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Formulation And Evaluation Of Nanoparticle-Based Drug Delivery System For Enhanced Bioavailability Of Poorly Soluble Drugs

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Abstract: The development of nanoparticle-based drug delivery systems (NDDS) has become a significant tool for addressing the problems associated with drugs that are not readily soluble in water and, as a result, have restricted bioavailability due to poor dissolution and permeability. NDDS, which include liposomes, polymeric nanoparticles, nanoemulsions, nanohydrogels, inorganic carriers, dendritic polymers, and nanocrystals, are used in order to enhance the solubility of medications, as well as their stability, controlled release, and targeted administration. These NDDS do not alter the chemical structure of the medicine in any way, shape, or form. These systems are able to improve absorption, extend circulation, and reduce systemic toxicity by utilizing nanoscale features such as large surface area, surface functionalization, and reactivity to both internal and external stimuli. These features are utilized in order to achieve these goals. Nanocrystal technology, for example, is a versatile approach that may be used for intravenous, parenteral, and oral administration. This is because it boosts bioavailability, saturation solubility, and dissolving rate. Megestrol acetate, sirolimus, and fenofibrate are a few examples of marketed medications that demonstrate how these strategies have been developed and used successfully in translation. In conclusion, NDDS is an exciting new invention that has the potential to change targeted and combination treatments by boosting both the efficacy of the therapy and the patient's compliance with the treatment requirements.

Keywords: Nanoparticle-Based Drug Delivery System (NDDS), Poorly Water-Soluble Drugs, Bioavailability Enhancement, Nanocrystals, Liposomes, Polymeric Nanocarriers, Nanoemulsions, Nanohydrogels

INTRODUCTION

The pharmaceutical industry is now confronted with the challenge of dealing with drugs that have poor water solubility and an insufficient bioavailability [1]. Several recent studies [2] have shown that a significant proportion of investigational medicines and about forty percent of the pharmaceuticals that are already on the market have poor solubility. Due to the fact that this issue causes a decrease in bioavailability and impairment in therapeutic effectiveness, it

is often necessary to provide greater dosages in order to get the same effect [3]. It has been difficult to dissolve and release medicines that are poorly soluble, which has slowed down the process of discovering and implementing a large number of unique chemical therapies from the beginning.

The bioavailability of oral solid dosage forms, which is the most common and patient-complied method of medication administration, has been reduced as a result of this [4]. Because of the medicine's low bioavailability; it is necessary to provide higher dosages of the medication to patients in order to get the same therapeutic effects [5]. However, the more severe adverse effects that result from larger dosages lead to a lower rate of medication compliance and the potential for harm to both the patients' physical and mental health [6]. There are a number of clinical issues that can arise as a result of the problem of low water solubility. These issues include, but are not limited to, the following: an increase in the cost of the medication, an increased risk of toxicity or ineffectiveness, variability in patient responses, and difficulties in maintaining a safe therapeutic index [7]. As a consequence of this, one of the primary concerns and challenges in the field of pharmaceutical and medical research has always been the identification of efficient solutions to the issues of low bioavailability and poor solubility of available medications. Nanomedicine delivery systems have emerged as a revolutionary way to the distribution of medications.

These systems overcome the typical restrictions that are created by drug solubility and bioavailability, and they provide a viable solution to these issues. The nanomedicine delivery systems consist of two primary components, which are as follows: First and foremost, these systems have the capability of precisely delivering drugs to the specific lesion sites based on the pathological alterations. This enhances the therapeutic effectiveness while significantly reducing the amount of damage that is caused to healthy tissues. In the second place, they have the ability to control the dose in such a way that the medication remains in the bloodstream at an effective and safe level, therefore minimizing or eliminating the possibility of adverse effects [8].

These delivery systems, which include nanoparticles with a size of less than 100 nm, provide a multitude of desired characteristics, including enhanced drug solubility, multifunctionality, controlled drug release mechanisms, and the ability to preferentially target sick cells [9]. By changing the structure of the medicine via the use of nanotechnology, these systems enhance

the drug's bioavailability and extend the amount of time it spends in circulation. This not only improves the stability of the medication and allows for more exact control over its release, but it also stops the drug molecules from decaying prematurely before they reach the lesion.

OBJECTIVES

1. To create and refine a drug delivery system based on nanoparticles for pharmaceuticals that are poorly soluble in water with the goal of improving solubility, stability, and controlled release while preserving biocompatibility and reducing toxicity.
2. To assess the formed nanoparticles' in vitro and in vivo performance in relation to traditional drug formulations, including particle characteristics, dissolution rate, bioavailability, and therapeutic effectiveness.

METHOD

When creating nanoparticle-based drug delivery systems (NDDS) for medications that have restricted solubility, it is necessary to give careful thought to the many components, including the drug, the carrier, the preparation, and the characterization. The medication that is poorly soluble in water may be identified by its physicochemical characteristics, which include its solubility, permeability, and dose requirements. These characteristics are utilized to determine the drug. In order to choose an appropriate nanocarrier system, it is essential to take into account the compatibility of the medicine, the release profile that is sought, and the particular delivery requirements. Liposomes, polymeric nanoparticles, nanoemulsions, nanohydrogels, inorganic carriers, dendritic polymers, and drug nanocrystals are all examples of approaches that might be considered. The preparation processes utilize either bottom-up approaches, such as controlled precipitation, or top-down techniques, such as high-pressure homogenization and medium milling, in order to assure the generation of nanoscale particles with a uniform size distribution. Additionally, the preparation procedures use both approaches. Through the use of stabilizers, surfactants, or polymers, which prevent aggregation and maintain the zeta potential, it is possible to guarantee both the physical stability and the excellent bioavailability of the substance. A comprehensive physical and chemical investigation is carried out on the nanoparticles that have been synthesized. This analysis includes the determination of zeta potential, the inspection of morphology using scanning or transmission electron microscopy (SEM/TEM), and the evaluation of crystallinity by X-ray diffraction (XRD). Drug loading, encapsulation efficiency, and in vitro release tests are used to evaluate the performance of the

formulation. Dissolution studies are used to evaluate the augmentation of solubility and the rate of drug release. In conclusion, the advantages of the nanoparticle-based delivery system have been validated by in vivo pharmacokinetic studies conducted on appropriate animal models. These investigations evaluate the augmentation of bioavailability and determine the efficiency of the therapeutic intervention. In the next step, these investigations are contrasted with conventional formulations.

