International Journal of Creative and Open Research in Engineering and Management
ISSN: 3108-1754 (Online)
Volume 02 Issue 10 October-2026 | Impact Factor: 3.5



Polymeric Nanoparticles for Enhancing the Oral Bioavailability of Poorly Soluble Antihypertensive Drugs: Formulation Design and Biopharmaceutical Evaluation

Akarsh Nishad[1], Avinash Kumar[1*], Manish Maurya[2*]

[1]Department of Pharmaceutics, Sardar Patel College of Pharmacy, Gorakhpur, Uttar Pradesh, India (Affiliated to Dr. A.P.J. Abdul Kalam Technical University, Lucknow)

*Corresponding author: Dr. Avinash Kumar, Associate Professor, Department of Pharmaceutics, Sardar Patel College of Pharmacy, Gorakhpur, Uttar Pradesh, India. E-mail: kmravinash.1992@gmail.com

How to Cite this Article:

Nishad, A., Kumar, A. & Maurya, M. (2026). Polymeric Nanoparticles for Enhancing the Oral Bioavailability of Poorly Soluble Antihypertensive Drugs: Formulation Design and Biopharmaceutical Evaluation. International Journal of Creative and Open Research in Engineering and Management, 02(10), 1-9. https://doi.org/10.55041/ijcope.v2i10.208

License:

This article is published under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

© The Author(s). Published by International Journal of Creative and Open Research in Engineering and Management.







https://doi.org/10.55041/ijcope.v2i10.208

ABSTRACT

Hypertension needs lifelong treatment, and almost all of that treatment is given by mouth. Several widely prescribed antihypertensives, including dihydropyridine calcium channel blockers, carvedilol and the lipophilic sartan prodrugs, dissolve poorly in gastrointestinal fluids, so their oral bioavailability is low and often variable. Nanoparticle formulations are one way to deal with this. This review looks at the biopharmaceutical basis of the problem, the drugs that actually have solubility-limited absorption, and the main nanocarrier platforms: polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions and self-nanoemulsifying systems, and drug nanocrystals. It then covers formulation materials, preparation methods, mechanisms of bioavailability enhancement, characterisation, and pharmacokinetic evaluation. Published studies on felodipine, carvedilol, candesartan cilexetil, olmesartan medoxomil and nifedipine are compared with our own laboratory work on PLGA nanoparticles of losartan potassium. That work produced a 186 nm, −28.6 mV batch with 86.7% encapsulation efficiency, which released 96.4% of the drug in 12 h compared with 71.6% for a conventional formulation. The evidence is strongest for faster dissolution and higher apparent solubility. Claims of greater permeation, lymphatic transport or avoidance of first-pass metabolism depend on the drug and the carrier, and are often inferred rather than measured. Gains in exposure have so far been shown mostly in rodents, and controlled human studies are rare. Losartan illustrates why classification comes before formulation: it is highly water-soluble, and its incomplete bioavailability comes from first-pass metabolism, not dissolution. We conclude that nanoparticle design for antihypertensives should start from biopharmaceutical data. Studies should also include proper comparators, biorelevant testing and pharmacokinetic endpoints, and should address safety, stability and scale-up early if clinical benefit is to be demonstrated.

Keywords: *Hypertension; Poorly soluble drugs; Polymeric nanoparticles; PLGA; Oral bioavailability; Biopharmaceutics Classification System; Lipid nanocarriers; Nanocrystals*

1. INTRODUCTION

1.1. Hypertension and the need for effective oral pharmacotherapy

Raised blood pressure is the leading modifiable risk factor for stroke, coronary heart disease, heart failure and chronic kidney disease. More than a billion adults are affected worldwide, and the burden has shifted steadily towards low- and middle-income countries [21]. The 2017 ACC/AHA guideline lowered the treatment threshold to 130/80 mmHg for many patients and recommends combining two first-line drugs early when blood pressure is well above target [31]. In practice, therefore, most patients take one or more antihypertensives every day for decades, and the dose they swallow has to produce a predictable plasma concentration each time.

