTION:

"There's Plenty of Room at the Bottom," presented in 1959 at the annual meeting of the American Physical Society, marked the beginning of the investigation of nanotechnology and nanoscience as emerging topics within materials science [1]. Nanostructured materials' morphology, size, shape, and dimensionality determine their physicochemical properties. Therefore, the development of novel materials with different sizes and shapes is a fundamental focal point of research. Afterward, a variety of nanomaterials, including fullerenes, graphene, nanotubes, nanofibers, nanorods, nanowires, nanoparticles, nanocones, and nanosheets were developed for the delivery of materials like drugs and other substances [2,3]. Of them, hierarchical 3D nanostructures in the form of flowers, or "nanoflowers," have garnered a lot of interest due to their reduced cost and environmentally benign preparation techniques, as well as their better surface-to-volume ratio when compared to spherical nanoparticles [4-8]. Nanoflowers are microscopic particles with a nanoscale range of 100–500 nm that have structural similarities to plant flowers, and these nanoflowers are important in the field of pharma because of the having advantages like their enormous surface area, nanoflowers show improved carrier immobility and charge transfer. The zinc oxide nanoflowers coated with silver had improved charge transfer and carrier immobility for SERS sensitivity, and Proteins and enzymes are unstable, therefore their immobilization on the metal's surface increases their stability. Concanavalin A's surface was immobilized by the enzyme-like glucose oxidase, which was stabilized by the metal ion calcium for nanoflower synthesis, along with this the effectiveness of the surface reaction increased with three-dimensional structural nanoflowers. [9-12]. There are numerous uses for these NFs in catalysis nanotechnology, medicine, biosensing, sensing, magnetism, cosmetics, and biomedicine [13].

STRUCTURE OF NANOFLOWER:

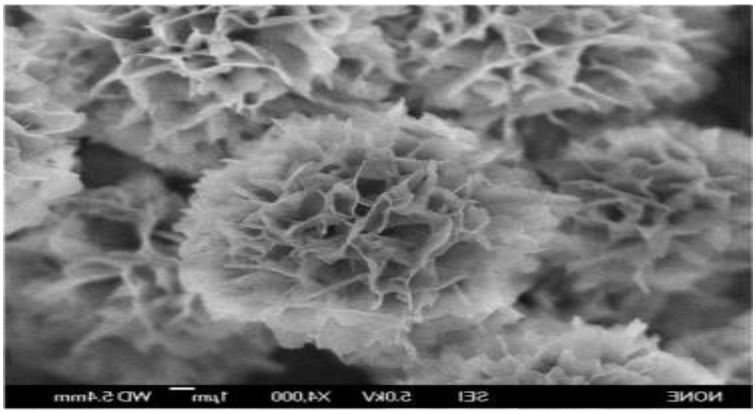

Fig No 1: SEM image of nanoflower [14]

The diameters of these nanoflowers are in the nanometer range. In a nanoflower with an average size of roughly 100–500 nm, the average diameter is roughly 2–5 nm, and the average petal size is roughly 0.1–5 µm. Because of their greater surface volume ratio, which also leads to aggregating the particles to form a closed structure rather than branching out, improved surface adsorption for the materials, enhanced sensitivity, increased efficiency, cost-effectiveness, and stability of the formulation, nanoflowers are the preferred method of drug administration [15]. When compared to other nanoformulations, these exhibit a better immobilization efficiency for the delivery of enzymes, greater productivity, a prolonged enzyme lifetime, better handling and recovery, and possibly even a rise in catalytic activity are all caused by the higher immobilization efficiency. [16].

TYPES OF NANOFLOWERS:

Various varieties of nanoflowers were created according to the materials and drugs that needed to be supplied. Metals such as carbon, metals, and other elements like cobalt, silver, gold, nickel, platinum, copper, and silicon can be used to make these [17].

Type of nanoflower	Method used	Materials used	Reference
Carbon NFs	Chemical vapour decomposition	Methane, hydrogen, argon, and iron as catalysts.	[18]
Cobalt NFs	Precipitation, reduction, and nucleation	Water/ethanol mixture by EDTA and hydrazine	[19]
Silver NFs	Chemical reduction of silver ions	Ascorbic acid, PVP, silver nitrate	[20]
Gold NFs	Reduction and electrodeposition	AuCl4, NaBH4, ascorbic acid.	[21-23]
Nickel NFs	Chemical reduction	Ni(NH3)6Cl2, hydrazine, ethanol, EG, NaOH, 1,2-propanediol	[24]
Platinum NFs	Electrodeposition	ZnO NPs, graphene sheets, $PtCl6^{2-}$	[25]
Copper NFs	Sonoelectrodeposition	Chloride, glucose, PVA, copper sulfate	[26,27]

Table No. 1: Types of nanoflowers by using metals

Metal oxides are also used to make nanoflowers such as zinc oxide, manganese oxide, nickel hydroxide, and titanium dioxide.

Type of nanoflower	Method used	Materials used	Reference
Zinc oxide NFs	Thermal/hydrothermal evaporation	zinc-coated Si(111),zinc powder	[28]
Titanium dioxide NFs	Hydrothermal oxidation	Hydrogen peroxide, HMTA, Nitric acid	[29,30]
Manganese dioxide NFs	Hydrothermal heating	KMnO4 solution, formamide	[31]

Nickel hydroxide NFs	Hydrothermal	Nickel-dimethylglyoxime complex, ethanolamine, nickel chloride, hydrogen peroxide, EG, sodium acetate, PEG 200, ethylene diamine, urea.	[32]

Table No 2: Types of nanoflowers using metal oxides

Based on their composition, nanoflowers can be divided into three categories: hybrid (containing both inorganic and organic components), organic, and inorganic.

