RESEARCH PAPER

Nanoparticulate systems for poorly soluble drugs

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ABSTRACT

The majority of new chemical entities discovered through modern drug development pipelines have poor water solubility, which leads to limited and irregular oral bioavailability, reduced drug exposure and increased risk of adverse reactions associated with excessive dosages. A key method of improving drug solubility is through the development of nanoparticulate drug delivery systems (NDDS) which will increase the effective solubility of the drug, provide a greater surface area available for dissolution, extend the residence time of the drug at the site of absorption and allow for targeted or controlled drug delivery.

This article reviews methods of developing and evaluating nanoparticulate drug delivery systems to improve the bioavailability of poorly soluble drugs. Common classes of drug delivery vehicles including polymeric nanoparticles, lipid-based nanoparticles, nanosuspensions and inorganic/hybrid nanoparticles are reviewed along with key characteristics of each class and the physical and biological attributes which impact their ability to improve the bioavailability of poorly soluble drugs. Key aspects of characterizing the physical and biological properties of drug delivery vehicles including size distribution, zeta potential, morphology, crystallinity, drug loading and stability will be reviewed, as well as in vitro testing (e.g., dissolution and release studies) and in vivo testing (e.g., pharmacokinetics).

Regulatory issues and scalability issues associated with transitioning NDDS to human clinical trials will be reviewed and how a Quality-by-Design (QbD) approach to the development of NDDS can be used to ensure consistent improvement in bioavailability and therapeutic effect of poorly soluble drugs.

Keywords: Nanoparticles, poorly soluble drugs, bioavailability, lipid nanoparticles, polymeric nanoparticles, nanosuspension, nanotechnology, QbD

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INTRODUCTION

A large number of new chemical entities developed through high throughput screening and combinatorial chemistry are lipophilic compounds with low aqueous solubility and high permeability. These types of compounds typically fall into one of two categories based upon the Biopharmaceutics Classification System (BCS): either BCS Class II (highly permeable, low aqueous solubility) or BCS Class IV (both permeability and solubility limit absorption). Although the rate and extent of dissolution of drugs in the gastrointestinal fluid determines the amount of drug absorbed when administered orally, this property presents a major challenge for the oral delivery of BCS Class II and Class IV drugs. Although conventional formulation strategies such as salt formation, particle micronization, and the incorporation of solubilizing agents (surfactants and co-solvents) can enhance the solubility of drugs to varying degrees, they are generally insufficient to address the limitations of drugs with high crystal lattice energy and complex molecular structure. Nanotechnology-based drug delivery approaches have emerged as a promising platform to overcome these limitations by modifying the manner in which drugs interact with biological systems. As drugs are converted into nanoparticles, whether as free drug crystals or as carrier-based systems (such as polymeric or lipid-based systems), several biopharmaceutical properties can be optimized; specifically: surface area increases significantly, apparent solubility and dissolution rates are enhanced, interaction with biological membranes are altered and drug distribution and elimination can be controlled. Additionally, nanocarrier systems can stabilize unstable drugs from degradation, modulate drug interactions with efflux transporters and enable alternate uptake mechanisms (such as lymphatic transport) that circumvent first pass metabolism.

2. Biopharmaceutical Challenges Associated with Poor Solubility of Drugs

Poor aqueous solubility results in slow and/or incomplete dissolution in gastrointestinal fluids, which leads to low and variable systemic exposure after oral administration. For BCS Class II drugs (poor solubility, high permeability), the primary limitation to absorption is the rate of dissolution, whereas for BCS Class IV drugs (both poor solubility and permeability limit absorption), both solubility and permeability limit absorption. The physical and chemical properties that define the poor aqueous solubility of drugs include high lipophilicity (log P > 3), high melting point and strong intermolecular interactions within the crystal lattice.

Major consequences of poor solubility include:

• Low fraction of dose dissolved at the absorption site

.• Food effects may influence dissolution depending upon the presence of bile salts and dietary lipids

.• Precipitation of supersaturated solutions may result in erratic absorption profiles.