POORLY SOLUBLE DRUGS: DEFINITION AND CLASSIFICATION

Research shows that dissolving rate, pH, distribution route, and first-pass effect influence bioavailability and medicine absorption [10]. Poorly soluble medications have limited bioavailability due to slow dissolving and restricted solubility, requiring higher therapeutic doses even when they have significant pharmacological effect [11]. This class contains most BCS Class II and IV compounds, which make up 40% of commercial drugs and most development prospects. Solubility standards and lowering in vivo bioequivalence are supported by Biopharmaceutical Classification System science. Orally administered Class II and IV drugs use reasonable formulation based on physicochemical and biological properties.

$$\mathrm{Dn} = \left(\frac{3D}{r^2}\right)\left(\frac{C_s}{\rho}\right)\langle T_{si}\rangle = \frac{\langle T_{si}\rangle}{T_{diss}} \quad (1)$$

$$\mathrm{Do} = \frac{M/V_0}{C_s} \quad (2)$$

$$\mathrm{An} = \frac{P_{eff}}{R} X \langle T_{si}\rangle = \frac{\langle T_{si}\rangle}{T_{diss}} \quad (3)$$

$$\mathrm{F} = 1 - e^{-2An} \quad (4)$$

BCS classifies active pharmacological substances using the absorption, dissolution, and dose numbers. Equation 1 gives effective permeability as a function of intestinal radius and residence time. Solubility, diffusion coefficient, particle size, and intestinal transit time impact the relationship between gastrointestinal residence time and drug dissolution time, as shown in Dn (Equation 2). Drug absorption is exponential (Equation 4), whereas Do is the ratio of given dose to drug solubility (Equation 3). Digoxin and griseofulvin studies demonstrate their

practicality. Smaller particles improve Dn absorption, but larger particles hinder dissolution and absorption [12]. Micronization hardly affects griseofulvin due to its high dose-to-solubility ratio, which inhibits absorption. Increasing solubility to reduce Do is critical. For drugs with limited bioavailability, improving solubility is the key strategy.

BCS Class II Drugs: Low Solubility, High Permeability

Morphine, chlorpromazine, and procaine are Class II medicines with high permeability and low solubility. Dissolving rate is the main factor limiting bioavailability for these drugs [13]. Small adjustments may have big effects. According to the Noyes-Whitney equation, surface area, diffusion coefficient, diffusion layer thickness, saturation solubility, quantity of dissolved drug, and dissolution medium volume affect dissolution rate and drug concentration. BCS Class II drugs may be made more soluble by changing crystal structures, particle size, self-emulsifying, and pH. In vitro-in vivo correlation (IVIVC) using pH-dependent solubility data (pH 1-8) is used to improve water solubility by modifying the drug's ionization state [14]. Organic solvents, however, are not advised due to their difficult formulations, significant precipitation risk, and poor IVIVC due to physiological pH variability. Self-emulsification outperforms pH adjustment because it better represents intestinal conditions. Dietary lipid interactions generate emulsions, whereas bile salt and phospholipid interactions make lipophilic drugs moist and soluble. Common synthetic surfactants utilized in in vitro dissolving studies include Tween 20, Sodium Lauryl Sulfate, and Dodecyl Trimethyl Ammonium Bromide [15]. Nanoemulsions have higher bioavailability than regular emulsions (Table 1). Singh et al. showed that nanoemulsions considerably enhanced primaquine oral bioavailability. Advances have been made, yet constraints remain. Salt generation may cause aggregation in neutral substances [16]. Particle size reduction fails for extremely fine, low-wettability powders.

BCS Class IV Drugs: Low Solubility, Low Permeability

Aluminum hydroxide and acetazolamide are BCS Class IV medicines with limited solubility and permeability. gastrointestinal factors such stomach emptying, motility, microbiota, enzyme activity, and intraluminal viscosity may impact these drugs' pharmacokinetics. Intraluminal viscosity is crucial when medicine dosages don't dissolve or absorb in transit [17]. Physiological factors may affect drug permeability. The dual constraints of solubility and permeability make it difficult to use physiological factors like stomach emptying and

gastrointestinal transit durations when designing and developing BCS Class IV drugs to optimize absorption. Researchers have not established the safety of increasing BCS Class IV drug permeability. BCS Class IV drugs may be manufactured like BCS Class II drugs to aid gastrointestinal absorption. However, permeability issues may restrict this strategy. BCS Class IV medications dissolve in the GI tract, but their innately poor permeability inhibits absorption, complicating formulation and therapy.

PRINCIPLES OF NANOMEDICINE DRUG DELIVERY SYSTEMS

Working Mechanisms of Nanomedicine Drug Delivery

Using nanomaterials as carriers, nanoparticle drug delivery systems exploit encapsulated medicines' protective qualities, high-energy catalytic activity of surface atoms, and microscopic size [18]. These processes enable drugs to bypass the body's inherent defenses, target them for slow cellular or subcellular release, and reduce or eliminate bodily fluids and immune clearance. These strategies aim to maximize pharmaceutical usage while avoiding toxicity and side effects [19]. These technologies provide promise for drug administration by eliminating some of the biggest issues with present methods, notably for drugs with poor solubility, stability, or targeted dispersion.

