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TRANSFORMING THE MEDICAL LANDSCAPE: AN IN-DEPTH ANALYSIS OF THE ADVANCEMENTS IN PHARMACEUTICAL NANOMEDICINE

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ABSTRACT

Nanotechnology is becoming more significant in the realms of medicine and medication delivery because traditional pharmaceutical agents and their antiquated formulations and delivery systems have serious limits. Since several nanotechnology applications have been created and a number of nanotechnology-based medications are currently available on the market, the impact of nanotechnology on healthcare is already being seen. The increasing number of drug candidates with poor solubility is reflected in the growing interest in drug nanoparticles and nano-cocrystals for research purposes; the primary use of these nanosystems is to increase solubility. Verifying these nanoparticles' lifetime functioning, the consistency of the formulation procedures, the produced systems' functional performance in a predetermined manner, and the systems' stability, it is vital to have a solid understanding of physic chemistry with the use of the appropriate analytical techniques. The bioavailability of a product can be affected by even minute variations in particle size, for instance, or size differences at the nanoscale. The Quality by design (QbD), which is defined by the FDA, is particularly useful for deciding on a stabilising agent and manufacturing process for pharmaceutical nanocrystals as well as determining Critical Quality Attributes (CQAs). The impact is amplified when dealing with the tiniest fractions of particles. Our goals were to assess the nanomedicines that have been given global market approval by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), to briefly discuss the difficulties encountered during their development, and to consider potential future developments. In addition, a brief discussion will cover the significance of nanotechnology in the creation of pharmaceutical products, the ideal characteristics of nanocarriers, the causes of the failure of some nanomedicines, and the critical factors in the development of nanomedicines.

KEYWORDS: FDA, Nanoparticles, Nanomedicines, Nanocarriers, CQA, and QBD.

1. INTRODUCTION

Drug nanocrystals are solid drug particles that have gained significant attention in recent years. They are mainly pure API and are prepared in aqueous media with stabilizers for the colloidal state. These systems are also known as nanosuspensions, which are stable against particle aggregation due to the presence of a layer of polymer or surfactant.[1] Cocrystals have emerged as a method of fine-tuning therapeutic ingredient solubility, dissolution, bioavailability, and other physiochemical qualities without affecting their molecular structure. They are multicomponent solids composed of two or more distinct molecular components in a single homogeneous crystalline phase with well-defined stoichiometry.[2] Nanocrystals can have different solubility properties due to their small size and higher surface area than bulk materials. Nano-cocrystals are minuscule crystalline structures made of two or more distinct substances, offering improved performance and unique functions in medication delivery, catalysis, and electronics. They are attractive prospects for cutting-edge technologies due to their carefully crafted qualities and regulated manufacture.[3]

Drug nanocrystals and nano-cocrystals differ from salts in that they don't require ionic interactions, making it possible to use non-ionic materials. The Noyes-Whitney equation states that drug crystal size reduction increases the specific surface area and dissolving rate. Drug nanoparticles can be created using "top-down" or "bottom-up" technology, with wet stirred media milling being preferred due to its continuous, scalable, solvent-

free, and environmentally friendly nature. Pharmaceutical nanocarriers have revolutionized the pharmaceutical industry by offering unique properties and capabilities that traditional bulk materials cannot provide. They have opened up new avenues for drug delivery, imaging, diagnostics, and therapy. Nanoparticles can encapsulate drugs, improve their solubility, stability, and bioavailability, allowing for controlled and targeted drug delivery, reducing side effects and improving patient compliance. In addition to drug delivery, nanoparticles can serve as contrast agents in various imaging techniques, enhance the delivery of antibiotics to bacterial infections, and tailor therapies to individual patient characteristics. Pharmaceutical nanocarriers are now most effectively used in therapeutic and diagnostic applications.

The FDA defines Quality by Design (QbD) as a systematic approach to development that emphasizes understanding and controlling the process and product, thereby improving the pharmaceutical product's lifespan. QbD is particularly useful in drug nanocrystals, where the stabilizing agent and manufacturing process are chosen, followed by the definition of Critical Quality Attributes (CQAs)[4] Nanotechnology and nanosciences have significant applications in various fields, including healthcare. Nanotechnology involves designing and using nanosized materials, devices, and techniques to diagnose, treat, and prevent diseases with precision. It holds immense potential to revolutionize healthcare by enabling targeted drug delivery, imaging at the cellular level, and personalized treatments.[5] Nanomedicines, also known as nanocarriers, are essential for increasing the bioavailability and potency of medications. They address issues like poor solubility, quick degradation, and nonspecific distribution by encapsulating therapeutic materials within nanoscale structures. Their small size allows them to pass through biological barriers, delivering the therapeutic cargo to desired cells or tissues, reducing systemic side effects and raising the drug's therapeutic index. Overall, nanomedicines can significantly enhance drug distribution, heighten therapeutic effect, and change the way medical treatments are delivered.[6]

2. TYPES OF NANO-PARTICLE IN MEDICINE

Nanoparticles (NPs)have a wide range of applications in medicine due to their unique properties, including their small size and high surface area, which make them suitable for drug delivery, imaging, and therapy. Here are some common types of nanoparticles used in medicine. These are just some examples of the types of nanoparticles used in medicine. Nanoparticles continue to play a crucial role in advancing drug delivery, imaging, and therapy in various medical applications. The various kinds of nanoparticles in the field of medicine are depicted in **Figure 1.**