• The need for larger doses or more frequent dosing to achieve adequate blood concentrations increases the risk of systemic toxicity.[3]

Limitations of traditional formulation strategies have led to an interest in nanoscale formulations. Micronization to the micrometre level has been shown to increase the surface area of drugs, but it does not necessarily increase the dissolution rate of poorly soluble drugs. Furthermore, micronization can result in aggregation of the drug. High levels of surfactants and co-solvents can induce gastrointestinal irritation or toxicity and are not always suitable for long term therapy. Solid dispersions can transform drugs into partially amorphous states or molecularly disperse the drug within a polymer matrix, thereby increasing the apparent solubility and dissolution of the drug. However, solid dispersions may exhibit physical instability.

Therefore, there is an ongoing interest in developing nanoscale formulations of poorly soluble drugs.

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3. NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS

Nanoparticle-based drug delivery systems for poorly soluble drugs may be categorized broadly into four general categories: (i) drug nanocrystals or nanosuspensions (carrier-free), (ii) polymeric nanoparticles, (iii) lipid-based nanoparticles (nanoemulsions) and (iv) inorganic or hybrid nanoparticles.

3.1 Drug Nanosuspensions

Nanosuspensions are submicron colloidal suspensions of pure drug particles in a liquid vehicle that are stabilized by surfactants or polymers. Typically, the particle sizes of nanosuspensions are in the range of 100–1000 nm. Preparation of nanosuspensions can be accomplished by top down methods (high pressure homogenization, media milling) or bottom up methods (precipitation of supersaturated solutions).

As the size of the particles decreases, the surface area per unit volume of particles increases dramatically. Therefore, the apparent solubility and dissolution rate of poorly soluble drugs can be improved by nanosizing according to the Noyes–Whitney and Ostwald-Freundlich equations.

The advantages of nanosuspensions include: high drug loading, compatibility with a broad spectrum of poorly soluble drugs and the ability to formulate into solid dosage forms through various methods (spray drying, lyophilization). The disadvantages of nanosuspensions include: potential instability of the dispersion over time (aggregation, Ostwald ripening) and the need for high energy processing conditions.

3.2 Polymeric Nanoparticles

Polymeric nanoparticles are typically spherical in shape and are approximately 50–300 nm in diameter. They are made from biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone, polylactic acid, chitosan, or alginate. Drugs can be molecularly dispersed throughout the polymer matrix (nanospheres), or the drug can be encapsulated within the polymer matrix and the drug-polymer interface (nano capsules). Preparation of polymeric nanoparticles involves several different methods including: emulsion-solvent evaporation, solvent diffusion, nanoprecipitation and salting-out. There are many factors that affect the size of the particles, the drug loading and the release profile of polymeric nanoparticles. Some of the most important factors include: the type of polymer used, the molecular weight of the polymer, the ratio of drug to polymer, the choice of solvent, the concentration of stabilizers, and the energy input into the system.

Surface modification of polymeric nanoparticles with hydrophilic moieties such as polyethylene glycol (PEG) or ligands (antibodies, peptides, sugars) can increase the circulation time of the particles, reduce opsonization, or provide active targeting capabilities.

Polymeric nanoparticles can provide sustained release of poorly soluble drugs, which can result in reduced fluctuation in plasma levels.

3.3 Lipid-Based Nanoparticles

Lipid nanoparticles including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs) and lipid nanoemulsions have been developed for the delivery of lipophilic, poorly soluble drugs.

Typically, lipid nanoparticles are prepared from physiological lipids (triglycerides, fatty acids, phospholipids) in combination with surfactants. The poorly soluble drug is then solubilized within the solid or liquid lipid core or within the oil droplets dispersed in the aqueous phase of the lipid nanoparticle.

SLNs contain a solid lipid core while NLCs are characterized by the incorporation of a mixture of solid and liquid lipids, creating an imperfect matrix that allows for a higher drug load and reduces the chance of drug expulsion during storage.

Methods for preparing lipid-based nanoparticles include: high pressure homogenization, hot/cold homogenization, microemulsion templates or solvent emulsification/evaporation.[15]

Lipid-based nanoparticles can improve the oral bioavailability of poorly soluble drugs through several mechanisms: solubilization in the lipid matrix, stimulating bile production, forming mixed micelles and possibly stimulating lymphatic absorption, thus reducing the first pass metabolism of the drug.

3.4 Inorganic and Hybrid Nanoparticles

Inorganic nanoparticles (mesoporous silica, gold, iron oxide) have the advantage of providing high surface area, tuneable pore diameters, and easy-to-modify surfaces. Mesoporous silica nanoparticles are capable of encapsulating poorly soluble drugs within their pores, typically transforming them into an amorphous state. Rapid dissolution of the drug can occur from the surface of the nanoparticle.