Table 1. Important Distinctions Between Nanoemulsion and Emulsion

Sr. No.	Emulsion	Nanoemulsion
1	Kinetically less stable	Kinetically more stable
2	Appearance: cloudy or opaque	Appearance: clear or transparent
3	Particle size ranges from 1–1000 µm	Particle size ranges from 1–100 nm
4	Anisotropic in nature	Isotropic in nature
5	Requires higher surfactant concentration (20–25%)	Requires lower surfactant concentration (5–10%)

6	Prepared using wet gum and dry gum methods	Prepared using high-energy or low-energy emulsification methods
7	Stability issues such as creaming, phase inversion, and sedimentation may occur	Such stability problems generally do not occur

TYPES AND CHARACTERISTICS OF NANOMEDICINE DRUG DELIVERY SYSTEMS

Liposomal Nanocarriers

Liposomes, closed lipid bilayer structures with an aqueous center, may encapsulate hydrophilic and lipophilic drugs. Due of their structural flexibility, they can transport medicines via membrane fusion and passive diffusion. Ethomal nanogels show potential for topical skin cancer medication delivery. This highlights liposomes' rising role in nanotechnology-based treatments [20]. Hydrophilic liposomal drug delivery is prevalent since it's non-toxic, biodegradable, and biocompatible. Solid lipid nanoparticles (SLNs) and nanostructured liposome carriers (NLCs) provide liposomal nanocarriers. Particle sizes between 50 and 1000 nm provide regulated medication release, targeted dispersion, and decreased carrier toxicity. Encapsulating oral anticancer pharmaceuticals like Tyrosine Kinase Inhibitors (TKIs) in SLNs protects them from acidic degradation, increases their surface area and adhesion for improved gastrointestinal absorption, and allows continuous drug release. Polyethylene glycol (PEG) coatings on SLNs may improve mucosal penetration and intestinal secretion clearance [21]. Drug loading and encapsulation efficiency, structural stability at room temperature, and lipid recrystallization prevention are better in NLCs than SLNs due to their solid and liquid lipids. NLCs increase tumor targeting, prolonged release, and intratumoral concentration of norcantharidin (NCTD), a strong anticancer agent with low absorption and high toxicity. These enhancements increase tumor inhibition and reduce negative effects compared to free medicine. Due to their biocompatibility, controlled release, stability, and high skin permeability, SLNs and NLCs may cure acne and psoriasis [22].

Polymer Nanocarriers

Polymer nanocarriers are extremely adjustable drug delivery platforms produced from natural or synthetic polymers utilizing simple synthetic processes. Self-assembly of amphiphilic block copolymers in water has produced polymer micelles, vesicles, and nanoparticles. These nanostructures feature hydrophobic and hydrophilic areas for medicine encapsulation and distribution. Polymer micelles feature a hydrophobic interior for low-solubility pharmaceuticals and a hydrophilic exterior for biocompatibility, immune evasion, and steric stability. The core-shell design regulates drug release, protects active compounds, and enhances drug loading. Through enhanced permeability and retention (EPR), the hydrophilic corona passively targets tumors and prolongs systemic circulation by lowering reticuloendothelial opsonization and absorption [23]. Drug loading into micelles may occur by covalent conjugation, direct dissolution, self-assembly, dialysis, and emulsion solvent evaporation. Lee et al. observed that folate-modified FA-PGA-PTX micelles targeted and controlled release, limiting harm to normal cells and selectively killing folate receptor-positive MCF-7 cancer cells. Polymer vesicles composed of amphiphilic block polymers may encapsulate hydrophobic and hydrophilic drugs in their closed bilayer hollow structure. The hydrophobic membrane integrates lipophilic molecules while the watery core holds hydrophilic drugs, prolonging release and improving encapsulation. Wang et al. observed that polymer vesicles administered doxorubicin and taxol synergistically, suppressing tumors better than single-drug approaches. Polymer vesicles' structural stability and large molecular weight lengthen release patterns. By improving ocular adhesion, corneal permeability, and bacterial targeting, ciprofloxacin-loaded polymer vesicles increased drug bioavailability and treatment efficacy in bacterial keratitis (Chen et al., 2024) [

Nanoemulsions

Water, oil, surfactants, and co-surfactants form nanoemulsions, which have droplet sizes between 10 and 100 nm. These thermodynamically unstable, low-viscosity systems seem translucent or partly transparent. Nanoemulsions may be O/W, W/O, or multiphasic, depending on the components utilized to emulsify the two incompatible liquids. Drug delivery nanoemulsions offer several advantages. Pharmaceuticals are more stable when coated in oil, which prevents oxidation and hydrolysis. Drug solubility, absorption, and bioavailability are improved by nanoemulsions. Ding L et al. [25] attributed the enhanced permeability and

retention (EPR) result to perfluorocarbon nanoemulsions inhibiting pancreatic tumor growth better than poly-cationic/siRNA complexes. Topical, intravenous, and oral delivery are possible due to their liquid condition. Niu Z et al. found that nanoemulsions increased coenzyme Q10 bioavailability by 1.8-2.8 times [26].Nanoemulsions hide bitter drugs and reduce flocculation, creaming, and sedimentation. Environmental factors including pH and temperature impact nanoemulsion stability, limiting its usage despite their advantages. Ongoing coagulation, droplet coalescence, and Ostwald ripening can reduce stability and shelf life.