Inorganic nanoflowers:

All of the materials that make up inorganic nanoflowers are inorganic, including metals, metal oxides, alloys, and metalloids. Alternatively, the inorganic materials can be coated or doped with metalloids, carbon, nitride, sulfide, phosphide, selenide, and telluride [33-44].

Organic nanoflowers:

Organic nanoflowers are either entirely made of organic molecules or include inorganic components as part of the medium that mostly consists of organic molecules [45-49].

Hybrid nanoflowers:

All parts of inorganic nanostructures that are connected to organic materials are referred to as organic-inorganic hybrid nanoflowers or hybrid nanoflowers [50].

Researchers have been interested in inorganic nanoflowers since the early 2000s because of their distinctive nanostructural features, which depend on their composition, crystal structure, and localized Surface Plasmon Resonance, as well as their superior catalytic efficiency and optical qualities [51, 52]. Additionally, catalysis and energy applications make extensive use of nanoflowers. In comparison to hybrid nanoflowers, inorganic nanoflowers have been the subject of less published investigations for biomedical applications, despite their advantages.

Polymers used in the synthesis of nanoflowers:

Polymers are essential in producing nanoflowers because they act as growth mediators, stabilizers, and templates.

- **PVP(Polyvinylpyrrolidone)**:

PVP is a common polymer used to stabilize and regulate the growth of metal nanoparticles. When creating metal nanoflowers, it can act as a stabilizing agent [53].

- **PEG (polyethylene glycol):**

Metal or metal oxide nanoflowers can be grown using PEG as a template or stabilizer. It can be functionalized for certain uses, including medication delivery, and it is biocompatible [54].

- **PAA (Poly acrylic acid):**

PAA can be used in the manufacture of metal nanoflowers as a shape-directing agent. It offers carboxylic acid functions that can work in tandem with metal ions to guide their development into structures resembling flowers [55].

- **Polydopamine (PDA):**

PDA has become a versatile material for functionalization and surface modification. It can be employed in the synthesis of different nanoflower structures as a growth mediator or as a template [56].

- **Polyvinyl alcohol (PVA):**

PVA can be used in the manufacture of metal nanoflowers as a reducing agent or stabilizer. Its hydroxyl groups can stabilize the resultant nanostructures and take part in reducing metal ions [57].

- **Triton X-100**:

Triton X-100 is a non-ionic surfactant that helps build complex nanostructures such as nanoflowers by stabilizing nanoparticle dispersions and regulating the growth kinetics of nanocrystals. It's possible that the surfactant's capacity to stabilize metal ions in solution and regulate their deposition kinetics helped to generate well-defined nanostructures with advantageous morphologies [58].

FABRICATION TECHNIQUES OF NANOFLOWERS:

To create novel techniques for nanoflower synthesis, research activities have been ongoing. In Kulkarni's book Nanotechnology: Principles and Practices, it is stated that there are four different ways to prepare nanomaterials: chemical, biological, physical, and hybrid [59-64].

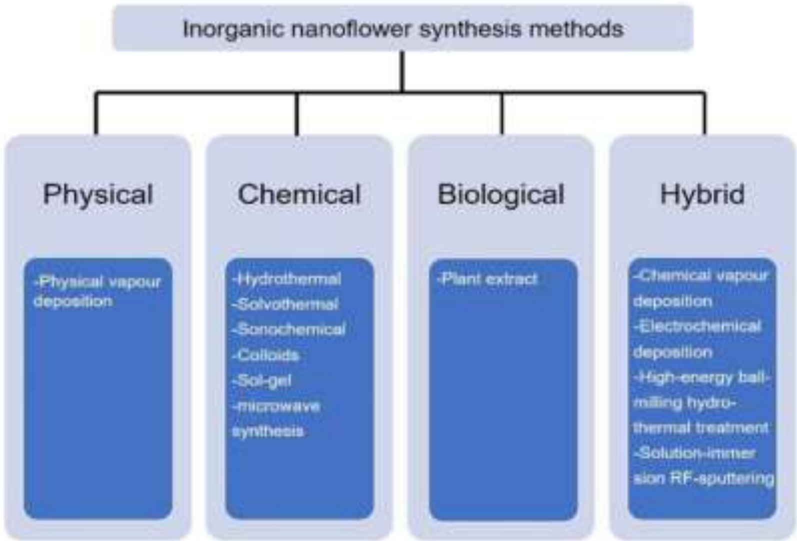

Fig No 2: different fabrication methods of nanoflowers [65]

1. **Physical methods:**

1.1 Physical vapor deposition:

A technique called physical vapor deposition (PVD) is used to apply coatings and thin films of nanomaterials to a substrate. Nanomaterials based on metals and metal oxides can be created with the PVD technique [66, 67] However, because of the high cost and higher reaction temperatures, there have only been a few documented research on Nano-flower production using the PVD approach. The topic of controlled growth of nanoflowers by PVD methods is very promising and has the potential to be further explored.

For example, Yu et al. have reported the production of beautiful Bi_2S_3 nanoflowers on a silicon substrate using a vapor deposition method [68]. The vapor deposition procedure is carried out by the researchers using a horizontal tube furnace. S powder and Bi_2S_3 powder are utilized as the first ingredients. Sulfur powder is positioned between the Bi_2S_3 and the gas inlet, and a ceramic boat filled with Bi_2S_3 powder is positioned in the middle of the furnace tube. A few centimeters aside from the Bi_2S_3 powder, downstream, are silicon wafers placed. High-purity argon gas is pushed through a well-sealed tube. Subsequently, the temperature is raised to 650 °C over two hours, with a heating rate of 8 °C per minute. The temperature is then progressively lowered to room temperature. Argon gas is continuously permitted to flow during the thermal treatment at a rate of around 100 cm (standard cubic centimeter per minute), serving as both a carrier gas and a source of protection. Furthermore, they have shown that altering the partial pressure of the reactants can change the morphology of the Bi_2S_3 nanostructures, resulting in anything from tower-like structures to bundles of nanorods.