Hybrid systems consisting of inorganic cores coated with a layer of polymer or lipid are currently under investigation to provide additional mechanical stability, increased loading capacity and controlled release.

However, the long term safety, biodistribution, and clearance of inorganic nanoparticles must be carefully evaluated prior to their use as drug delivery systems.

The first step in developing an NDDS is to select a suitable carrier system based on the desired characteristics of the final product including solubilization, permeability, biodistribution, etc., and the drug's physicochemical properties. Particles for NDDS can be fabricated using a variety of methods such as emulsion-based techniques (nanoemulsions, microemulsions, multiple emulsions), spray drying, supercritical fluids, electrostatic atomization, coacervation, complexation, solid dispersion, and others.[13],[14] The choice of method depends on factors such as the type of drug, its solubility, molecular weight, degree of ionization, and desired particle size and morphology.

4. FORMULATION STRATEGIES TO ENHANCE BIOAVAILABILITY

4.1 Particle Size Reduction and Surface Area Enhancement

Smaller particles (typically <100 nm) result in larger surface areas per unit mass, smaller diffusion layers and enhanced dissolution rates. Many poorly soluble drugs (BCS Class II) exhibit faster dissolution and greater maximum plasma concentration and area under the curve after conversion to nanocrystals from microcrystals. Surfactants and polymers are commonly employed as stabilizers to limit aggregation and control crystal growth during fabrication and storage.

4.2 Amorphization and Supersaturation

Amorphous states possess higher Gibbs free energies than their crystalline counterparts; thus, drugs formulated in amorphous states exhibit enhanced apparent solubilities and dissolution rates. However, amorphous states are also less stable and tend to recrystallize over time. Spatial confinement within nanopores and polymer-drug interactions (e.g., hydrogen bonding and ionic interactions) can stabilize amorphous states and prolong supersaturated conditions in the GI tract.

Supersaturating formulations are designed to create transiently elevated levels of dissolved drug, which drives absorption. Precipitation inhibitors (commonly hydrophilic polymers) are added to delay the onset of precipitation and maintain drug in solution long enough to allow for absorption.

4.3 Permeation Enhancement and Mucosal Interaction

Besides affecting solubility and dissolution, nanoparticles can interact with mucus and epithelial barriers to modulate permeability. Mucoadhesive polymers such as chitosan and related cationic polymers can temporarily open tight junctions and increase paracellular transport. Receptor-mediated endocytosis can also increase transcellular uptake of ligand-modified

nanoparticles. The ability of nanoparticles to penetrate mucus is dependent upon their surface hydrophilicity and charge; neutral or slightly negatively charged hydrophilic surfaces generally exhibit better penetration than positively charged surfaces, which may adhere to mucus and extend the residence time of the nanoparticle.

4.4 Lymphatic Transport and Avoidance of First-Pass Metabolism

Lipid-based nanocarriers can facilitate intestinal lymphatic transport if they mimic the structure of chylomicrons, especially when they contain long chain triglycerides and sufficient amounts of surfactant.[7] Drugs that are highly lipophilic (logP > 5) and bind well to lipoproteins can subsequently enter the systemic circulation via the lymphatic pathway, bypassing the liver and avoiding the first pass effect. This phenomenon has been utilized for the development of orally administered lipophilic drugs with high hepatic extraction ratios.

5. EVALUATION OF NANOPARTICLE-BASED FORMULATIONS

5.1 Physicochemical Characterization

Physicochemical characterization of NDDS is essential to ensure reproducible quality, stability and performance of the NDDS. Characterization of NDDS typically involves the measurement of:

• Particle size and polydispersity index (PDI) using dynamic light scattering (DLS).
• Zeta potential to evaluate the surface charge and predict the colloid stability of the NDDS.
• Morphology and surface structure using transmission or scanning electron microscopy.
• Drug loading capacity and encapsulation efficiency.
• Physical state of drug (crystalline vs amorphous) by differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD).
• Surface chemistry and functional groups using Fourier transform infrared spectroscopy (FTIR) or X-ray photoelectron spectroscopy (XPS).

Changes in the above parameters are monitored during stability studies under various storage conditions.