1.2. Importance of oral drug delivery in long-term hypertension management

Tablets and capsules dominate antihypertensive therapy because they are cheap, stable, easy to fix in combination and simple for patients to take. For a disease that usually causes no symptoms, convenience directly affects adherence, and adherence affects outcomes. The oral route also has a cost. A dose has to dissolve, cross the intestinal epithelium and survive gut-wall and hepatic metabolism before it reaches the circulation. Any step that behaves erratically shows up as day-to-day variation in exposure, and for drugs with a short half-life, as uneven blood-pressure control across the dosing interval.



1.3. Poor aqueous solubility as a barrier to drug absorption

A large share of new chemical entities, and a fair number of established cardiovascular drugs, are lipophilic and crystalline, with aqueous solubility in the low microgram-per-millilitre range [13,32]. For these molecules the amount of drug in solution at the absorption site, and not the permeability of the gut wall, sets the ceiling on absorption. The result is low and variable bioavailability, a strong dependence on food and gastric pH, and a tendency to raise the dose instead of improving the formulation [15].

1.4. Limitations of conventional formulation approaches

Salt formation, micronisation, surfactant addition, cyclodextrin complexation and solid dispersion have each helped individual drugs [4,16]. Each also has limits. A salt needs an ionisable group and may convert back to the free form in the gut. Micronisation rarely gets below 2–5 µm, which is not enough for drugs with very low solubility. Solid dispersions can recrystallise on storage, and high surfactant loads irritate the gut. These limits are the main reason interest has moved to sub-micron carriers.

1.5. Potential of nanotechnology in oral drug delivery

At sizes of roughly 100–500 nm the specific surface area of a drug or drug-loaded carrier rises sharply. The drug may also be held in an amorphous or molecularly dispersed state, and the particle surface can be engineered to interact with mucus and epithelium [9,22]. Polymeric nanoparticles, lipid nanoparticles, nanoemulsions and drug nanocrystals all use some of these effects. Nanocrystal products are already on the market for several poorly soluble drugs, which shows that the approach can be manufactured at scale [13,20].

1.6. Scope and objectives of the review

This review asks a practical question: when does a nanoparticle formulation actually improve the oral performance of an antihypertensive drug, and what evidence is needed to show it? We first set out the biopharmaceutical background. We then identify the antihypertensives whose absorption is genuinely limited by solubility, and compare the carrier platforms, materials and preparation methods. Mechanisms, characterisation and pharmacokinetic evaluation follow, along with a critical comparison of published studies, including our own work on PLGA nanoparticles of losartan potassium. The review closes with safety, regulatory and translational issues and the research priorities that follow from them.

2. BIOPHARMACEUTICAL CHALLENGES OF POORLY WATER-SOLUBLE ANTIHYPERTENSIVE DRUGS

2.1. Classification of drugs according to solubility and permeability

Oral absorption can be reduced to two questions: how much drug is in solution at the absorptive surface, and how fast it crosses that surface. Expressing both as dimensionless numbers, the dose number and the absorption number, made it possible to predict which drugs would be dissolution-limited and which permeability-limited, well before any formulation was made [1].

2.2. Biopharmaceutics Classification System (BCS)

The Biopharmaceutics Classification System divides drugs into four classes [1]. A drug is "highly soluble" when the highest single dose dissolves in 250 mL or less of aqueous media across pH 1.2–6.8. It is "highly permeable" when absorption is at least 85–90% of the dose. Class I drugs (high solubility, high permeability) rarely cause formulation problems. Class II drugs (low solubility, high permeability) are the natural candidates for nanosizing, because faster dissolution translates almost directly into more absorption. Class III drugs (high solubility, low permeability) and Class IV drugs (low on both counts) are not helped by dissolution enhancement alone. The Biopharmaceutics Drug Disposition Classification System adds a link to elimination: highly metabolised drugs tend to be highly permeable, and transporter effects matter more for some classes than others [33]. This helps explain why some antihypertensives absorb well but still reach the circulation poorly.