To obtain precise control over the production and arrangement of nano-flowers, research is required to investigate new methodologies and enhance current PVD techniques. This entails examining a range of factors, including substrate characteristics, precursor composition, and deposition circumstances, to develop PVD procedures that are specially designed for nanolayer growth.

2. Chemical method:

2.1. Hydrothermal and solvothermal methods:

One of the most popular and often used techniques for creating a variety of nanostructured materials, including nanoflowers, is the hydrothermal process. This approach is easy to use, affordable, environmentally beneficial, and controllable. It is very beneficial for the large-scale synthesis of nanoflowers because of these features. Hydrothermal processes allow for the precise control of both temperature and pressure, which results in the production of hierarchical 3D nanostructures that develop isotropically in all directions. Furthermore, precise control over the shape and size of the nanoflowers is made possible by the ease with which reaction parameters, such as the composition and concentration of precursors and reducing agents, the reaction time, and the presence or type of templates or surfactants, can be changed [69,70]. The aggregation propensity of nanomaterials must be addressed, though, as this might hurt the final structure's shape and uniform distribution.

2.2. Solvothermal method:

The sole difference between the solvothermal and hydrothermal methods is that the former is carried out in a non-aqueous medium. For example, 5 mm of $Cu(NO_3)_2\$3H_2O$ powder is dissolved in 100 mL of deionized water in the first stage. The second stage involves mixing 100 mL of deionized water with a 1 mm hexamethylenetetramine aqueous solution. The solutions from stages one and two are mixed and 1 milliliter of 30% NaOH is added in the third step. At room temperature, the resultant mixture is constantly swirled for 60 minutes. The suspended mixture is then put inside an autoclave and sealed tightly. After that, the autoclave is kept in an oven for three hours at 110 °C. The final solution is centrifuged and cleaned with deionized water when everything is finished and the oven has cooled to room temperature. Ultimately, the product (CuO nanoflowers), which are distinguished by their black hue, is achieved after drying in a vacuum oven at 60 °C for two hours [71].

2.3. Sonochemical/Ultrasonic method:

It has been often reported in recent studies that the hydrothermal approach is used in conjunction with other synthesis processes to create nanoflowers with a variety of shapes. Qu and colleagues presented a novel method for the controlled manufacture of three different kinds of three-dimensional puffy ZnO nano-flowers with different nanostructures. This process starts with a straightforward ultrasonic treatment and ends with a hydrothermal procedure. One variety, known as ZnO-0, has clean edges and is produced directly via the hydrothermal reaction without the need for an earlier ultrasonic treatment. The samples are treated with ultrasonic waves at 250 W and 950 W, respectively, before the hydrothermal process to produce the other two varieties, ZnO-250 and ZnO-950, which have uneven edges. The experimental results showed that the ZnO nanoflowers' size, specific surface area, crystallite dimension, inherent donor defects, and reactive radical signals all decreased with increasing ultrasonic treatment intensity [72].

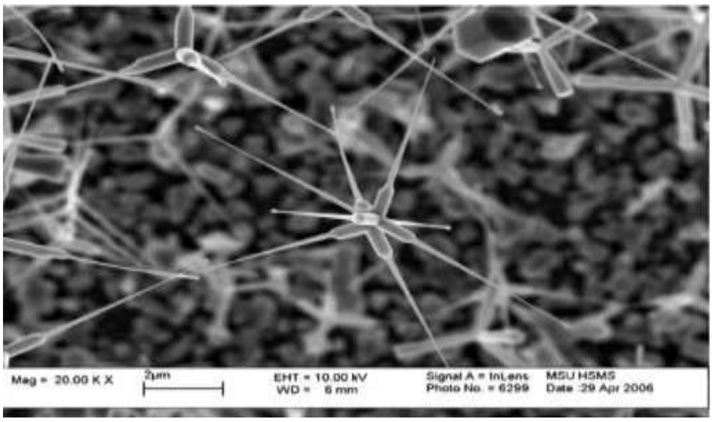

Fig No 3: SEM image of zinc oxide nanoflowers (snowflakes) [73]

2.4. Sol-gel method:

Metal oxide nanoparticles in particular can be synthesized via the sol-gel process, a wet chemical technique [74]. Because the sol-gel method uses low temperatures, it is affordable and allows for proper control over the products' chemical makeup. [75].

2.5. Colloidal synthesis:

Colloidal synthesis is a scalable and reasonably priced technique that provides simultaneous control over the morphology and content of nanoflowers. To illustrate, the use of colloidal synthesis is used to synthesize $M_{1-x}W_xSe_2$ nanoflowers with exact control over both composition and morphology [73]. An outline of the experimental process utilizing the colloidal technique to synthesize $MoSe_2$ nanoflowers is provided below: A combination containing 20 mg (0.1 mmol) of Na_2MoO_4, 8 mL of oleic acid, and 2 mL of 1-octylamine is made and degassed under vacuum at 120 °C for about 10 minutes in a 100 mL three-neck flask. After that, Ar(g) is used to purge the reaction vessel, and it is gradually heated to 240 °C at a rate of about 5 °C per minute. This causes a clear, dark, reddish-brown solution to form. Next, a syringe pump is used to continuously inject 2 mL of the ODE-Se stock solution (0.1 M), which is a solution of 1-octadecene and Se, at a rate of 0.1 mL min^{-1}.

Following the injection. The solution is matured at an internal temperature of roughly 300 °C for a further half hour. After that, the reaction mixture is quickly cooled by removing the heating mantle's thermos. After adding 10 milliliters of toluene and 10 milliliters of ethanol, the resultant $MoSe_2$ particles are precipitated and centrifuged. The black precipitate is finally suspended in ethanol to create a dark purple colloidal suspension after being rinsed three times in a 1:1 ratio of toluene to ethanol (with centrifugation steps in between washes) [76].