Nanohydrogels

Water-insoluble nanohydrogels are networks of nanoscale, three-dimensional cross-linked polymers. Their advantageous surface characteristics, high water content, little cytotoxicity, and excellent biocompatibility enable targeted drug release, reduced macrophage phagocytosis, and enhanced cellular recognition. Granata G et al.[27] found that self-assembled injectable nanohydrogels avoided curcumin's chemical and photochemical degradation while delivering the medication continuously. These technologies combine hydrogel mechanical properties with nanomicelle distribution efficiency to improve medicine administration. Nanocomposite hydrogels may be made by encapsulating nanoparticles in nanohydrogels or by electrostatic or covalent cross-linking. This approach reduces structural fragility and strengthens mechanically. A hydrogel comprising self-assembling hyaluronic acid nanocomposite and elastic nanovesicles was produced by El-Refai E et al. [28]. In vivo, this hydrogel penetrated the knee joint six times better than hyaluronic acid gels. Cross-linked nanostructure and tunable degradation behavior make nanohydrogels promising for stimulus-responsive and customized drug delivery. By reacting to temperature, ionic strength, and pH, they release their medicament for site-specific therapy. Nanohydrogels have also been studied for hydrophobic and hydrophilic drug delivery. This might enhance cancer therapy by synchronizing release and reducing systemic toxicity. Their biocompatibility and extracellular matrix-like structure help repair and regenerate cartilage, nerves, and vascular tissues, making them promising scaffolds for regenerative medicine. Nanohydrogels' medication delivery and tissue engineering potential will improve with study into biological interactions, long-term safety, and scalable manufacture.

Inorganic Nanocarriers

Metals, metal oxides, and magnetic compounds make up inorganic nanocarriers in an inorganic nanoscale drug delivery system. Their advantages include their small size, large specific surface area, great biocompatibility, easy surface modification, high drug loading capacity, and easy manufacture. Mesoporous silica, a common inorganic nanocarrier, has an interconnected pore structure that may reduce the drug diffusion barrier, making medications easier to dissolve. Zhang et al. found that mesoporous silica enhances Telmisartan (TEL) oral bioavailability and dissolution [29]. The relative bioavailability ratio of TEL loaded onto MSNs to Micardis was 154.4%±28.4%. Compared to crude TEL powder, MSN-loaded TEL dissolved faster. Assays on the human colon cancer (Caco-2) cell line showed that MSNs enhanced drug permeability, reduced drug loss, and improved oral drug absorption. This new cancer therapy method shows promise.

Dendritic Polymer Nanocarriers

Dendritic polymers' three-dimensional, highly-ordered structure sets them apart from manufactured nanomaterials. Their size, shape, structure, and functional groups may be precisely controlled via molecular manipulation. These materials were synthesized using solid-phase, convergent, divergent-convergent, and initiating core methods. Their usual structure comprises terminal functional groups, internal repetitive units, and an initiating core. Dendritic polymers have functional groups on their peripheries to serve different functions. High drug loading capacity, controlled drug release, increased solubility, less adverse drug reactions, and facile surface modification are notable. Zhuo et al. [30] constructed a cyclic core using PAMAM dendrimers. By slowly releasing the 5-fluorouracil-conjugated medicine in phosphate-buffered saline, a human body-like environment, negative effects may be decreased. Another study used dendritic polymers to carry genes. These polymers prevented DNA degradation and increased tumor gene expression sixfold over PEI transfectant. The transfection was likely effective and steady. Thus, dendritic polymers provide novel medicine delivery options in gene therapy and are a safe, effective, and possibly helpful vector.

Smart and Stimuli-Responsive Nanocarriers

Healthcare advances have led to the widespread use of smart responsive nano drug delivery systems (NDDS) to treat many diseases, including cancer. We may classify these systems by

how they respond to light, temperature, pH, and enzymes. They can target drugs accurately by manipulating external factors like pH to change the drug delivery system's physicochemical properties. Cerium dioxide inhibits mitochondrial oxidative stress and treats sepsis-induced acute renal failure by scavenging ROS. Unlike cerium dioxide nanoparticles, which agglomerate and do not target mitochondria, Hui Yu et al. [31] produced a ROS-responsive NDDS that greatly decreased inflammation and oxidative stress by targeting mitochondria. Wang et al. [32] developed a pHresponsive LDP nanopolymer system because human cells and tissues have different pH values. This system releases constantly at pH=7.4 and quickly at pH=5.0. Its higher toxicity against CAL-72 cells than free DOX showed its ability to modulate drug release and prolong circulation. Thus, sophisticated, responsive NDDS improve medicine targeting and release control. They show potential in treating cancer and other complex microenvironmental illnesses.

NANOCRYSTALS AND NANOTECHNOLOGY-BASED DRUG DELIVERY

Drug nanocrystals may help water-insoluble medications. Drug nanocrystals may be delivered orally, parenterally, or intravenously (IV), which is beneficial. Nanocrystal particles are 200–600 nm smaller than suspension particles. The number 33. Nanocrystals feature strong surface contact, quantum tunneling, and confinement effects despite their small size. Nanocrystals transport nanoscale drug particles in water via surfactants, unlike the nanometer matrix skeleton method. No carrier is needed for this system. For better dissolution, drug nanocrystals have smaller particle diameters and increased surface area. Converting metastable or nanocrystalline nanocrystals to amorphous states may boost their bioavailability due to their higher surface energy. As is known, crystalline drug nanocrystals of the same size have lower saturation solubility than amorphous ones. For maximal saturation solubility increase, nanometer size and amorphous nanocrystals are best. Nanocrystals are characterized like suspensions, including particle size, appearance, color, test, smell, and pollutants. Zeta potential, crystalline state, solubility, and in vivo efficacy are additional nanocrystal measures. Laser diffraction (LD), dynamic light scattering (DLS), and scanning ion occlusion sensing (SIOS) are effective particle size determination methods. SEM, TEM, and AFM are used to characterize physical properties. Researchers also used advanced approaches including nanoparticle tracking analysis (NTA) and dual polarization interferometry.

INFLUENCE OF PARTICLE SIZE ON BIOAVAILABILITY

Active pharmacological components (ABCs) of oral medications enter the circulation. Particle size, water solubility, stomach retention, and intestinal epithelial cell diffusion rate may considerably alter pharmaceutical intestinal absorption. Nanocrystals may also distribute and absorb regular drugs. Nanocrystal oral absorption in the GIT is greatly impacted by particle size. The size of medication nanocrystals should delay or increase disintegration, enabling the drug to be targeted to the brain or other organs/tissues. Insoluble compounds may be nanosized to improve BA.