2.3. Drug dissolution and gastrointestinal absorption

The Noyes–Whitney relationship, $dC/dt = (D \cdot A/h)(Cs - C)$, states that dissolution rate is proportional to the exposed surface area (A) and to the gap between saturation solubility (Cs) and bulk concentration (C) [24]. Dissolution has to finish within a limited intestinal transit time of about three to four hours in the small bowel. A drug with a high dose and low Cs therefore leaves part of its dose undissolved, however permeable it is.

2.4. Influence of particle size, crystal form, and surface properties

Reducing particle size increases A in proportion to the inverse of the diameter. Below about 1 µm it also thins the diffusion layer and slightly raises Cs through curvature effects. Polymorphs, solvates and amorphous forms differ in free energy, so the same drug can show different solubility depending on its solid form. Poor wettability, typical of hydrophobic crystals, slows the start of dissolution. Hydrophilic stabilisers and surfactants are used partly to counter this [17].

2.5. Gastrointestinal pH, bile salts, and food effects

Many antihypertensives ionise. Weak bases such as carvedilol dissolve better in the acidic stomach and may precipitate in the small intestine. Acidic sartans such as valsartan behave the other way. Bile-salt and phospholipid micelles, which increase after a meal, solubilise lipophilic drugs, so food often raises their exposure markedly [9,25]. A useful formulation should reduce these swings, not simply add to them.

2.6. Intestinal transport, first-pass metabolism, and efflux mechanisms

Dissolved drug crosses the mucus layer and the enterocyte membrane, mostly by passive transcellular diffusion. Some drugs are pumped back into the lumen by P-glycoprotein. Enterocyte CYP3A4 and hepatic CYP enzymes then remove a further fraction. Felodipine (about 15% bioavailability) and nifedipine are classic CYP3A4 substrates. Losartan undergoes extensive CYP2C9/CYP3A4-mediated first-pass conversion to its active carboxylic acid metabolite, E-3174 [27,33]. These losses happen after dissolution and are largely unaffected by faster dissolution.

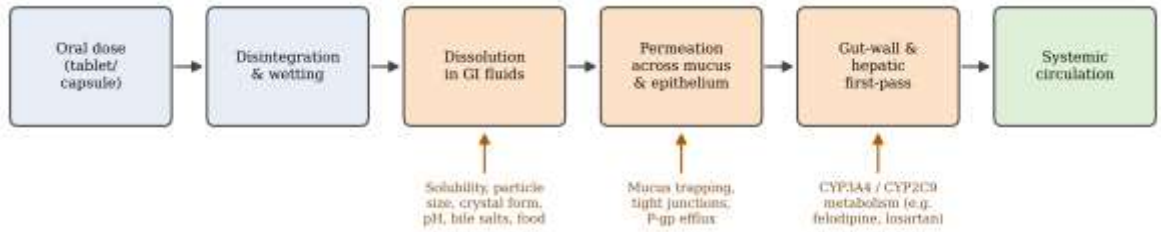


Fig. 1: Sequential barriers to oral absorption of antihypertensive drugs and the factors acting at each step

2.7. Distinguishing solubility-limited absorption from permeability-limited absorption

This distinction is often blurred in the formulation literature. If a drug is highly soluble, a faster dissolution profile cannot by itself increase bioavailability. Any benefit must come from permeation, transporter or metabolic effects, and these must be shown directly. A drug that is truly solubility-limited, by contrast, should show increased exposure in proportion to the extra dissolved drug delivered. Before choosing a carrier, a formulator should therefore establish the dose number, the pH–solubility profile, apparent permeability (for example in Caco-2 monolayers [2]) and the main elimination route.