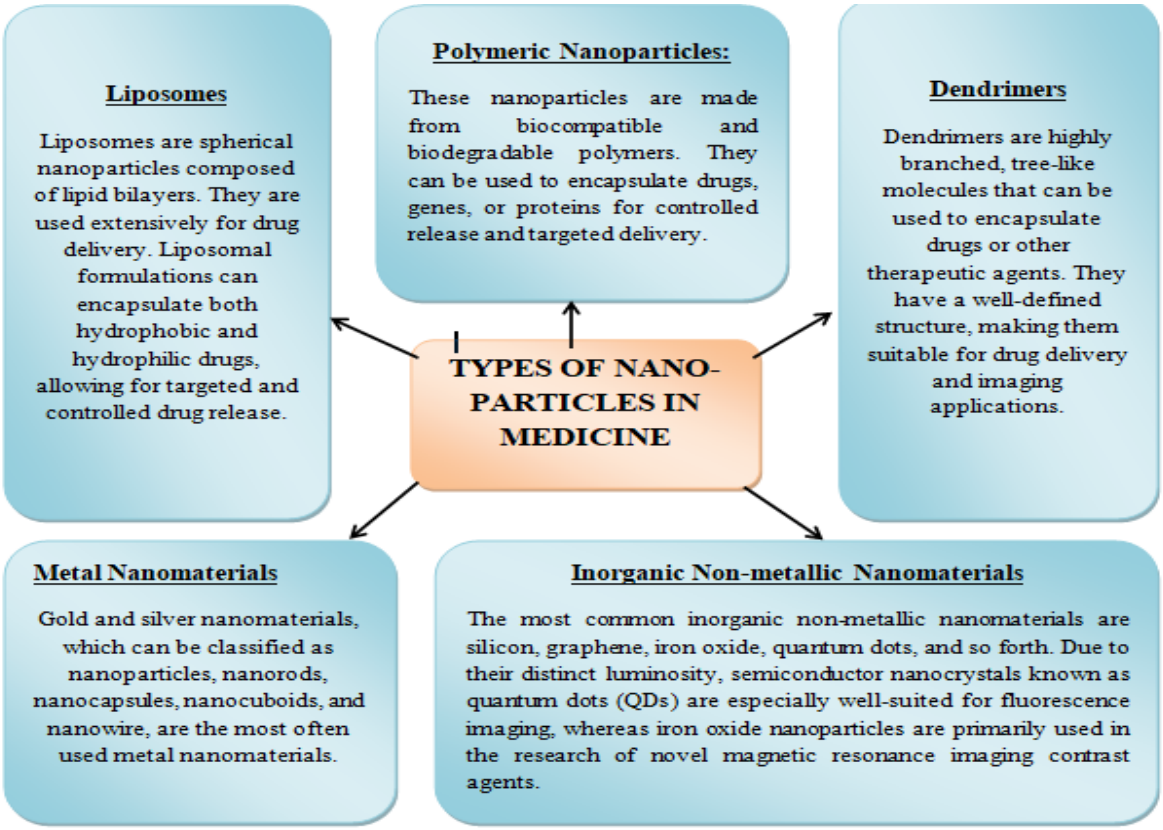

Figure 1: Various kinds of nanoparticles in the field of medicine.[7]

3. IDEAL PROPERTIES OF NANO-PARTICLE

Nanoparticles are extremely tiny particles with typical sizes between 1 and 100 manometers. Due to their small size and high surface area-to-volume ratio, these particles have unique features that make them valuable for a variety of applications in industries like health, electronics, energy, and materials research. Depending on their intended uses, nanoparticles' desired characteristics can vary, however certain in general are desirable. Table 1 below is here to describe various aspect of nano particle.

Table 1: Various aspect of nano particle to describe the ideal properties.[8-10]

Aspect	Description
Size and Uniformity	To ensure consistent performance in a variety of applications, nanoparticles should have a controlled and homogenous size distribution. Performance may be predicted and variability is reduced by narrow size dispersion.
High Surface Area to Volume Ratio	The high surface area to volume ratio of nanoparticles promotes their reactivity and interaction with other substances. For catalysis, this characteristic is very crucial.
Chemical and Physical Stability	Nanoparticles must be resistant to aggregation, degradation, and chemical changes in order to function effectively over time and in a variety of environments.
Biocompatibility	Nanoparticles used in biomedical applications should be biocompatible, meaning they don't hurt living things. For applications including medication distribution, medical imaging, and therapy, this characteristic is essential.
Controlled Release	Nanoparticles with controlled and sustained release of their payloads, such as medications or nutrients, can enhance the efficacy and efficiency of therapeutic or delivery systems.
Low Toxicity	Cells and other organisms shouldn't be adversely affected by nanoparticle toxicity. Both consumer and environmental applications depend on their safety.
Targeting Capability	Medical nanoparticles have the potential to target certain tissues or cells, improving the accuracy of treatments and reducing adverse effects.

4. CHARACTERIZATION OF NANOPARTICLES

The characterization of nanoparticles is a branch of Nano metrology that deals with the characterization, or measurement, of the physical and chemical properties of nanoparticles. Size and shape are two of the primary factors investigated in the characterisation of nanoparticles. Additionally, we can quantify the size distribution, level of aggregation, surface charge, surface area, and, to a certain extent, assess the surface chemistry. Different techniques are used for characterization of-nano-particles are depicted in **Table 2**.