5.2 In Vitro Dissolution and Release Studies

Biorelevant dissolution testing in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) or fasted/fed state simulated intestinal fluids (FaSSIF/FeSSIF) is performed to assess whether dissolution rates and extents have been improved by the NDDS. Release profiles of the drug from the NDDS are analysed using kinetic models (zero order, first order, Higuchi, Korsmeyer-Peppas) to determine the mechanism(s) of release (diffusion and/or erosion). Understanding how to maintain supersaturation and the kinetics of precipitation are particularly important for amorphous or supersaturating NDDS.

5.3 Permeability and Cell-based Assays

Caco-2 cell monolayers and other intestinal models are commonly used to assess the impact of NDDS on drug permeability. Enhanced apparent permeability coefficients (P_app) relative to the permeability of the free drug indicate that permeability has been improved. Efflux interactions can be evaluated using bidirectional transport and the addition of efflux inhibitors. Mucin coated inserts or ex vivo tissues can be used to study mucoadhesion and mucopenetration.

5.4 In Vivo Pharmacokinetics and Biodistribution

Evaluation of the pharmacokinetic profile and biodistribution of the drug in an appropriate animal model remains the ultimate test of whether the NDDS has provided enhanced bioavailability. Pharmacokinetic parameters such as C_max, T_max, AUC, and t½ are measured for both the NDDS and the conventional dosage form. Improved bioavailability is characterized by an increased AUC and occasionally by a decreased CV. Biodistribution studies using radiolabelled or fluorescently tagged NDDS can demonstrate the organ specificity and targeting efficiency of the NDDS.

5.5 Safety Evaluation

Evaluation of the safety of NDDS requires the determination of acute and chronic toxicity, immunogenicity, oxidative stress, and histopathology of major organs. Given that some NDDS may be able to cross biological barriers and reside in tissue, long term studies are required to ensure safety.

6. REPRESENTATIVE EXAMPLES OF BIOAVAILABILITY ENHANCEMENT

Many studies have shown that NDDS formulations can produce substantial improvements in the bioavailability of poorly soluble drugs. For example, lipid nanoparticles of poorly soluble anticancer drugs (such as paclitaxel and docetaxel) have demonstrated several fold increases in AUC when administered orally versus parenteral administration. Nanosuspensions of drugs such as fenofibrate and itraconazole have produced higher C_max and faster onset of action than corresponding micronized dosage forms. Polymeric NDDS formulations of nonsteroidal anti-inflammatory drugs have permitted sustained release of the drug and improved gastric tolerance. Mesoporous silica-based systems have also enhanced the bioavailability of weakly basic and poorly soluble drugs by maintaining them in an amorphous state.

While the degree of bioavailability enhancement is dependent on the drug, the NDDS formulation and the route of administration, these examples illustrate that rationally designed NDDS can transform biopharmaceutical performance and potentially enable the successful development of compounds that would otherwise fail due to poor bioavailability.

7. REGULATORY, SAFETY AND SCALE-UP CONSIDERATIONS

As regulatory agencies become increasingly aware of the potential of nanomedicines, they require detailed characterization and risk assessments. Guidelines recommend an understanding of critical quality attributes of the NDDS, manufacturing processes, and potential nano-specific toxicities. Additionally, batch-to-batch consistency of particle size, distribution, and surface properties of the NDDS must be demonstrated.

Potential safety issues associated with NDDS include immunogenicity, CARPA, unforeseen organ accumulation, and long-term retention or degradation products of the NDDS. Some excipients that are common in conventional formulations (i.e. lipids, surfactants, and polymers) may assume different biological behaviors at the nanoscale. Therefore, thorough toxicological evaluations are needed.

Scaling up from laboratory to commercial production introduces additional complexities. Homogenizers, microfluidizers, and continuous manufacturing platforms can facilitate large-scale production of nanosystems. However, critical process parameters (i.e. pressure, temperature, cycle number, mixing speed) must be carefully controlled. To achieve this, a Quality by Design (QbD) approach should be adopted to link material and process variables to critical quality attributes and ensure robustness and regulatory compliance.

8. CONCLUSION

Nanoparticle-based drug delivery systems present a versatile and flexible means to overcome the inherent limitations of poorly soluble drugs. These systems can be engineered to manipulate particle size, physical state, carrier composition and surface properties to enhance dissolution, improve permeability, utilize alternative uptake pathways and provide controlled or targeted delivery of the drug. If properly characterized and evaluated in vitro and in vivo, NDDS can lead to significant enhancements in bioavailability and therapeutic efficacy.