3. ANTIHYPERTENSIVE DRUGS WITH SOLUBILITY-RELATED FORMULATION CHALLENGES

3.1. Overview of major antihypertensive drug classes

First-line drug classes are thiazide-type diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). Beta-blockers, mineralocorticoid antagonists and others are added for specific indications [31]. Solubility problems cluster in the dihydropyridine CCBs, some ARB prodrugs and the lipophilic beta-blockers. Most ACE inhibitors and hydrophilic beta-blockers are water-soluble.

3.2. Calcium channel blockers

Nifedipine and felodipine are practically insoluble in water, light-sensitive, and subject to heavy CYP3A4 first-pass metabolism. Their products already depend on special technologies such as osmotic pumps and extended-release matrices. Nifedipine nanocrystals made by high-pressure homogenisation dissolved markedly faster than the unmilled drug [14]. PLGA nanoparticles of felodipine improved its absorption and antihypertensive effect in animal models [26]. Amlodipine is often wrongly called a poorly soluble Class II drug, but its besylate salt is generally treated as highly soluble, with 64–90% bioavailability, and it gains little from nanosizing.

3.3. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Most ACE inhibitors (enalapril, lisinopril, ramipril) are water-soluble. Several ARBs are not. Candesartan cilexetil and olmesartan medoxomil are lipophilic ester prodrugs with very low aqueous solubility and oral bioavailability of about 15% and 26%, respectively. Telmisartan is practically insoluble across the intestinal pH range. Valsartan's solubility is strongly pH-dependent. These drugs are reasonable candidates for nanocarriers [3,10]. Losartan potassium, by contrast, is freely soluble in water. Its bioavailability of about 33% reflects first-pass metabolism, and it behaves as a BCS Class III compound [27]. Nanoparticle work on losartan therefore has to justify itself on permeation, metabolic or release-modulation grounds rather than on solubility.

3.4. Beta-blockers

Carvedilol is a weakly basic, highly lipophilic BCS Class II drug with 25–35% bioavailability, limited by pH-dependent solubility and by first-pass metabolism. Lipid nanoparticles with a polymer coat raised its oral bioavailability in rats compared with a drug suspension [30]. Atenolol and metoprolol are hydrophilic and do not need nanotechnology to dissolve.

3.5. Other antihypertensive agents with relevant formulation challenges

Hydrochlorothiazide is sometimes placed in BCS Class III or IV because of its moderate solubility and low permeability. Even so, its bioavailability (about 65–75%) is adequate, and dissolution enhancement offers little. Spironolactone and eplerenone are poorly soluble and are sometimes used in resistant hypertension, but published nanoparticle work on them has mostly targeted other indications. Following the inclusion criterion of this review, these drugs are noted but not examined in detail.

3.6. Comparative physicochemical properties of selected drugs

Table 1 summarises the drugs discussed. The final column records the factor that mainly limits each drug's oral exposure, since that factor should determine whether a nanoparticle approach makes sense at all.



Table 1: Physicochemical properties and biopharmaceutical classification of selected antihypertensive drugs

Drug (class)	MW (g/mol)	Aqueous solubility	Oral F (%)	BCS class	Main limitation to oral exposure
Nifedipine (DHP-CCB)	346.3	Practically insoluble	45–56	II	Dissolution; CYP3A4 first-pass
Felodipine (DHP-CCB)	384.3	Practically insoluble	~15	II	Dissolution; extensive CYP3A4 first-pass
Amlodipine besylate (DHP-CCB)	567.1	Slightly soluble	64–90	I	None of practical significance
Carvedilol (β/α-blocker)	406.5	Practically insoluble (pH-dependent)	25–35	II	Dissolution at intestinal pH; first-pass
Candesartan cilexetil (ARB prodrug)	610.7	Practically insoluble	~15	II	Dissolution; ester hydrolysis
Olmesartan medoxomil (ARB prodrug)	558.6	Practically insoluble	~26	II	Dissolution
Telmisartan (ARB)	514.6	Practically insoluble at pH 3–9	42–58	II	Dissolution (pH-dependent)
Valsartan (ARB)	435.5	Poor in acid; soluble at neutral pH	~25	II/III	pH-dependent dissolution; permeability
Losartan potassium (ARB)	461.0	Freely soluble	~33	III	First-pass metabolism (CYP2C9/3A4); permeability
Hydrochlorothiazide (diuretic)	297.7	Very slightly soluble	65–75	III/IV	Permeability