Increased Surface Area

The quantitative investigation on the drug dissolving process was initially reported by Noyes and Whitney, who also presented the Noyes-Whitney equation:

$$\frac{dm}{dt} = \frac{DS}{Vh}(C_s - C_t) \quad (5)$$

The equation includes drug surface area (S), diffusion coefficient (D), saturation solubility (Cs), concentration (Ct), volume of dissolving fluid (V), and drug concentration (Ct). The equation shows that diffusion, not chemical reaction, controlled dissolution. Surface area and saturation solubility affect drug dissolution speed. In actuality, increasing the drug's surface area had a far bigger effect on dissolving than increasing its saturated solubility. Micronization technology has been used to enhance the solubility of non-water-soluble drugs, but it has not proven effective in providing a large enough surface. Nanocrystals are colloidal dispersions 200–600 nm in size. Assuming medication particles are approximately spherical, lowering particle size from 10 m to 200 nm improved specific surface area by 50 times. Nanocrystal technology may reduce particle size, increase solubility, and surface area for water-insoluble pharmaceuticals, improving dissolving and bioavailability.

Enhanced Saturation Solubility

Water solubility is an essential physicochemical property of medications. Drugs must be dissolved before entering the circulation and functioning therapeutically. Increased saturation solubility may improve absorption by increasing the gut lumen-blood concentration gradient. Gibbs-Kelvin equations reflect microscopic particle solubility in bulk solutions.

$$\ln\left(\frac{xR}{x_\infty}\right) = \frac{2\sigma^\alpha \gamma v_2^\gamma}{k_B RT} \quad (6)$$

Variables to consider: xR, which is the solubility of small solid particles in the appropriate bulk solution, x, which is related to radius (R),, which is the relative concentration of the solute in the phase,, which is the surface tension of the solid particle at its boundary in the phase,, which is equivalent to 2 times the solid particle's volume per molecule, kB The equation indicates that decreasing particle radii increases sample solubility. Increased solubility reduces the impact of particle size to dose absorption fraction in practice. Nanocrystals alter solubility saturation, surface area, and diffusion layer thickness [34]. Figure 1 shows that oral nitrendipine and itraconazole nano- or micro-suspensions alter plasma drug concentrations.

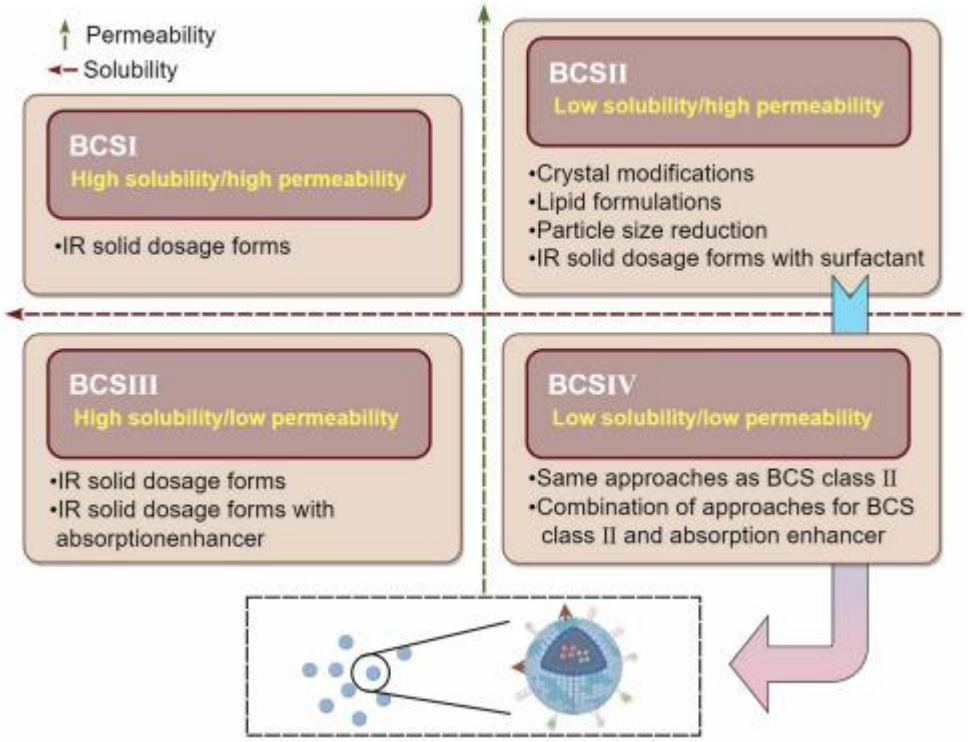

Figure 1. Formulation options that are feasible based on the Biopharmaceutics Classification System (BCS).

Improved Dissolution Rate

APIs from dosage forms and their breakdown in gastric fluid precede drug absorption. Diffusion transport rate greatly altered the dissolution kinetics of low-solubility and drug suspension medicines. With smaller particles came thinner diffusion layers and shorter dissolved molecule diffusion lengths. Merck studied Figure 2 compounds vs milled API. Wet

milled nanocrystals enhanced exposure by around twofold throughout a wide concentration range. Despite low solubility (<1 g •mL−1), nanocrystals' constant dispersion allows for extended GIT absorption. Patravale et al. [35] used the following equation to explain drug solubility and absorption, accounting for spherical particle shape, time-varying diffusion layer thickness, starting dosage, and particle mass distribution:

$$\frac{dX_{si}}{dt} = \frac{3DX_{0i}^{2/3}X_{si}^{1/3}}{h_i r_{0i}\rho}\left[C_s - \frac{X_{dt}}{V}\right] \quad (7)$$

The solid drug dose for the i-th particle size range is Xsi, the diffusion coefficient D, the density, the saturation solubility Cs, the total amount of drug dissolved at any given time Xdt, and the estimated volume of liquid in the GIT V. Due to their large surface area, nanocrystals stick better to the intestinal wall than ordinary particles. Increased concentration gradient between the intestinal wall and blood stream and decreased saturation solubility enhance absorption rate and quantity. This model indicates that turning pharmaceutical powder into nanocrystals speeds up water-insoluble drug dissolution. Modifying their surfaces may also affect nanocrystal dissolution in vitro.