Table 2: Different techniques are used for characterization of-nano-particles.[11]

Sl No	Technique	Purpose or uses Technique
1.	DLS (Dynamic Light Scattering)	Hydrodynamic size, detection of agglomerates
2.	Electron diffraction	Crystal structure, lattice parameters, study order–disorder transformation, long-range order parameters
3.	ICP-MS (Inductively Coupled Plasma Mass Spectrometry)	Elemental composition, size, size distribution, NP concentration
4.	NMRS (Nuclear Magnetic Resonance spectroscopy)	Ligand density and arrangement, electronic core structure, atomic composition, influence of ligand on NP shape, NP size
5.	TEM(Transmission Electron Microscopy)	NP size, size monodispersity, shape, aggregation state, detect and localize/quantify NPs in matrices, study growth kinetics
6.	UV-Vis (UV-Visible Spectroscopy)	Optical properties, size, concentration, agglomeration state, hints on NP shape
7.	XAS (X-ray absorption spectroscopy)	X-ray absorption coefficient (element-specific) chemical state of species, interatomic distances, Debye–Waller factors, also for non-crystalline NPs
8.	XRD (X-ray diffraction)	Crystal structure, composition, crystalline grain size

4.1. TEM(Transmission Electron Microscopy)

Transmission electron microscopy (TEM) is a microscopy technique that takes advantage of the interaction between a thin sample and a uniform current density electron beam, with energies typically ranging from 60 to 150 keV. A portion of the electrons in the electron beam are transmitted when it hits the sample, while the remainder are dispersed either elastically or in elastically.[12] Size, sample density, and elemental makeup are just a few of the variables that affect how much of an interaction there is. The information gathered from the sent electrons is used to construct the final

image. As was made obvious in the preceding sections, NPs' distinct set of physical characteristics, including their optical, magnetic, electronic, and catalytic properties as well as how they interact with biological systems, determined by their size and morphology.

Since TEM offers direct views of the sample as well as the most precise estimation of the homogeneity of the nanoparticles, it is the method most frequently used to analyse nanoparticles size and form. However, there are several restrictions that must be taken into account while employing this method, such as the challenge of measuring a high number of particles or inaccurate images caused by orientation effects. Other techniques that analyse more NPs can produce more accurate findings when describing extremely homogeneous samples, such as SAXS for bigger and spherical NPs or XRD by utilizing the boundary of the XRD reflections and the Scherer formula.[13] To ensure sample uniformity, a prior analysis must be carried out.

One method used to characterize the creation of various super-lattice nanocomposites, which can be isostructural to a number of atomic crystal systems, is transmission electron microscopy (TEM). The final structure and composition of these new three-dimensional arrays, which are made of various NPs (such as metals, magnetic NPs, and quantum dots), can be modified by adjusting the colloid surface charge or directional bonding with DNA.[14]

4.2. DLS (Dynamic Light Scattering)

A popular method for determining the size of NPs in colloidal suspensions in the nano- and sub micrometer ranges is dynamic light scattering (DLS). Continuous Brownian motion is present in the NPs scattered in a colloidal solution. The NP hydrodynamic diameter in solution—that is, the diameter of the NP and the solvent molecules that diffuse at the same rate as the colloid—is calculated using DLS, which measures light scattering as a function of time and the Stokes-Einstein assumption. To prevent a multiple scattering effect in DLS, a relatively low NP concentration is required.[15]

The quick, simple, and accurate operation of DLS for suspensions as well as the fact that it is an ensemble measurement approach, producing a good statistical representation of each NP sample, is its benefits. For homogenous, monodisperse samples, it is very reproducible and sensitive.

DLS aided in the observation of specific secondary surfactants irreversible penetration into reverse micelles. Although UV-Vis and DLS are quick and inexpensive techniques, caution must be taken when interpreting the results, particularly for the samples listed above that do not contain a single NP population. For polydisperse samples, complementary studies with AFM and TEM/SEM will undoubtedly be required. DLS tests revealed that, depending on the material under study, the NPs do not always maintain their nanoscale size when they are in solution.[16]

4.3. UV-Vis (UV-Visible Spectroscopy)

The technique of UV/Visible spectroscopy is used to measure the amount of light that is absorbed and scattered by a sample (the extinction, which is the total amount of absorbed and scattered light, is known as this number). In its most basic form, a sample is positioned between a light source and a photo detector, and the UV/visible light intensity is measured both before and after the sample is exposed to the light beam. To determine the sample's wavelength dependent extinction spectrum, these measurements are contrasted at each wavelength. Usually, the data is presented as an extinction function of wavelength. To make sure that spectral features from the buffer are not included in the sample extinction spectrum, each spectrum is background corrected using a buffer blank.

Although non-plasmonic nanoparticles also exhibit optical properties that rely on size and concentration, their spectrum is less sensitive to the dispersion characteristics than those of plasmonic nanoparticles.[17]

4.4. ICP-MS (Inductively Coupled Plasma Mass Spectrometry)

In a single, quick investigation, ICP-MS can also determine the size distribution and number concentration of NPs. The matrix of the sample solution is a key factor. In order to determine size, they presented an online coupling of liquid chromatography or gel electrophoresis with ICP-MS and compared the outcomes with those obtained using alternative methods. They also pointed out that, while the results from TEM reveal information on the diameter of the Au core, DLS results are often expected to yield larger values than those from other techniques because the parameter being assessed is the hydrodynamic radius of the nanoparticles. Their findings demonstrated how closely related the chemical composition of the NP surface is to the on-line GE-ICP-MS performance. There was good agreement across the various techniques employed to estimate the size of their Au NPs.[18]

ICP-MS was also used to identify arsenic. Samples of contaminated water were effectively cleaned of significant levels of the inorganic species. To track the identification and characterisation of NPs in complex matrices, including food and biological tissues, ICP-MS was used. Calculations were made for NP size, size distribution, and particle concentration. For each of the four types of NPs under study, the size detection limits were 20 nm for Au and Ag NPs, 50 nm for titania NPs, and 200 nm for silica NPs. The authors concur with other studies that in order to get a more accurate picture of the NP characteristics, it is necessary to combine ICP-MS with separation methods such hydrodynamic chromatography and field flow fractionation.[19]

4.5. XRD (X-ray diffraction)

One of the most widely used methods for characterizing NPs is X-ray diffraction (XRD). The lattice parameters, phase, crystalline grain size, and crystalline structure are typically revealed by XRD. By utilizing the Scherrer equation and the broadening of the most intense peak of an XRD measurement for a particular sample, the latter parameter is calculated. The advantage of using XRD techniques is that they produce statistically representative, volume-averaged values. These techniques are frequently used on samples in powder form, typically after drying their corrsesponding colloidal solutions.[20]