DHP-CCB, dihydropyridine calcium channel blocker; ARB, angiotensin II receptor blocker; F, oral bioavailability. Values are approximate, compiled from product monographs and references [1,27,33].

3.7. Selection criteria for nanoparticle-based formulation development

A drug is a strong candidate when four conditions hold together. First, its dose number is well above one, so the dose cannot fully dissolve in intestinal fluid. Second, its permeability is high. Third, its bioavailability is low or variable in ways that matter clinically. Fourth, a dose reduction or a more consistent effect would be useful. Felodipine, nifedipine, carvedilol, candesartan cilexetil, olmesartan medoxomil and telmisartan meet most of these conditions. Losartan and amlodipine meet few of them.

4. NANOPARTICLE-BASED ORAL DRUG DELIVERY SYSTEMS

4.1. Definition and classification of pharmaceutical nanoparticles

Regulators generally treat a product as involving nanotechnology when it contains materials engineered in the 1–100 nm range, or materials up to about 1 µm that show size-dependent properties [29]. For oral delivery, the useful categories are carrier-based systems, in which drug is dissolved or dispersed in a polymer or lipid matrix, and carrier-free systems, in which the particle is the drug itself with a thin stabiliser layer (Fig. 2).

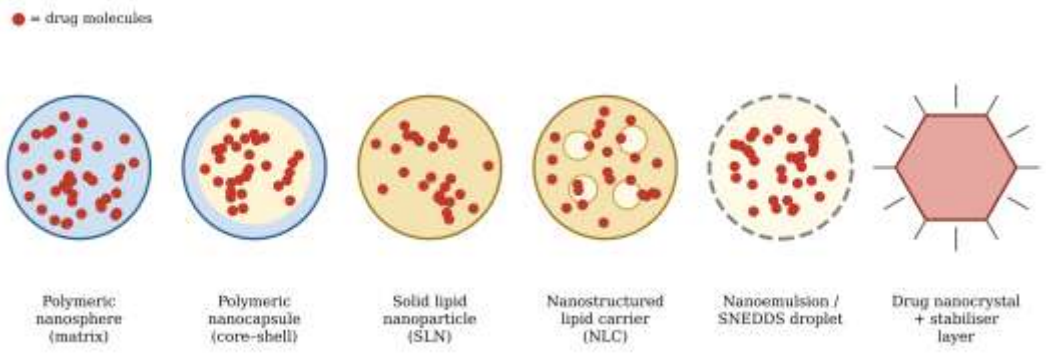


Fig. 2: Schematic representation of oral nanoparticle platforms

4.2. Polymeric nanoparticles

Polymeric nanoparticles are either nanospheres, where drug is distributed through a polymer matrix, or nanocapsules, where an oily or aqueous core is surrounded by a polymer wall [18]. Biodegradable polyesters such as PLGA and PLA, and polysaccharides such as chitosan and alginate, are the most common materials. Polymeric systems can hold the drug in an amorphous form, protect it from gastric conditions and control release through polymer composition and molecular weight [8]. On the other hand, drug loading is often below 10–15%. The solvents used in manufacture need to be removed and tested, and a slow-releasing matrix can actually reduce the amount of drug released within the absorption window.