2.6. Microwave synthesis:

Because of its speed, ease of use, affordability, and environmental friendliness, the microwave synthesis process has several advantages.104% to the best of our knowledge, numerous nanoflowers based on nickel are produced using microwave reactions. This is achieved through molecular contact, which is made possible by targeted indirect heating inside the solution [77-80]. For instance, 50 mL of distilled water dissolves 40 mmol of Ni(NO3)2$6H2O. After adding 3 mL of ammonia to the mixture, 5 weight percent of the cationic surfactant cetyltrimethylammonium bromide (CTAB) is added. For ten minutes, the resultant solution is swirled. The solution is placed inside a polypropylene-capped autoclave container and microwave-irradiated for 15 minutes at a power of 300 watts. To get rid of soluble contaminants, the green precipitates are repeatedly washed with distilled water and ethanol. The precipitates are then dried after that for 12 hours at 80 °C in a hot oven to produce $Ni(OH)_2$ samples. NiO nanoflowers are produced by calcining the as-prepared powder samples for two hours at 400 °C in the air. Using the same quantity of precursor, surfactant, and ammonia, the researcher also used a hydrothermal approach, conducting the reaction for 15 minutes at 140 °C. When analyzed using scanning electron microscopy (SEM), the procedure of microwave treatment produces nanostructures with a higher degree of agglomeration than samples developed using the hydrothermal method, but with similar flower-like morphologies. This is explained by molecules being indirectly heated by microwave radiation [81].

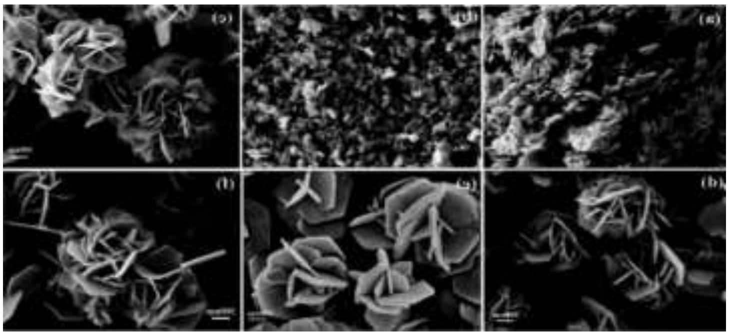

Fig No 4: SEM images of NiO nanoflowers at different magnifications [82]

3. Biological methods:

3.1. Green synthesis:

The process of creating metal nanoparticles by green synthesis, sometimes referred to as biosynthesis, with plants, herbs, or microorganisms has attracted a lot of interest [81]. Especially in the medical field. Plant extracts have become increasingly popular as a non-toxic, simple, and scalable way to produce metal nanoparticles [83].

Kalanchoe daigremontiana extract is used as a natural reducing agent to create silver nanoflowers [84]. It has been accomplished to synthesize CuO nano spindles in an environmentally friendly manner and then assemble them into nanoflowers by adjusting the solvents (ethanol and water) that are combined with the extract of Dodonaea angustifolia.

[85] Additionally, eugenol (4-allyl-2-methoxyphenol), a naturally occurring reducing agent, is isolated from the leaves of Ocimum sanctum (tulsi) and used in the synthesis of CuO nanoflowers.[86] Au/ZnO hybrid nanoflowers are made by a straightforward, eco-friendly, biomimetic process that uses extract from the leaves of Azadirachta indica (neem) as a capping agent and a reducing agent [87].

4. Hybrid methods:

4.1. Electrochemical deposition:

One very common method for creating nanoparticles is electrochemical displacement. Electrochemical deposition synthesis has been acknowledged as a possibly better technique than different methods because of its beneficial characteristics. Some of these are: (1) the process can be completed in a single step at room temperature, which cuts down on process time; (2) the particles' size and shape can be effectively controlled, resulting in the formation of uniform deposits with high purity; (3) it is simple to anchor the particles onto the substrate firmly; and (4) the process has environmentally friendly qualities [88, 89]. Potentiostatic pulse plating has been reported as an easy-to-replicate method for creating 3D Pt nanostructures on silicon substrates at room temperature. An Aqueous solution with 1 M H2PtCl6 and 1 M H2SO4 is combined and left to stand at room temperature for 5 hours. Next, utilizing potentiostatic pulse plating in a three-electrode cell system with a saturated calomel reference electrode (SCE), the Pt catalyst is electrodeposited onto a τat silicon substrate. There was a 5 ms duration for the positive potential pulse (+0.05 V) and a 1 ms duration for the negative potential pulse (−0.02 V). The process of bipolar pulse electrodeposition makes it easier to create three-dimensional Pt nanopowders on a silicon substrate. After Pt electrodeposition, the sample is dried and cleaned with deionized (DI) water to get rid of surface impurities [90].

4.2. Chemical Vapour Deposition:

In chemical vapor deposition (CVD), a solid substance is deposited from a vapor using a chemical reaction that takes place on or near a substrate surface that is typically heated. One single crystal, thin layer, or powder is the resultant solid substance. Materials with a broad variety of physical, tribological, and chemical properties can be developed by adjusting the experimental conditions, such as the substrate material, substrate temperature, reaction gas mixture composition, total pressure gas flows, etc. The exceptional throwing power of the CVD process is one of its distinguishing features; it allows for the creation of coatings with consistent thickness and low porosity on substrates with intricate shapes. The capacity to do localized or selective deposition on patterned surfaces is another crucial aspect [91].