4.6. XAS (X-ray absorption spectroscopy)

Both extended X-ray absorption fine structure (EXAFS) and X-ray absorption near edge structure (XANES, often referred to as NEXAFS) are components of X-ray absorption spectroscopy (XAS). XAS calculates a material's X-ray absorption coefficient as a function of energy. For XAS element selectivity, each element has a set of distinctive absorption edges that correspond to the various binding energies of its electrons.[21] EXAFS is an efficient means to determine the chemical state of species that may exist even in extremely low concentrations because it is a highly sensitive technique. Since XAS spectra are typically acquired using synchrotrons, this method is not common or easily accessible. By taking into account the excitation of an inner shell electron to those states, XANES examines the density of states of empty/partially filled electronic states.The atomic structure and electrical characteristics of these NPs were analyzed using XANES and EXAFS, which revealed that the capping thiol molecules triggered the sulfidation of Pd clusters both on the surface and within the bulk.[22]

4.7. NMRS (Nuclear Magnetic Resonance spectroscopy)

Another crucial analytical method in the quantitative and structural evaluation of nanoscale materials is nuclear magnetic resonance (NMR) spectroscopy.

It is based on the NMR phenomenon, which is when a strong magnetic field is applied to a nucleus with non-zero spin, causing a slight energy difference between the'spin-up' and'spin-down' states. Electromagnetic radiation in the radio wave region can be used to study the transitions between these states. The interaction or coordination between the ligand and the surface of diamagnetic or antiferromagnetic NPs is frequently investigated using NMR. However, it is not appropriate to describe ferri- or ferromagnetic materials because the high saturation magnetization of such materials results in changes in the local magnetic field, which shift the signal frequency and create sharp drops in the signal level.[23]

In order to better understand the reaction pathways for NP synthesis, NMR can screen the chemical conversion of NP precursors in both the solution and solid phase, with high spatial and chemical resolution, under different reaction circumstances, and for various metal identities. NMR is also helpful for monitoring the ligand exchange process and the final products when the initial capping ligands need to be changed.[24]

4.8. Electron Diffraction

A vital microscopy technique for examining the crystal structure of NPs is electron diffraction (ED), also known as selective area electron diffraction (SAED). The majority of experiments are carried out using electron backscatter diffraction (EBD) TEM or SEM. These devices use an electrostatic potential to accelerate electrons to the required energy and wavelength before they contact with the sample under study. A crystalline solid's periodic structure serves as a diffraction grating, scattering electrons in a predictable way. It might be feasible to determine the structure of the crystal that produced the observed diffraction pattern by working backward from it. Buffet spoke about the investigation of multiple-twinned materials using electron diffraction and HRTEM.[25]

5. CONSIDERATIONS IN GENERAL FOR QUALITY CONTROL ANALYSIS AND METROLOGY

Quality control (QC) is a procedure or set of procedures intended to ensure that a manufactured product or performed service adheres to a defined set of quality criteria or meets the requirements of the client or customer. QC testing is important for nanoparticles for several reasons. The importance of quality control test in nano-particles is given in Table 3.

Table 3: Importance of quality control test in nano-particles.[26]

Aspect	Importance
Safety	Nanoparticles can have unique properties that may pose safety concerns. QC testing helps verify that nanoparticles are free from contaminants or impurities that could be harmful to human health or the environment.
Efficacy	The performance of nanoparticles in various applications, such as drug delivery, imaging, catalysis, or electronics, is directly related to their size, shape, surface properties, and other characteristics. QC testing ensures that nanoparticles meet the required specifications for their intended use.
Cost Efficiency	By identifying and addressing issues early in the production process, QC testing can help prevent costly manufacturing errors and product recalls.
Research and Development	In research settings, QC testing helps scientists characterize and understand nanoparticles better. It ensures that experimental results are reliable and reproducible, enabling the advancement of nanotechnology.

Quality Assurance	QC testing is a critical component of quality assurance programs, which are essential for industries that rely on nanoparticles to produce high-quality products consistently.
Customer Confidence	Companies that consistently produce high-quality nanoparticles through rigorous QC testing can build trust and confidence with their customers. This can lead to long-term partnerships and customer loyalty.

In summary, QC testing for nanoparticles is crucial to ensure their safety, efficacy, consistency, and compliance with regulations, which, in turn, helps advance nanotechnology and build trust in nanoparticles-based products and materials.

Although there are numerous parameters that can be used to define a single NM, only a select few are actually available for routine analysis using commercially available instruments or have been covered by ISO standards such as size, surface charge, shape, surface area, and reactive surface.

Strict metrology principles are used to obtain validation, which demonstrates that the analytical technique is sufficiently acceptable, trustworthy, and adequate for the elements of its scope. With CRM or RM, the validation is typically accomplished.A substance that has been metrologically characterized for one or more specified qualities using a valid technique is called CRM. RM is a uniform and stable material with respect to one or more predetermined qualities. It is suitable for use in the measurement of the given property. When it is feasible, it is crucial to validate the analytical process using a material that has been approved for use with the analytical method. There aren't many CRM and RM that can be used to validate NM characterisation methods.[27]

5.1. Examples of several medications for studying the physicochemical characteristics of NMs using various methods[28]

Carbamazepine, a medication found in various crystal forms, was created using electrospraying and XRD and DSC analyses. Rapid airwater absorption caused the medication to quickly change to a dehydrated state, resulting in poor storage stability. Theophylline cocrystal structures were validated using SSNMR and FTIR, and intramolecular hydrogen bonding was found in the cocrystals. Binary cocrystals of palmitic acid and nicotinamide were formed based on hydrogen bonding between the pyridine acceptor in nicotinamide and the carboxylic acid donor in palmitic acid.