4.3. Lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles (SLN) use physiological lipids that are solid at body temperature, such as glyceryl behenate, stearic acid and tripalmitin, stabilised with surfactants [19,23]. Nanostructured lipid carriers (NLC) blend solid and liquid lipids to create an imperfect crystal lattice. This holds more drug and limits drug expulsion during storage. Both carriers are digested by intestinal lipases, and the digestion products form mixed micelles that keep lipophilic drugs in solution [25].



4.4. Nanoemulsions and self-emulsifying drug delivery systems

Nanoemulsions are kinetically stable oil-in-water dispersions with droplets below roughly 200 nm. Self-nanoemulsifying drug delivery systems (SNEDDS) are anhydrous mixtures of oil, surfactant and co-solvent that form such droplets on contact with gastrointestinal fluid. They are filled into capsules and have a long commercial record for lipophilic drugs [25]. Drug is presented already dissolved, but high surfactant content and the risk of precipitation on dilution or digestion need attention.

4.5. Nanocrystals and nanosuspensions

Drug nanocrystals are 100% drug apart from the stabiliser, so drug loading is unmatched. They are made by wet media milling, high-pressure homogenisation or precipitation [20]. Their advantage comes mostly from surface area and a modest rise in saturation solubility. Food effects and variability are often reduced [13,17]. The success of several marketed nanocrystal tablets makes this the most industrially mature platform.

4.6. Hybrid and surface-modified nanocarriers

Lipid–polymer hybrids, chitosan-coated lipid particles, PEGylated or poloxamer-coated mucus-penetrating particles and ligand-decorated carriers combine features of the simpler systems. A cationic chitosan coat promotes mucoadhesion and can open tight junctions transiently. A dense, neutral PEG layer instead lets particles diffuse through mucus [11]. These designs add complexity, and they should be used only when the problem they solve has been shown.

4.7. Comparative advantages and limitations of different platforms

Table 2 compares the platforms by mechanism, typical loading and main limitations. No platform is best in every respect. The choice should follow from the drug's limiting factor, dose and solid-state behaviour.

Table 2: Comparison of oral nanoparticle platforms and their mechanisms of action

Platform	Typical size (nm)	Drug loading	Principal mechanisms	Key limitations
Polymeric nanoparticles (PLGA, PLA, chitosan)	100–300	Low–moderate (1–15%)	Amorphous drug, surface area, protection, controlled release, mucoadhesion (chitosan)	Solvent residues, slow release may cut absorption, cost
Solid lipid nanoparticles	80–300	Low–moderate	Lipid digestion and micellar solubilisation, surface area, possible lymphatic uptake	Drug expulsion on storage, polymorphic transitions
Nanostructured lipid carriers	80–300	Moderate	As SLN with higher loading and less expulsion	Complex composition, stability testing needed
Nanoemulsions / SNEDDS	20–200	Moderate–high (dissolved)	Drug presented in solution, digestion-mediated solubilisation	High surfactant, precipitation on dilution or digestion
Drug nanocrystals / nanosuspensions	100–500	Very high (~100% drug)	Surface area, increased saturation solubility, adhesiveness	Ostwald ripening, aggregation, needs solidification
Hybrid / surface-modified carriers	100–300	Variable	Mucoadhesion or mucus penetration, tight-junction modulation	Manufacturing complexity, regulatory burden

Compiled from references [8,11,13,18,19,20,23,25].

5. FORMULATION MATERIALS AND NANOPARTICLE ENGINEERING

5.1. Selection of polymers, lipids, surfactants, and stabilizers

Excipients should be chosen for drug–carrier miscibility, regulatory acceptability by the oral route, and the release rate needed. Polymer–drug solubility parameters, partitioning experiments and screening of drug solubility in molten lipids are simple tools that save much trial and error. Stabilisers such as polysorbate 80, poloxamer 188/407, polyvinyl alcohol, HPMC, PVP and lecithin act sterically or electrostatically, and the right concentration depends on the surface area being generated [17].