4.3. Multi-step synthesis for complex structures:

There have been reports of creating nano-flower structures using a mix of several synthesis techniques due to their increasing complexity and diversity of composition. Ag@NiO core-shell nanolayer arrays were synthesized in a single step by solution immersion and RF sputtering, as reported by Zhao et al. The bulk ilmenite FeTiO3 is first subjected to ball milling, and then it is treated mildly hydrothermally in an aqueous NaOH solution. This procedure results in nanostructured FeTiO3, which has a unique nanflower shape [92].

CHARACTERISATION OF NANOFLOWERS:

Raman Spectroscopy: Characterizing the vibrational modes and chemical bonding in nanoflowers is made possible by Raman spectroscopy. Specific chemical species, flaws, and surface functional groups on the nanostructures can all be identified using it [93].

Scanning Electron Microscopy: Surface morphology and nanoflower structure can be seen at high resolution using SEM, which is extensively used for this purpose. Details are provided regarding the dimensions, forms, and configuration of the petals or branches that make up the flower-like nanostructures [94].

Transmission electron microscopy: TEM provides atomic-level information about the flaws, crystallinity, and internal structure of nanoflowers. Energy-dispersive X-ray spectroscopy (EDS) and selected-area electron diffraction (SAED) are two methods that enable the detection of crystal orientation, lattice fringes, and elemental composition [95].

X-ray diffraction: The phase composition and crystallographic characteristics of nanoflowers are examined using XRD. It offers important details regarding orientation relationships within the nanostructures, lattice characteristics, and crystalline structure [96].

Surface area and porosity analysis: The surface area, pore volume, and pore size distribution of nanoflowers are measured using methods like Brunauer-Emmett-Teller (BET) analysis and mercury intrusion porosimetry (MIP). These measurements are vital for applications like catalysis and adsorption [97].

Chromatography: Size analysis of the nanoflowers can be evaluated by liquid, hydrodynamic, gel permeation, and gas chromatography was employed [98, 99, 100].

APPLICATIONS OF NANOFLOWERS:

Nanoflowers in the cancer treatment:

Currently, a significant revolution in cancer detection, therapy, and prevention has been brought about by the combination of nanotechnology, cancer biology, and medical sciences [101,102]. These advancements are starting to find use in clinical settings. HeLa cells were treated with the rutile phase of titanium dioxide nanoflowers, which were produced using a hydrothermal process [103]. Good effects of removal and destruction were produced by the nanoflowers.

For MW thermal cancer therapy, layered molybdenum disulfide nanoflowers were employed [104]. According to recent studies, molybdenum disulfide nanoflowers can be employed in vitro or in vivo and have great selectivity, reactivity, and biocompatibility [105,106]. To improve the physiological condition and biocompatibility of molybdenum disulfide nanoflowers, BSA was added. Benzene rings and disulfide groups were used to carry out the albumin binding process with molybdenum disulfide nanoflowers. The nanoflowers' great biocompatibility was revealed by hemolysis testing. Furthermore, to examine the cytotoxicity and metabolic activity of the nanoflowers, the vitality of the human hepatocellular liver carcinoma cell line (HepG2) and human cervical cancer (Hela) cells was assessed, confirming the low toxicity of the nanoflowers.

Gold nanoflowers with a mean diameter of 10 nm were created, and thiolated polyethylene glycol was adsorbed to the surface to modify the plasmon absorption and emission peaks' location and intensity at 605 nm [107]. Following that, the nanoflowers were used in cancer treatment and bioimaging. Moreover, gold nanoflowers were created using the seed-mediated growth technique and covered in a silica layer [108]. By causing a red shift in absorbance from 684 nm to 718 nm due to the glass coating, photothermal treatment with a quick release of doxorubicin was able to effectively combat cancer cells.

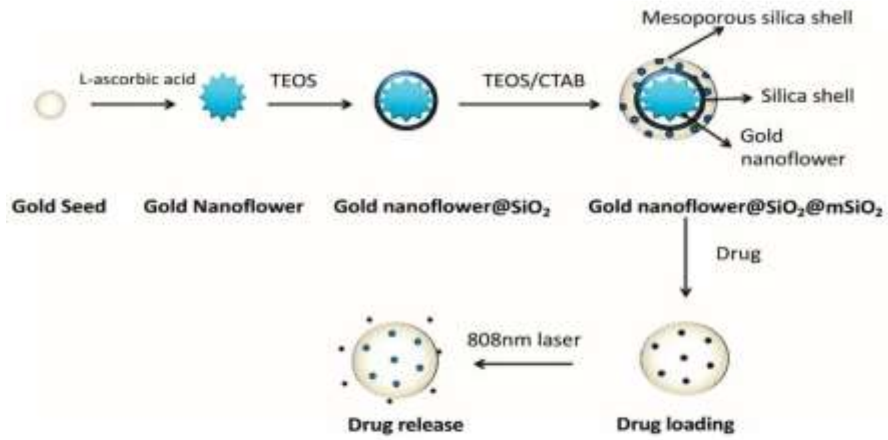

Fig No 5: Schematic representation of the synthesis of gold nanoflowers for oral cancer treatment. [109].

A silica shell-coated gold nanoflower core was employed; this unique structure was exploited for an enhanced drug loading and release cycle. One of the novel targeted medication delivery techniques that can be employed is the strong drug carrier scenario that this flower-like nanostructure has supplied.

The morphologies of fusiform flowers, petal flowers, and rod flower-shaped ZnO nanostructures demonstrated cytotoxicity against Hela cells while having little cytotoxic effects on normal cells [110]. ZnO nanoflowers with petals had the greatest potential for Zn2+ release and a more potent cytotoxic effect.