5.2. Importance in dissolution testing of nanoparticles in the pharmaceutical industry

In the pharmaceutical field, the dissolution testing of nanoparticles is a critical step in assessing the performance and bioavailability of nanoparticle-based drug formulations. The dissolution behavior of nanoparticles can significantly affect drug release, absorption, and therapeutic efficacy.[29] Here's how the dissolution test of nanoparticles is typically conducted in the pharmaceutical industry.[30]

5.2.1. Sample Preparation

- Prepare a representative sample of the nanoparticle-based drug formulation, which includes the nanoparticles loaded with the active pharmaceutical ingredient (API).
- Ensure that the sample accurately reflects the intended drug product, including factors like particle size, drug loading, and surface coating.

5.2.2. Choice of Dissolution Medium

- Select an appropriate dissolution medium that simulates the physiological conditions the drug product will encounter. For oral dosage forms, this often involves using simulated gastric fluid (SGF) for the stomach and simulated intestinal fluid (SIF) for the small intestine.
- The choice of medium may vary depending on the drug's intended site of absorption and pH-dependent solubility.

5.2.3. Experimental Setup

- Employ a dissolution apparatus that complies with the pharmacopeial standards (e.g., USP, EP) such as a dissolution tester (e.g., USP Apparatus II) equipped with paddle or basket stirrers.
- Maintain the temperature and agitation rate specified in the pharmacopeial monograph or as appropriate for the study.

5.2.4. Sample Placement

- Place the nanoparticle-based drug formulation (e.g., tablets, capsules, suspensions) into the dissolution vessel containing the dissolution medium.
- Ensure that the dissolution conditions are maintained throughout the test.

5.2.5. Sampling and Analysis

- Collect samples of the dissolution medium at predetermined time intervals.
- Analyze these samples using suitable analytical methods, such as UV-Vis spectroscopy or HPLC (High-Performance Liquid Chromatography), to quantify the concentration of the API released from the nanoparticles into the medium.
- For nanoparticle-specific analysis, techniques like dynamic light scattering (DLS) or electron microscopy may be used to assess particle size and stability.

5.2.6. Data Analysis

- Calculate the dissolution profile, typically represented as the cumulative percentage of drug released over time.

- Evaluate the dissolution data to determine parameters such as dissolution rate, dissolution efficiency, and release kinetics.

5.2.7. Regulatory Compliance

- Ensure that the dissolution testing complies with regulatory requirements outlined in pharmacopeial monographs (e.g., USP, EP) and any specific guidance documents provided by regulatory agencies.

5.2.8. Reporting and Interpretation

- Document the dissolution test conditions, results, and any relevant observations.
- Interpret the dissolution data in the context of drug release characteristics, ensuring that the nanoparticle formulation meets the desired release profile and bioavailability requirements.
- The dissolution test of nanoparticles in the pharmaceutical field is crucial for quality control, ensuring consistent drug release from nanoparticle-based formulations, and demonstrating the bioequivalence or efficacy of these formulations compared to conventional drug products. It helps pharmaceutical researchers and manufacturers optimize drug formulations and assess their performance in vivo.

6. Importance of Nanotechnology in medicine and healthcare

The word "nanomedicine" is used to describe the use of nanotechnologies in healthcare and medicine. In order to prevent, diagnose, monitor, and treat diseases, nanomedicine uses technology at the nanoscale and nano-enabled procedures. Nanotechnologies have significant potential in the medical field, including in imaging and diagnostic tools, drug delivery systems, tissue-engineered constructs, implants, and pharmaceutical therapeutics.[31] They have also advanced the treatment of many diseases, including diabetes, bacterial and viral infections, cancer, cardiovascular disease, and musculoskeletal conditions. **Table 4** below is here to describe importance of Nanotechnology in Developing Pharmaceutical Medicines.

Table 4: The Importance of Nanotechnology in Developing Pharmaceutical Medicines.[32]

Importance of Nanotechnology in Pharmaceutical Medicines	Explanation
Enhanced Drug Delivery	Utilizing nanoscale drug delivery systems can improve the targeted delivery of drugs to specific cells or tissues, increasing drug efficacy while minimizing side effects.
Enhanced Therapeutic Efficacy	By encapsulating drugs in nanoparticles, it is possible to protect them from degradation, leading to sustained and controlled release, thereby enhancing their therapeutic efficacy.
Imaging and Diagnosis	Enable early disease detection, accurate diagnosis etc.
Improved Solubility and Bioavailability	Nanotechnology enables the formulation of poorly soluble drugs, enhancing their solubility and bioavailability, which can lead to better absorption and therapeutic effects in the body.
Personalized Medicine	Nanotechnology allows for the customization of drug formulations based on individual patient characteristics, enabling tailored treatments for improved therapeutic outcomes and patient compliance.
Reduced Toxicity and Side Effects	Through targeted drug delivery and controlled release, nanotechnology can minimize off-target effects, reducing overall toxicity and enhancing the safety profile of pharmaceutical medicines.
Targeted Drug Delivery	Nanoparticles can be engineered to specifically target diseased cells or tissues, reducing systemic exposure and toxicity while enhancing the accumulation of drugs at the intended site.

7. Production Methods of Nanoparticles

Nanocrystals can be produced using milling, precipitation, and homogenization techniques. Top down technologies, which have to start with a large-size medication powder and decrease in size, are most applicable to industry. Bottom-up processes, which start with a dissolved molecule and precipitation, are currently not used for commercial goods. Factors such as solvent removal, management difficulties, and poor solubility of medications in organic and aqueous media contribute to these challenges.