5.2. Biodegradable polymers, including PLGA and chitosan

PLGA hydrolyses to lactic and glycolic acids. Its degradation rate depends on the lactide:glycolide ratio, molecular weight and end group, so release can be tuned from days to months [8]. For oral antihypertensives, low-molecular-weight, acid-terminated grades are usually preferred, so that most of the drug is released within the gastrointestinal transit time. Chitosan is cationic and mucoadhesive, and it is often used as a coating or as an ionically crosslinked matrix with tripolyphosphate. Its solubility depends on pH and is lost above about pH 6.5, which limits its behaviour in the distal small intestine [18].

5.3. Lipid composition and surfactant selection

Lipid chain length and polymorphism control drug loading and expulsion. Glycerides with mixed chain lengths form less ordered lattices than pure triglycerides. Surfactant HLB, concentration and the use of co-surfactants determine particle size and how stable the dispersion remains during digestion [19,23].



5.4. Drug–excipient compatibility

FTIR, DSC and HPLC assays of stressed binary mixtures are the usual screens. Ester prodrugs such as candesartan cilexetil and olmesartan medoxomil can hydrolyse in aqueous dispersions. Dihydropyridines photodegrade, so processing under amber light and protective packaging are needed.

5.5. Particle size, polydispersity, and surface charge

For oral dissolution enhancement, a hydrodynamic diameter of about 100–300 nm with a polydispersity index (PDI) below 0.3 is a common target [7]. Zeta potential values of about ±20–30 mV or more suggest electrostatic stability. Sterically stabilised systems can be stable at lower values, so zeta potential should not be read on its own.

5.6. Crystallinity, amorphous drug states, and solid-state properties

Many polymeric and lipid carriers hold drug in an amorphous or molecularly dispersed state, and this raises apparent solubility [5]. That state is thermodynamically unstable. Recrystallisation during storage, or on contact with water, can wipe out the benefit, so solid-state monitoring should continue through stability studies.

5.7. Surface modification and gastrointestinal stability

Particles meet acid, pepsin, bile salts, lipases and ionic strengths that can make them aggregate. Steric coats such as PEG and poloxamer, and enteric polymer coats, improve survival. In the carvedilol SLN study, for example, a polymer coat removed the need for intraduodenal dosing in the animal model [30].

5.8. Excipient safety and suitability for oral administration

PLGA, chitosan, most glyceride lipids, polysorbates, poloxamers and lecithin have established oral safety records. The amounts used per dose, the residual organic solvent and the chronic daily intake still have to be justified against inactive-ingredient limits, especially for drugs taken for life.

6. PREPARATION METHODS FOR ORAL NANOPARTICLE FORMULATIONS

6.1. Nanoprecipitation

In nanoprecipitation (solvent displacement), drug and polymer are dissolved in a water-miscible solvent such as acetone or ethanol and added to an aqueous stabiliser solution. As the solvent diffuses away, the polymer precipitates and particles of about 100–300 nm form within seconds [12]. The method is simple and uses little energy, and it suits hydrophobic drugs. Water-soluble drugs partition out of the forming particles, which keeps encapsulation low.

6.2. Emulsion–solvent evaporation

Drug and polymer are dissolved in a water-immiscible solvent such as dichloromethane or ethyl acetate, emulsified into an aqueous stabiliser by homogenisation or sonication, and the solvent is then evaporated to harden the particles. Double emulsions (w/o/w) are used for hydrophilic drugs [18]. Residual solvent has to be measured and kept within ICH Q3C limits.