Because of its enormous surface area, graphene can transport a lot of medication. Because cancer cells have a higher pH than normal cells, designing systems with a lower pH will increase drug release. This will cause the drug to be absorbed into graphene, separate from graphene in the patient's limb, and released in the tumor sites, where normal cells will limit treatment. To combat medication resistance in cancer cells, this issue is very crucial [111]. Conversely, lattice protonated titanate is infinitely thin and has a two-dimensional structure resembling graphene. Layered protonated titanate is useful because of its immobilizing biomolecules, adsorbents, and photocatalyst characteristics. It also has a high density for negative surface charges. Human epidermal growth factor receptor 2 cells were lysed by the graphene-layered protonated titanate nanoflowers. These nanoflowers also enhanced the cytotoxic effects of doxorubicin and enhanced treatment with nuclear accumulation and cancer imaging.

Nanoflower type	Size of NF (nm)	Application type	Treated cancer type	Method against target	Final result
TiO2 nanoflowers	102	Treatment	HeLa cells	UV photocatalysis	Lead to HeLa cells
Gold nanoflowers	100	Diagnosis/ treatment	4T1 tumor	Photothermal therapy	Imaging and therapeutic functionalities.
Gold nanoflowers	>100	Treatment	HeLa cells	Photothermal	Successfully treated.
Gold nanoflowers	450	Treatment	HepG-2 cells	Photothermal	Successfully treated.
DNA nanoflowers	<200	Treatment	Leukemia and breast cancer cells	Cell titer 96 cells proliferation assay	Useful in targeted drug delivery
Quantum dots conjugated titanate nanoflowers	600	Diagnosis/ Treatment	HER2/ MCF7 cells	Fluorescence imaging	Imaging and therapeutic functionalities
DNA nanoflowers	200	Diagnosis/ Treatment	CEM and HeLa cancer cells	UV-visible spectrometer	High performance
Gold nanoflowers	310-820	Diagnosis/ Treatment	Human Lung A549 cancer cells and mouse melanoma B16BL6 cells	Surface-enhanced Raman scattering	Imaging and therapeutic functionalities
Gold nanoflowers	150-200	Treatment	HepG2 cells	Photothermal	Successfully treated

Table no 3: Used nanoflowers and their properties in cancer treatment. [112]

Gold nanoflowers have the largest surface and contacting areas (45–150 nm) and the best level of biocompatibility. [113]

Nanoflowers in Cardiovascular disease treatment:

Cardiovascular illnesses account for 80% of deaths worldwide in low- and middle-income countries, making them the primary cause of death for both men and women [114].

To treat cardiovascular disorders, zinc oxide (ZnO) nanoflowers were created [115]. The creation of new blood vessels from preexisting ones is known as angiogenesis [116]. Numerous physiological functions, including growth, wound healing, reproduction, and embryonic development, depend on this mechanism [117,118]. ZnO nanoflowers' proangiogenic qualities allow them to be exploited for angiogenesis in ischemia patients, a goal that will greatly advance cardiac treatment. The findings demonstrated that the presence of hydrogen peroxide (H2O2) as a redox signaling molecule that contributed to the angiogenesis process was a likely strategy for angiogenesis by ZnO nanoflowers [115]. Targeted angiogenesis is a critical and significant issue for ischemic treatment or any other angiogenesis process [119,120]. Kim et al. [121] and Patra et al. [115] proposed targeted angiogenesis by nanoparticles through enhanced permeability and retention, and this mechanism has also been confirmed. ZnO nanoflowers were employed by Barui et al. to create novel blood arteries [122]. Using a home microwave (MW) oven, zinc (II) nitrate and ammonia are combined to create ZnO nanoflowers. The outcomes demonstrated that, in a variety of in vitro and in vivo tests, the nanoflowers can stimulate proangiogenic activity. The reactive oxygen species (ROS) production mechanism was revealed to explain angiogenesis and auxiliary roles (for endothelial cell (EA.hy926 cells) movement in wound healing assays) found for ZnO nanoflowers.

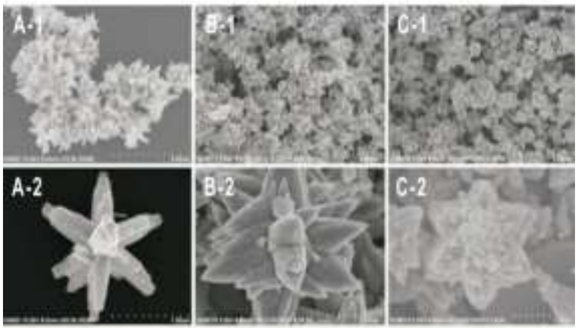

Fig no 6: SEM images of zinc oxide nanoflowers (A) rod flower, (B) fusiform, (C) and petal morphologies. [123]

Nanoflower application in microbiology:

Over the past ten years, the field of nanotechnology has grown, which has opened up new avenues for the study of nanostructures' antibacterial properties [124]. Due to their tiny size and high surface-to-volume ratio, which allow them to interact directly with biological membranes and destroy microbial membranes, nanostructures have antibacterial capabilities [125]. Researchers looked into the bactericidal effects of silver nanoflowers with 3, 4, and 5-fold chiral symmetry on Candida albicans, Staphylococcus aureus, and Escherichia coli [126]. The oblique angle deposition approach, a type of physical vapor deposition, was used to create the silver nanoflowers [127]. Even though the antimicrobial properties of silver are not new, silver nanostructures with unique features have been created utilizing nanotechnology [128-131]. The most antibacterial properties were demonstrated by the 5-fold symmetry-silver nanoflowers. Three morphologies, including rod flowers (length of approximately 870 nm), fusiform flowers (length of approximately 1.5 μm), and petal flowers (length of approximately 600 nm), were achieved in a study using a low-temperature hydrothermal technique [132].