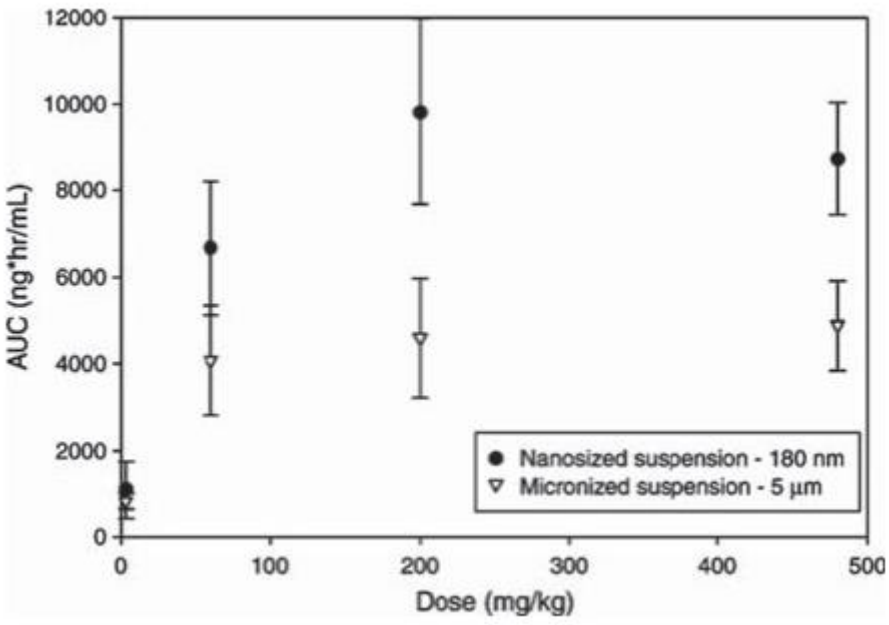

Figure 2. Comparing the APIs for a development candidate in a dosage proportionality study that are nanosized (180 nm) and micronized (5 m). The compound's solubility is low.

STABILIZATION STRATEGIES FOR NANOCRYSTALS

Role of Zeta Potential

The zeta potential, a crucial characteristic for electrostatic interactions in dispersion systems, reflects the surface charge created at the electrical double layer (EDL) when a solid, liquid, or gas interacts with aqueous media. It must accurately forecast nanocrystal suspension physical stability to ensure medication dissolution and bioavailability (BA). Nanocrystals stabilized by electrostatic repulsion alone need a minimum absolute zeta potential of 30 mV, but systems stabilized by electrostatic and steric forces may stable at 20 mV. Therefore, proper stabilizers are needed to provide the optimal surface charge. Cyclosporine A (CsA) nanocrystals produced from chitosan hydrochloride and gelatin demonstrated greater oral bioavailability and positively charged surfaces than standard CsA microemulsions. These studies demonstrate that nanocrystals with adequate surface charge may enhance BA.

Effect of Stabilizers on Nanocrystal Stability

Suboptimal physicochemical properties hinder transport across biological barriers, notably epithelial tissues like the gastrointestinal system, causing many promising drug candidates to fail throughout development. Attention to detail is needed to optimize nanocrystal formulations for cellular absorption and transport. Unlike conventional formulations, which dissolve quickly and undergo extensive hepatic metabolism, appropriately stabilized nanocrystals can enter enterocytes via endocytosis or M-cell uptake, drain into the mesenteric lymphatic system, bypass first-pass metabolism, and improve BA (Figure 3).

Stabilizers like surfactants, polymers, or a combination of both prevent nanocrystals from clumping. Average drug-to-stabilizer ratios range from 1:20 to 20:1 depending on formulation. Nanocrystal systems utilize less stabilizer than other nanoparticle formulations, although higher concentrations (1-100 wt% relative to drug) may increase stability. Main stabilizing mechanisms include electrostatic repulsion and steric hindrance. Polymers adsorb onto particle surfaces and limit coalescence via entropic repulsion, giving steric stabilization. Charged surfactants provide electrostatic stability. A combo of HPC-LF and SDS stabilized miconazole nanocrystals better than PVP or HPMC alone. PVP, Pluronics (F68, F127), HPMC, HPC, and vitamin E polyethylene glycol succinate (TPGS) are steric stabilizers, whereas SDS is an electrostatic stabilizer. Because surfactants may form drug molecule agglomerates, effective

and lasting stabilization requires rapid and vigorous adsorption, large surface coverage, and long desorption times.

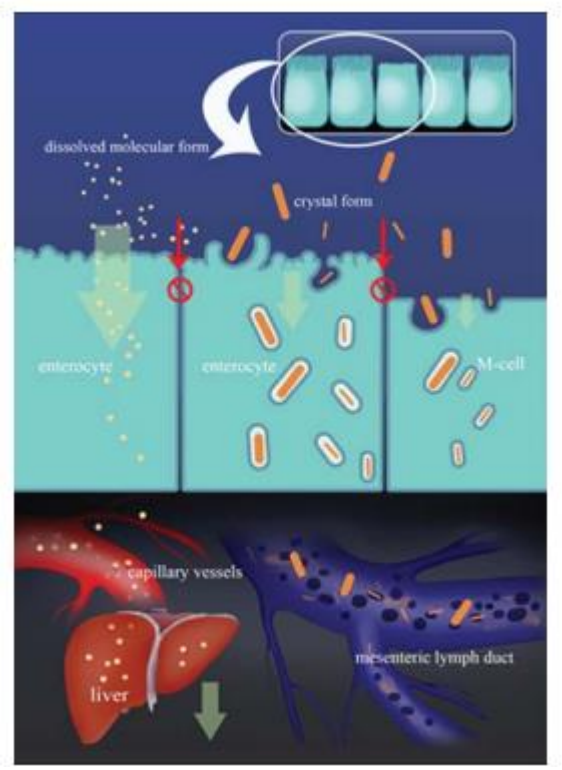

Figure 3. An example of the fictitious oral absorption mechanism for nanocrystals of nimodipine (NMD) [36].