However, significant challenges exist with respect to long-term safety, regulatory compliance and cost effective, large-scale manufacture. Future work should focus on designing NDDS rationally under a QbD framework, further elucidating the mechanisms of in vivo behavior and developing predictive in vitro-in vivo correlations relevant to nanoformulations. Collaboration among formulation scientists, clinicians, toxicologists, and regulators will be critical to realizing the full potential of NDDS in providing improved treatments for patients with poorly soluble drugs..

REFERENCE

1. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods. 2000;44(1):235–249.
2. Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. Pharm Res. 1998;15(1):11–22.
3. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012:195727.
4. Misra R, Acharya S, Sahoo SK. Cancer nanotechnology: application of nanotechnology in cancer therapy. Drug Discov Today. 2010;15(19–20):842–850.
5. Wang AZ, Langer R, Farokhzad OC. Nanoparticle delivery of cancer drugs. Annu Rev Med. 2012;63:185–198.
6. Crielaard BJ, Rijcken CJF, Quan L, Van Der Wal S, Altintas I, Van der Pot M, et al. Glucocorticoid-loaded core–cross-linked polymeric micelles with tailorable release kinetics for targeted therapy of rheumatoid arthritis. Angew Chem Int Ed Engl. 2012;51(29):7254–7258.
7. Porter CJH, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discov. 2007;6(3):231–248.
8. Gao P, Guyton ME, Huang T, Bauer JM, Stefanski KJ, Lu Q. Enhanced oral bioavailability of a poorly soluble drug PNU-91325 by supersaturable formulations. Drug Dev Ind Pharm. 2004;30(2):221–229.
9. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today. 2007;12(23–24):1068–1075.
10. Keck CM, Müller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm. 2006;62(1):3–16.
11. Müller RH, Gohla S, Keck CM. State of the art of solid lipid nanoparticles. Eur J Pharm Biopharm. 2000;50(1):161–177.
12. Mundargi RC, Babu VR, Rangaswamy V, Patel P, Aminabhavi TM. Nano/micro technologies for delivering macromolecular therapeutics using poly(D,L-lactide-co-glycolide) and its derivatives. J Control Release. 2008;125(3):193–209.
13. Csaba N, Alonso MJ. Nanoparticles for nasal vaccination. Adv Drug Deliv Rev. 2021;171:75–87.
14. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release. Chem Rev. 2016;116(4):2602–2663.
15. Beloqui A, Solinís MÁ, Rodríguez-Gascón A, Almeida AJ, Préat V. Nanostructured lipid carriers: promising drug delivery systems for future clinics. Nanomedicine. 2016;12(1):143–161.
16. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev. 2002;54(Suppl 1):S131–S155.
17. Vallet-Regí M, Rámila A, del Real RP, Pérez-Pariente J. A new property of MCM-41: drug delivery system. Chem Mater. 2001;13(2):308–311.
18. Slowing II, Vivero-Escoto JL, Wu CW, Lin VSY. Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. Adv Drug Deliv Rev. 2008;60(11):1278–1288.
19. Rumondor ACF, Ivanisevic I, Bates S, Alonzo DE, Taylor LS. Evaluation of drug–polymer miscibility in amorphous solid dispersions using synchrotron X-ray pair distribution function analysis. Pharm Res. 2009;26(11):2523–2534.
20. Prego C, García M, Torres D, Alonso MJ. Transmucosal macromolecular drug delivery. J Control Release. 2005;101(1–3):151–162.
21. Ensign LM, Cone R, Hanes J. Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. Adv Drug Deliv Rev. 2012;64(6):557–570.
22. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13(2):123–133.
23. Artursson P, Palm K, Luthman K. Caco-2 monolayers in experimental and theoretical predictions of drug transport. Adv Drug Deliv Rev. 2001;46(1–3):27–43.
24. Wong HL, Bendayan R, Rauth AM, Xue HY, Babakhanian K, Wu XY. A mechanistic study of enhanced doxorubicin uptake and retention in multidrug resistant breast cancer cells using a polymer–lipid hybrid nanoparticle system. J Pharmacol Exp Ther. 2006;317(3):1372–1381.
25. Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect. 2005;113(7):823–839