Next, an investigation was conducted into how ZnO nanoflowers affected the bacteria Escherichia coli and Staphylococcus aureus. The petal ZnO nanoflowers outperformed the other two types of nanoflowers in their biocidal impact, indicating a strong antibacterial capacity in the nanoflowers. Furthermore, compared to rod nanoflowers, fusiform nanoflowers demonstrated a higher biocidal effect. It has been examined how form influences a nanostructure's effectiveness in preventing the growth of microorganisms. The extremely small size and high surface-to-volume ratio of the nanoparticles contribute to their antibacterial qualities; the enhanced interaction surface area that is supplied enables the nanoparticles to come into direct touch with the microbial membranes and destroy them by releasing ions [133-136]. Five distinct sizes of platinum (Pt) nanoflowers were created, and the outcomes of an antibacterial assessment conducted on Pseudomonas aeruginosa revealed that the bacteria is compatible with nanoflowers larger than 5 nm but harmful to those smaller than 3 nm [137]. In a study, a simple one-pot hydrothermal method was used to chemically produce titanium dioxide (TiO2) nanoflower. This nanoflower, which exhibited a 3.2 eV band gap, was employed as a component of an antibacterial composite (Ag/TiO2/ZnO) to combat Escherichia coli [138]. In one study, copper oxide (CuO) nanoflower was employed as an antifungal agent to combat Candida albicans. Cu foil in an alkaline solution was used to create this nanoflower, which had a size range of 40 to 200 nm [139].

Application of nanoflowers in Biosensors and Sensors:

These days, a wide variety of sensors and biosensors are manufactured using nanostructures, which has produced significant advancements in this field [140]. Enhancing the degree of immobilization of biomaterials would boost the sensitivity, catalytic effects, and viability of sensors and biosensors. This is the goal of using nanoflowers in the structure of biosensors. Pb2+ was the analyte in a study by Zhang et al. that created a DNAzyme sensor [141]. Pb2+ is a poison that causes pollution, and its detection can help with both medical and environmental diagnostics [142]. When it comes to immunological assays, gold nanoflowers are more useful than other nanoflowers due to their higher optical extinction, superior colloidal stability, larger total surface area, ability to enhance antibody immobilization, and strength in optical extinction. He and colleagues created an immunosensor for loxacin detection, utilizing gold nanoflower as a signal enhancer [143]. A suitable and larger surface has been made available with gold nanoflower for the targeted analyte capture. The aforementioned nanoflower was used to create a surface that was stable enough for antibodies to adhere to, allowing for the successful and precise detection of more analytes with more active antibodies.

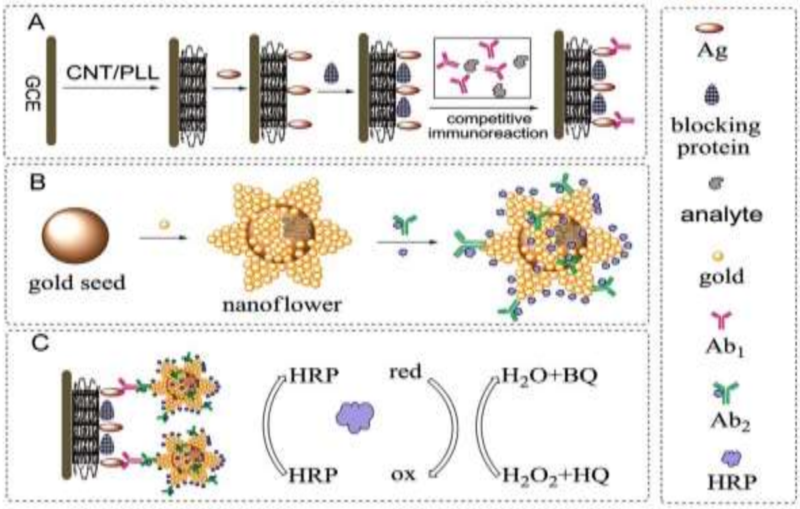

Fig No 7: Schematic elements and platform of designed related immune sensors by He et al. (144).

Nanoflower type	**Production method**	**Size**	**Analyte**	**Electrochemical detection method**
Pt nanoflowers	Electrodeposition		Urea	Cyclic voltammetry
ZnO nanoflowers	Chemical	80nm	Glucose	Cyclic voltammetry
ZnO nanoflowers	Chemical	4 µm	H_2O_2	Cyclic voltammetry
ZnO nanoflowers	electrodeposition	350nm	H_2O_2	Cyclic voltammetry
CuO nanoflowers	Chemical	100-300nm	Glucose	Linear sweep voltammetry
NiO nanoflowers	Chemical	2-3 µm	l-ascorbic acid	Cyclic voltammetry
Gold nanoflowers	Chemical	40-100nm	H_2O_2 and Trichloroacetic acid	Cyclic voltammetry
ZnO nanoflowers	Electrodeposition	100nm	DNA	Cyclic voltammetry
Ag-doped ZnO nanoflowers	Chemical	70 ± 20 nm	Phenylhydrazine	Current-voltage technique
CuO nanoflowers	Chemical	400nm	Ascorbic acid	Cyclic voltammetry

Table No 4: Types of nanoflowers for the application of biosensors and sensors (145)

Application of nanoflowers in Biochemical and Cellular studies:

For the synthesis of laccase-inorganic composite nanoflowers and bovine serum albumin (BSA), a novel sonochemical technique was created [146]. As epinephrine was used as a substrate to test the nanocomposite's enzymatic activity, it produced an increase in laccase nanoflower activity of about 150% as compared to free laccase with prolonged activity. The use of the nanocomposite was for the colorimetric detection of adrenaline.

Chemical factors including the concentration of the reagents used, the pH of the solutions, the temperature during the production process, the production methods, protocols, and equipment all have a significant impact on the final morphology of the nanoflowers. Depending on the objectives, different morphologies and sizes of nanoflowers can be produced.