7.1. Precipitation Methods

The creation of nanocrystals for use in medicinal applications depends heavily on precipitation techniques. Submicron-sized medication particles called nanocrystals have higher bioavailability, solubility, and dissolution rates.[33] These techniques make it possible to create stable, tightly regulated nanocrystals that can be used in a variety of drug delivery systems. The following four sentences outline various precipitation techniques used to prepare nanocrystals for use in pharmaceuticals.

7.2. Anti-solvent Precipitation

Making nanocrystals for use in pharmaceuticals, anti-solvent precipitation is a common process. In this procedure, the medication is quickly injected or combined with an anti-solvent, a non-solvent, after being dissolved in a solvent, usually an organic one. The drug molecules precipitate as nanocrystals due to the anti-solvent's sudden fall in drug solubility. The size and morphology of nanocrystals are greatly influenced by

variables such the drug-to-solvent ratio, the choice of solvent and anti-solvent, and mixing conditions.[34]

7.3. Bottom-Up Precipitation

Bottom-up precipitation techniques use molecularly dissolved drug species to control the nucleation and development of drug nanocrystals. This method often calls for careful adjustment of temperature, supersaturation, and additives to encourage the creation of drug particles that are nanoscale in size. Nanocrystals with exact size and size distribution are produced using techniques such controlled crystallization, supercritical fluid precipitation, and anti-solvent crystallization, making them appropriate for medicinal formulations.

7.4. Top-Down Precipitation

Mechanical reduction of bulk medicinal ingredients into nanocrystals is a top-down precipitation approach. Bead milling, wet media milling, and high-pressure homogenization are some of the methods used to reduce bigger drug particles into nanocrystals. These techniques are useful because they enable the production of nanocrystals from weakly water-soluble medicines without the need of solvents or chemical alterations. Process variables such as milling duration, medium type, and milling speed can be changed to alter the particle size and distribution.

7.5. Supercritical Fluid Precipitation

This is a cutting-edge method for creating nanocrystals, particularly for pharmaceuticals that are poorly water-soluble. It involves using supercritical fluids as both a solvent and an anti-solvent, such carbon dioxide. The medication is dispersed in a supercritical fluid, and the quick pressure and temperature changes when it comes into contact with a supercritical anti-solvent cause the drug to precipitate as nanocrystals. Drugs that are sensitive to conventional solvents can be processed using this approach, which enables exquisite control over nano-crystal size.[35]

7.6. Milling Methods

The capacity of nanocrystals to improve the solubility and bioavailability of poorly water-soluble medicines has made them an increasingly essential component of the pharmaceutical industry. Pharmaceutical companies prepare nanocrystals using a variety of milling techniques, each of which has benefits and drawbacks.[36]

7.6.1. Cryomilling

Cryomilling is a technique for reducing drug particles to the nanoscale by milling at very low temperatures, usually with liquid nitrogen. Low temperatures make it suited for compounds that are thermally sensitive since they limit drug degradation and agglomeration during milling. Nanocrystals with a restricted size distribution can be created using Cryomilling. Due to the usage of cryogenic fluids, it might necessitate specialised equipment and handling concerns.

7.6.2. Media Milling

The drug particles are broken down into nanocrystals by media milling, which uses grinding media like beads. Drug particles are in suspension in a liquid medium and are ground down to nanoscale size by colliding with the grinding media. Media milling is flexible for different medication formulations because it can be done in both wet and dry circumstances. Particle size and dispersion may be controlled precisely thanks to this. However, the qualities of the finished product can be impacted by the selection of milling media and formulation parameters.

7.6.3. Pearl Milling

Using a revolving agitator and grinding pearls, the process of "pearl milling," often referred to as "stirred media milling," lowers medication particle size. Because it uses less energy than HPH, this approach is appropriate for medications that are thermally sensitive and provides excellent control over particle size and distribution. When developing at an early stage or in the lab, it is frequently recommended. Scaling up pearl milling, however, can be difficult, and it's essential to consider the milling media and operating circumstances.

7.7. Homogenization Methods

7.7.1. High-Pressure Homogenization (HPH)

The manufacture of nanocrystals frequently uses the high-pressure homogenization technique. In this method, tremendous pressures—typically above 1000 bar—are used to push drug particles through a small opening. Particle size is reduced to the nanoscale range by the strong mechanical forces produced during this process. Industrial pharmaceutical production can benefit from HPH because of its scalability and reproducibility. However, the method can be energy-intensive and may not be appropriate for medications that are sensitive to heat.[37]

7.7.2. Rotor-Stator Homogenization

To produce strong shear forces within the drug suspension, rotor-stator homogenization uses a high-speed rotor and a stator with cutting-edge blades. By using this technique, one can produce nanocrystals and reduce particle size. Due to the fact that it produces less heat than other methods like HPH, it is especially useful for medications that are sensitive to heat. Continuous and batch processing can both use rotor-stator homogenization.

7.7.3. Micro fluidization

To homogenise materials and produce nanocrystals, micro fluidization uses high-pressure pressures. The drug suspension is pumped through a micro fluidic chamber in this method, subjecting the liquid streams to strong shear and impact pressures. Because the process parameters may be precisely controlled by the controlled micro fluidic channels, homogeneous and stable nanocrystals are produced. Both research and commercial contexts can make use of micro fluidization, which is appropriate for delicate medicinal molecules.

8, Considerations in Nanomedicines Development

8.1. Chemistry, Manufacturing, and Controls (CMC) Considerations

The CMC is crucial for the successful translation of nanotechnology-based therapies from the laboratory to clinical applications. It involves understanding the composition, structure, and surface characteristics of nanomaterials, controlling manufacturing processes, and ensuring regulatory compliance. Manufacturing involves creating reliable, scalable, and economical techniques for nanomedicines, while control involves rigorous quality control procedures. This includes developing analytical techniques for characterizing nanoparticles, evaluating stability, and ensuring the finished product meets standards. Thorough testing is essential for product safety and effectiveness.[38]

8.2. Economic Consideration

The sum of money needed to develop and scale up the production of nanomedicines must be taken into account. When comparing potential nanomedicines programmes to other development portfolios, investor profiles must take into account the entire risk of CMC development. For some businesses, instruments, production equipment, and other facilities may incur costs; as a result, these facilities must be considered in investment strategies for the development of nanomedicines that are in line with clinical needs.