MECHANISMS FOR IMPROVING SOLUBILITY OF POORLY SOLUBLE DRUGS VIA NANOMEDICINE

Nanotechnology Approaches

Two nanotechnology-based drug delivery methods include encapsulating medicines in nanocarriers and nanonizing the active ingredient. Nanoscale drugs may bypass physiological barriers including the blood-brain barrier (BBB) and nasal epithelial barriers, opening up novel delivery routes. Nanocarriers' large surface area allows them to be functionalized with several ligands, improving drug delivery by enhancing cellular absorption and therapeutic efficacy. Nose medication delivery techniques employing nanoemulsions and liposomes improve mucosal adhesion and permeability, increasing drug diffusion and absorption across the nose epithelium. Nanocarriers employ receptor-mediated or adsorption-mediated transport to traverse the blood-brain barrier, although directly nanonized medications mostly diffuse via

capillary endothelial pores. Butyl cyanoacrylate nanoparticles coated with polysorbate-80 bound apolipoproteins to improve blood-brain barrier (BBB) transport, and Lu et al. found that cationized bovine serum albumin nanoparticles had eight times more BBB permeability than non-cationized formulations.

Surface Modification Techniques

Nanocarrier surface modification by adsorption or covalent ligand attachment improves cellular targeting and absorption. This affects surface charge, hydrophilicity, aggregation, and fluidity. Direct covalent conjugation and indirect insertion of positively charged ligands into carrier membranes enable active targeting. In order to treat gliomas, Li et al. constructed dual-targeted PAMAM dendrimers modified with transferrin and tamoxifen. These dendrimers crossed the blood-brain barrier and accumulated only in tumors, improving efficacy and reducing adverse effects. Zhao et al. [38] modified dendritic poly-L-lysine nanoparticles with placenta-like chondroitin sulfate A-binding peptides. These nanoparticles specifically transported drugs to choriocarcinoma sites, inhibiting the tumor.

Carrier-Mediated Delivery Strategies

Poorly soluble drugs are encased in liposomes or polymeric micelles to increase their apparent solubility and make them simpler for cells to absorb via passive diffusion, membrane fusion, or endocytosis. Erlotinib, an EGFR inhibitor for non-small cell lung cancer, isn't bioavailable. Wang et al. coupled erlotinib with azido-modified DNA strands to improve its solubility and intracellular delivery using nano-DNA structures' higher permeability, retention, and solubility. Traditional nanocarriers have toxicity and immunological clearance issues, thus biomimetic nanomedicine systems were developed. These systems target, circulate, and evade the immune system by encapsulating drugs in cell membranes. Wang et al. [39] observed that nanoparticles in macrophage and cancer cell membranes improved immunological evasion, homotypic adhesion, and tumor accumulation, slowing colorectal cancer growth. Thus, biomimetic nanomedicine systems may improve therapeutic effectiveness, bioavailability, and solubility.

MECHANISMS OF ENHANCED BIOAVAILABILITY IN NANOMEDICINE

Many drugs have low therapeutic efficacy due to physiological absorption barriers and poor drug stability. Nanodrug delivery systems circumvent these challenges by using materials that

boost drug bioavailability. These include pH responsiveness, bioadhesion, biocompatibility, biodegradability, surface modifiability, and processability.

Enhancing Cellular Uptake: Surfactants, microemulsion-based devices, and SMEDDS promote drug permeability across mucosal and intestinal epithelia, improving absorption. Pancreatic enzymes and bile salts breakdown lipid-based nanocarriers, which aid intestinal absorption and transmembrane transport. Solid lipid nanoparticles (SLNs) protect pharmaceuticals from chemical degradation due to their biocompatible and biodegradable matrix, enhancing cell uptake. Nanocarriers may also improve cancer cell drug accumulation and absorption by targeting tumor tissues via active transport channels including bile acid transporters and folate receptors. Targeted cellular internalization is improved by receptor-mediated endocytosis via surface ligand modification.

Promoting Intracellular Drug Release: P-gp inhibition efflux is a SMEDDS emulsifier that enhances intracellular drug retention. Nanocarriers that react to pH variations may encapsulate medications in hostile settings and release them at physiological pH by swelling or breaking down. Enzyme-responsive systems, such as PEGylated liposomes modified with cell-penetrating peptides, reverse their surface charges when tumor-associated enzymes like MMP-2 are present to increase tumor-specific uptake Alternating magnetic fields induce magnetothermal effects, which improve intracellular delivery. The controlled release of doxorubicin from Fe_3O_4-laden liposomes allows the utilization of collaborative magnetothermal-chemotherapy methods.

Preventing Premature Metabolism: Pharmaceutics are protected from enzymatic degradation by hydrophobic interactions between nanocarriers and digestive enzymes. The methods involve porous inorganic nanoparticle carriers. Biodegradable, thermosensitive nanoparticle hydrogels that are injected at room temperature and form in situ depots at body temperature improve therapeutic efficacy. This prolongs drug release and retention in vivo. Polyethylene glycol (PEG)-modified nanoparticles displayed decreased macrophage-mediated phagocytosis, longer systemic circulation, and increased drug bioavailability.