A hybrid of α-chymotrypsin and calcium phosphate nanoflowers was developed by Yin et al. [147]. N-benzoyl-L-tyrosine ethyl ester was used to measure the enzyme activity after the nanoflowers introduced a novel immobilized enzyme pathway. The nanoflower structure's immobilized α-chymotrypsin exhibited an approximately 266% increase in activity. As a biomimetic catalyst, another nanoflower hybrid of calcium phosphate, albumin, and glucose oxidase was created [148]. The Fenton's reaction was followed by the nanoflowers, which demonstrated a high-temperature resistance and provided a novel strategy against complex natural catalytic enzyme reactions. Gold nanostructures have improved surface Raman scattering properties, which makes them useful for live cell imaging [149].

Human hepatocellular carcinoma cancer cell line was imaged in real time using gold nanoflowers [150]. Using a combination of chitosan and seed-mediated growth, Nhung et al. produced gold nanoflowers [151]. The near-IR absorption of gold and the biocompatibility of chitosan [152] gave rise to the potential uses of nanoflowers in biomedical applications, surface enhanced resonance scattering, and biomolecule immobilization.

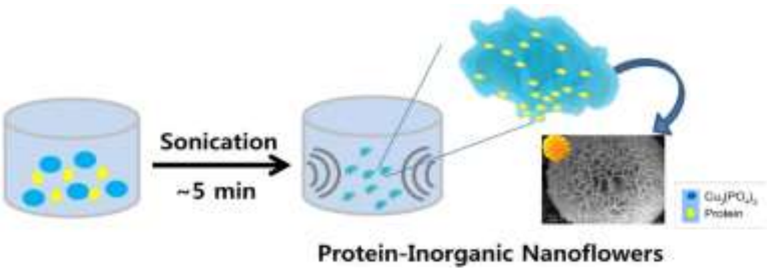

Fig No 8: Synthesis of ultrafast sonochemical protein nanoflowers (153)

Copper phosphate hybrid nanoflowers containing various biomolecules were created [154, 155]. Horseradish peroxidase's enzyme activity was increased by 300% when it was added to the copper phosphate nanoflowers [154].

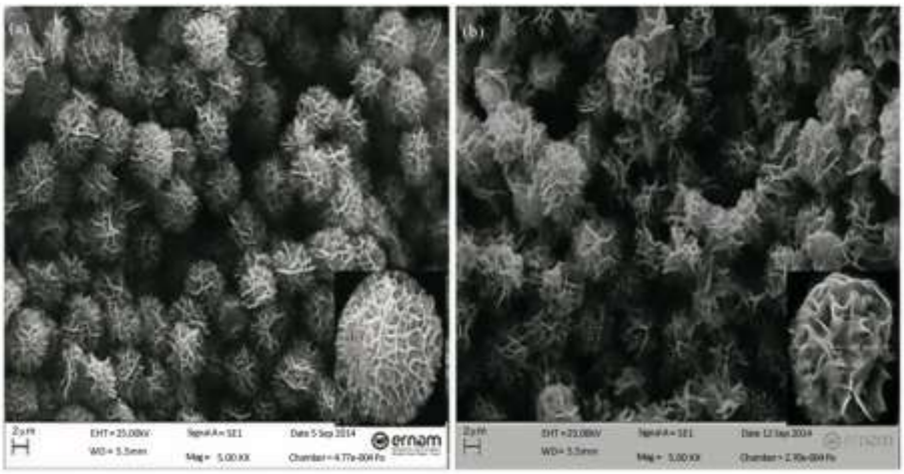

Fig No 9: SEM images of combined horseradish peroxidase (HRP)-Cu^{2+} hybrid nanoflowers of two different magnifications. (156)

Applications of nanoflowers in Healthcare:

One study used solvothermal preparation of nickel nanoflowers to eliminate dyes in wastewater treatment [157]. The adsorption process took place in less than 10 minutes, and nickel nanoflowers demonstrated an adsorption capability of 36.8 mg congo red g-1. BSA-copper phosphate, and glucose oxidase copper phosphate hybrid nanoflowers could decompose the pollutant organic dye rhodamine B by 97% within 4 h [158].

One of the major issues in modern living is pharmaceutical pollution [159]. Medications are frequently ingested by humans and animals, dumped into the environment by drug manufacturers, and expired and added to patients' necessary medications. Zhou et al. reported a novel method using ZnO nanoflowers made using a sol-gel technique to break down and eliminate norfloxacin [160]. The patent presented hydroxyapatite nanoflowers, which have applications in plastic surgery, orthopedics, clinical dentistry, and other fields. These nanoflowers are also highly eco-friendly [161]. These nanoflowers' three-dimensional structure allows them to perform unique functions and makes them biocompatible because they are present in the hard tissues of the human body.

Conclusion & Future Developments

Targeted drug delivery systems and nanotechnology have advanced significantly with the introduction of nanoflowers as nanocarriers. Their distinct structural features such as their large surface area, numerous functional sites, and increased stability offer significant advantages over conventional nanocarriers. Improved loading capacities, regulated release profiles, and targeted distribution are made possible by these qualities, all of which are essential for maximizing therapeutic efficacy and reducing adverse effects. The effective use of nanoflowers in a range of biological applications, including imaging, diagnostics, and cancer treatment, highlights their potential as an adaptable and potent instrument in contemporary medicine. Researchers should focus on the key perspectives in nanoflower manufacturing by using optimized methods and efficient ways for the delivery of doasage forms**.** The key to the future of nanoflowers is to maximize their sophisticated medication delivery potential. To build effective and efficient nanoflowers, researchers need investigate a variety of inorganic elements and materials. Developing environmentally sustainable synthesis techniques will be essential to increasing the uses of nanoflowers in pharmaceutics.

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