8.3. Regulatory Considerations

Nanomedicines development is a rapidly growing field with significant healthcare applications. Global regulatory bodies like the FDA and EMA closely examine nanomedicines products to ensure safety and efficacy. Key considerations include characterizing nanomaterials, understanding their potential toxicity, and evaluating their body behaviour. Quality control requirements and preclinical and clinical studies are also crucial. Researchers must navigate a complex regulatory environment to ensure adherence to current standards and influence future legislation.[39]

9. Products in the market

The pharmaceutical market and healthcare system are expected to be significantly impacted by pharmaceutical nanomedicines products. Since 1995, the FDA and EMA have approved around 70 nanomedicines items for sale, with a further twice that number currently undergoing clinical testing. Nanotechnology is increasingly used in drug development, with new nanomedicines of already-approved medications being tested for efficacy. However, most licensed nanomedicines have shown decreased toxicity rather than increased efficacy. Since 1989, 78 nanomedicines have been authorized and distributed worldwide, with 31 and 66 approved by the FDA and EMA, respectively. Various subcategories of nanomedicines, including inorganic, protein-based, dendrimer-based, lipid-based, polymer-based, and nanocrystals, are now commercialized due to their benefits to the healthcare system. The List of globally marketed nanomedicines approved by the FDA and EMA are described in **Table 5**.

Table 5: List of globally marketed nanomedicines approved by the FDA and EMA.[40]

Trade Name	Company	Date of Approval	Active Ingredients	Indication
Cimzia®	UCB	FDA (2008), EMA (2009)	IgG Fab' fragment	Rheumatoid arthritis, Crohn's disease
Curosurf®	Chiesi	FDA (1999)	poractantalfa	(RDS)
Doxil®	Johnson & Johnson	FDA (1995), EMA (1996)	doxorubicin (adriamycin)	metastatic ovarian cancer, HIV-associated Kaposi's sarcoma
Emend®	Merk&Co.Inc	FDA(2003)	Aprepitant	Antiemetic drug
Feraheme™	AMAG Pharmaceuticals	FDA (2009).	ferumoxytol	Anemia
Inflexal®	CrucellBerna Biotech	EMA (1997)	Inactivated influenza virus vaccine	prevents influenza infection
Invega®	Janseen Pharmaceuticals	FDA(2009)	Paliperidone	Schizophrenia
Megace ES®	Par pharmaceuticals	FDA(2005)	Megestrolacetate	Antianorexic
Ontak®	Eisai	FDA (1999)	diphtheria toxin	leukemia, T-cell lymphoma
Rapamune®	Wyeth Pharmaceuticals Inc	FDA(2010) EMA(2001)	Sirolimus (rapamycin)	Immunosuppressant
Ryanodex®	Eagle pharm	FDA(2014)	Dantrolene sodium	Malignant hyperthermia
Tricor®	Abbott Laboratories	FDA(2004)	Fenofibrate	Antihyperlipidemic
Zanaflex®	Acorda	FDA(2002)	Tizanidine HCL	Muscle relaxant
Zevalin®	Bayer Pharma	FDA (2002	90Yibritumomab tiuxetan	Lymphoma

9.1 Products in pipeline

In general, it may be said that the advantages of nanocrystals technology can be used to improve the efficacy of numerous other poorly soluble medications. Many products are already in clinical studies or on the verge of release. Due to the significant dangers of

information breaches and concern over competitors in the pharmaceutical sector, information regarding these medications and goods is scarce. Nevertheless, the following examples provide an idea of prospective future products and the list of nanomedicines which are in clinical trial described in **Table 6.**

Table 6: List of nanomedicines which are in clinical trial.[40-41]

Trade name	Drug	Indication	Company	Status
Nucryst	Silver	Anti bacterial	Nucryst Pharmaceuticals	Phase II
Semapimod	Guanyl hydrazone	TNF-α inhibitor	Cytokine Pharmasciences	Phase II
Paxceed	Paclitaxel	Anti inflammatory	Angiotech	Phase III
Theralux	Thymectacin	Anti cancer	Celmed	Phase II
Livatag	doxorubicin	hepatocellular carcinoma	Onxeo	Phase III
ThermoDox	doxorubicin	hepatocellular carcinoma	Celsion	Phase III

10. APPLICATION

10.1. Nanoparticles in imaging and diagnosis

Nanoparticles are crucial in medical imaging and diagnosis due to their enhanced ability to detect and visualize diseases and explained in **Table 7**. They can improve contrast in various imaging techniques like MRI, X-ray, and ultrasound. Nanoparticles also serve as flexible carriers for the combining therapy and diagnostics. They can deliver drugs directly to disease locations and function as diagnostic probes, providing data on treatment effectiveness and disease development. Examples include dendrimer, silica nanoparticles, and liposomes.[42]

Table 7: List of Nanomedicine and their application in Diagnosis.[42-45]

Nanomaterials	Imaging and Diagnostic Application	Description
Carbon Nanotubes	Contrast Agents, Drug Delivery	Tubular carbon structures can be used to enhance contrast in imaging or deliver drugs.
Dendrimers	Contrast Agents, Molecular Imaging	Highly branched molecules with precise structures that can be functionalized for imaging.
Gold Nanoparticles	Photo acoustic Imaging, X-ray Contrast Agents	Gold nanoparticles absorb light and can generate acoustic signals, improving imaging accuracy.
Iron Oxide Nanoparticles	Magnetic Resonance Imaging (MRI)	Magnetic nanoparticles enhance MRI contrast by altering relaxation times in tissues.
Liposomes	Drug Delivery, Ultrasound Imaging	Lipid-based nanoparticles can encapsulate drugs and act as contrast agents in ultrasound.
Magnetic Nanowires	Magnetic Resonance Imaging	Nanowires offer improved magnetic properties, enhancing their use as MRI contrast agents.