ADVANTAGES OF NANOCRYSTALS IN DRUG DELIVERY

As a drug delivery technology, drug nanocrystals have quicker dissolving, better saturation solubility, larger drug loading, predictable oral absorption, improved dose-bioavailability

proportionality, and enhanced patient compliance. Nanocrystals enhance oral bioavailability despite first-pass metabolism by increasing medication concentration at the absorption site and adhering to the intestinal mucosa. This increases gastric concentration gradients and residence time. Nanocrystals' enhanced permeability and retention (EPR) permits passive targeting after intravenous administration, regulating drug accumulation in tumor tissues. Ligand functionalization allows active targeting. Nanocrystals may minimize food-related variability in bioavailability by enhancing the solubility and permeability of poorly soluble medications, as proven by their considerably increased and food-independent absorption of cilostazol compared to micronized formulations. Nanocrystals' extensive use, surface modification flexibility, and ease of large-scale manufacture have led to the commercialization of many formulations from the lab.

PREPARATION TECHNIQUES AND COMMERCIAL FORMULATIONS

Preparation Methods: Top-Down, Bottom-Up, and Hybrid Approaches: Drug nanocrystals may be made top-down, bottom-up, or both. Best utilization depends on medication physicochemical properties such hardness and solubility, target particle size, and budget. Media milling and high-pressure homogenization are energy-intensive top-down methods that may reduce particles from microns to nanoscale [40]. Alternative bottom-up procedures include controlled precipitation of therapeutic compounds from supersaturated fluids, where they nucleate and form crystalline or amorphous nanoparticles. Specific control is needed to prevent particle growth and regulate solid-state properties. The bottom-up strategy is appropriate for thermolabile and poorly soluble drugs due to its low energy consumption, soft working conditions, simple equipment, and cost-effectiveness.

Commercially Available Nanocrystal Products: Pharmaceutical companies have widely exploited nanocrystal technology to enhance medication pharmacokinetics and pharmacodynamics [41]. Sirolimus, the first nanocrystal medication FDA-approved, has stability and bioavailability issues as an oral solution. New sirolimus nanocrystal tablets with improved absorption and formulation stability were launched in 2000. After 2003 approval, megestrol acetate nanocrystals exhibited greater solubility, bioavailability, and patient compliance than previous formulations. Successful commercial examples include fenofibrate nanocrystals. FDA-approved TriCor® tablets dissolve faster, absorb food-independently, and work with less dosage.

ADVANTAGES AND CHALLENGES OF NANOMEDICINE DRUG DELIVERY SYSTEMS

Nanodrug delivery systems (NDDS) increase poorly soluble medications' solubility, stability, controlled release, circulation time, and targeted distribution without modifying their chemical structure. These technologies enable mucosal and peptide oral delivery by improving permeability and formulation performance. Encapsulating drugs in nanocarriers protects them against environmental risks, enzymatic breakdown, and adverse physiological conditions, improving their stability and efficacy. An NDDS must penetrate physiological and specialized barriers in the gastrointestinal system, intracellular compartments, and the blood-brain barrier to remain in circulation longer. "Stealth" nanoparticles are generated via surface modifications, mainly PEGylation, to escape reticuloendothelial clearance, lengthen circulation half-life, and reduce premature breakdown. Nanocarriers offer passive and active targeted pharmaceutical delivery by accumulating medicine at disease sites with no off-target damage from physicochemical responsiveness or ligand-receptor interactions. In addition to increasing treatment outcomes, their unique optical, magnetic, and chemical properties enable diagnostics and controlled, multi-drug release in combination therapy.

Table 2. Current Developments and Case Studies in Nanomedicine

Categories	Year of Approval	Pharmaceutical Formulations	Companies	Clinical Applications
Liposomal Nanoparticles	2015	Irinotecan	Merrimack Pharmaceuticals (Cambridge, UK)	Metastatic pancreatic cancer
	2021	Recombinant CSP	ClaxoSmithKline (Middlesex, UK)	Malaria
	2021	BNT162b2	Pfizer (New York, NY, USA) & BioNTech (Mainz, Germany)	COVID-19

Polymeric Nanoparticles	2012	Docetaxel	Samyang Pharmaceuticals (Seoul, Republic of Korea)	MBC, NSCLC, and ovarian cancer
	2015	PTX	Oasmia Pharmaceuticals (Uppsala, Sweden)	Ovarian cancer
Drug Nanocrystals	2018	Aripiprazole lauroxil	Alkermes Inc (Waltham, MA, USA)	Schizophrenia
	2021	Cabotegravir	Viiv Healthcare Co. (Brentford, London, UK)	HIV-1 infection
Other Nanomedicines	2010	Iron molecule with unbranched carbohydrate in nanoparticles	Pharmacosmos (Rorvangsvei, Holbaek, Denmark)	Iron deficiency anemia
	2013	Polynuclear iron (III) oxyhydroxide iron particles	ForInt. (Waltham, MA, USA)	Iron deficiency anemia
	2015	Recombinant anti-hemophilic factor VIII	Baxalta (Montgomery, AL, USA)	Hemophilia A

Abbreviations: FDA – Food and Drug Administration; EMA – European Medicines Agency

CONCLUSION

A platform that is both flexible and efficient is provided by drug delivery technologies that are based on nanoparticles. This platform is used to increase the bioavailability of drugs that are not very soluble. The solubility, dissolution, stability, and targeted administration of NDDS

have all been significantly enhanced, which has resulted in a significant increase in the therapeutic efficacy of the drug while simultaneously reducing the systemic toxicity. Nanocrystals, for example, provide a basic way that is both effective and readily scaled up to boost the bioavailability of pharmaceuticals whether they are taken orally or intravenously. Furthermore, nanocrystals are economically feasible. Recent developments in surface modification, smart responsive carriers, and combination therapy have broadened the potential of non-destructive drug delivery systems (NDDS) to provide accurate and tailored treatment. For the pharmaceutical formulation business, these technologies are a game-changer because they address persistent difficulties with medication distribution and open the way to new therapies for complex illnesses. In other words, they are a game-changer.

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