10.2. Nanoparticles in drug delivery

Drugs are often administered to specific targets during therapy, often using external approaches like radiotherapy and surgery. Nanotechnologies are making significant contributions to drug delivery strategies, such as using liposomes to administer high-toxicity medications like doxorubicin without harming the heart or kidneys. For example, paclitaxel combined with polymeric mPEG-PLA micelles is used in chemotherapeutic treatment of metastatic breast tumours. The effectiveness of nanotechnologies in drug delivery is attributed to their enhanced in vivo distribution, circumvention of the reticuloendothelial system, and favourable pharmacokinetics.[46]

10.3. Nanoparticles in cancer treatment

Nanomedicine is revolutionizing cancer treatment by providing innovative solutions to conventional medicines. Nanoparticles, designed to deliver anticancer medications with precision, can be functionalized to target specific tumour cells or tissues, reducing chemotherapy side effects and improving therapeutic effectiveness and describe in **Table 8**. This allows for lower drug doses and improved patient compliance. Nanoparticles are also crucial for imaging and diagnostics, enabling early cancer identification and real-time monitoring of therapy outcomes. They can be used as contrast agents in imaging procedures like MRI, CT, and PET. Nanotechnology also enables personalized medicine, allowing treatments to be tailored to a patient's specific genetic and molecular profile.[47-48]

Table 8: Outlining various nanomedicine clinical agents used in cancer treatment.[49]

Nanomedicine Clinical Agent	Description	Application in Cancer Treatment
Abraxane (Nanoparticle Albumin-Bound Paclitaxel)	Paclitaxel nanoparticles bound to albumin.	Used in breast, lung, and pancreatic cancer treatment.
Cimzia (CertolizumabPegol)	Polyethylene glycol (PEG)-conjugated anti-TNF alpha antibody.	Treatment of Crohn's disease and rheumatoid arthritis often associated with cancer.
Doxil (Liposomal Doxorubicin)	Liposome-encapsulated doxorubicin.	Treatment of various cancers, including breast and ovarian cancer.
Feraheme (Ferumoxytol)	Super paramagnetic iron oxide nanoparticles.	Used as an MRI contrast agent for cancer imaging.
Lipodox (Liposomal Doxorubicin)	Liposome-encapsulated doxorubicin.	Treatment of Kaposi's sarcoma, a cancer often seen in AIDS patients.
NanosomalDocetaxel	Docetaxelloadednanoparticles.	Used for various solid tumor treatments.

10.4. Nanoparticles in cardio vascular syndrome

Nanomedicine has significantly improved diagnostics for cardiovascular diseases (CVD), enabling more accurate identification of biomarkers and structural problems. It also aids in drug delivery, reducing off-target effects and increasing treatment efficacy and broadly describe in **Table 9**. Nanoparticles-based vectors can also be used for CVD gene therapy, potentially revolutionizing treatment methods.[50]

Table 9: outlining some nanomedicine clinical agents used in the treatment of cardiovascular diseases.[51-53]

Nanomedicine Clinical Agent	Description	Application in Cardiovascular Disease Treatment
Lipitor (Atorvastatin Nanoparticles)	Nanoparticles-based formulation of atorvastatin, a statin drug.	Used to lower cholesterol levels and reduce the risk of cardiovascular events like heart attacks and strokes.
Nano-based Gene Therapy (Various)	Nanoparticles vectors for delivering therapeutic genes.	Investigated for gene therapy approaches to treat conditions like heart failure and genetic cardiovascular disorders.
Nanocarriers for Drug Delivery (Various)	Different nanoparticles used to deliver drugs for CVD treatment.	Delivery of drugs like anticoagulants, antiplatelets, and vasodilators to improve drug efficacy.
Nanotrap (Nanoparticles-based Contrast Agents)	Nanoparticles for enhanced MRI and CT imaging.	Used for improved imaging of blood vessels and cardiac structures for diagnostic purposes.
Nanosensors for Monitoring (Various)	Nanoscale sensors for continuous monitoring of cardiac biomarkers.	Monitoring of biomarkers like troponin and B-type natriuretic peptide (BNP) to assess heart health and diagnose heart conditions.

11. CONCLUSION

Advances in nanomedicine are expected to revolutionize medical practice by creating complex and precise nanoscale equipment and medicines. These advancements will enable targeted drug delivery systems, improving therapeutic efficacy and reducing side effects. Early disease identification through nanoscale sensors and diagnostics will allow medical personnel to intervene at the earliest stages of illness, potentially changing the course of diseases like cancer, cardiovascular diseases, and neurodegenerative illnesses. Nanomedicines influence extends beyond diagnostics and drug delivery, providing biomaterials and scaffolds for tissue repair and regeneration. It will also improve patient recovery and comfort, offering alternatives to traditional surgical interventions. Nanotechnology will also create complex brain-computer interfaces, enabling direct communication between the human brain and external technologies.

Nanomedicine is a revolutionary medical technology that has the potential to revolutionize disease identification, treatment, and prevention. It offers precise drug delivery systems, early illness diagnosis, personalized medical strategies, regenerative therapies, and advanced diagnostic equipment. These advancements could improve patient outcomes, reduce side effects, and enhance therapy efficacy. However, challenges such as legal and moral issues remain. As nanotechnology advances, we may see a patient-centric healthcare system, personalized treatments, and early disease detection. This could significantly enhance quality of life and tackle challenging medical issues, making nanomedicine a crucial factor in healthcare provision.

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