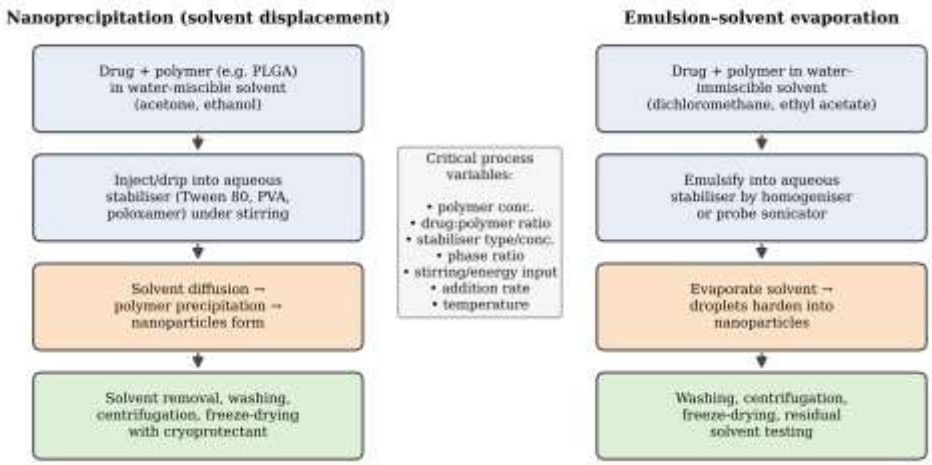


Fig. 3: Workflow of nanoprecipitation and emulsion–solvent evaporation methods for polymeric nanoparticles

6.3. High-pressure homogenization

High-pressure homogenisation, either piston-gap or microfluidiser, forces a coarse suspension or pre-emulsion through a narrow gap at 500–2000 bar. It is used for nanocrystals [14] and for hot or cold SLN/NLC production [23]. It scales well, but it may need many cycles, and temperature control matters for heat-labile drugs.

6.4. Wet media milling

A drug suspension in stabiliser solution is milled with zirconia or polymeric beads. This is the basis of most marketed nanocrystal products and is the most scalable top-down process [20]. A combined approach, ball milling followed by probe sonication, gave olmesartan medoxomil nanosuspensions of about 470 nm [3]. Bead erosion and long milling times are the main concerns.



6.5. Solvent injection and emulsification techniques

Solvent injection, in which ethanol or acetone carrying lipid and drug is injected into stirred water, and spontaneous or phase-inversion emulsification are low-energy routes to lipid particles and nanoemulsions. They work well at laboratory scale but depend heavily on mixing geometry.

6.6. Preparation of lipid-based nanoparticles

SLN and NLC are usually made by hot homogenisation (drug in molten lipid, dispersed in hot surfactant solution, then homogenised and cooled), cold homogenisation, microemulsion dilution or ultrasonication [19,23]. Candesartan cilexetil SLN, for instance, were produced by hot homogenisation followed by ultrasonication [10].

6.7. Process variables affecting particle characteristics

Polymer or lipid concentration, drug:carrier ratio, stabiliser type and concentration, organic:aqueous phase ratio, energy input, addition rate and temperature are the key variables (Table 3). They interact, so one-factor-at-a-time studies are a poor guide. Factorial or response-surface designs, like the 3^2 design used for felodipine PLGA nanoparticles [26], are more efficient and more convincing.

Table 3: Preparation methods and formulation variables affecting nanoparticle performance

Method	Suitable systems	Key variables	Effect on product	Advantages / drawbacks
Nanoprecipitation	PLGA, PLA nanospheres; nanocapsules	Polymer conc., solvent type, solvent:water ratio, addition rate, stabiliser	↑ polymer conc. → ↑ size; ↑ stabiliser → ↓ size, ↓ PDI	Simple, low energy / poor loading of hydrophilic drugs
Emulsion–solvent evaporation	PLGA, PCL; w/o/w for hydrophilic drugs	Homogenisation speed/time, phase ratio, PVA conc.	↑ energy → ↓ size; ↑ internal phase → ↑ size	Versatile / chlorinated solvents, residual solvent
High-pressure homogenisation	Nanocrystals, SLN, NLC	Pressure, cycles, temperature, stabiliser	↑ cycles → ↓ size until a plateau	Scalable, solvent-free / heat, many cycles
Wet media milling	Nanocrystals	Bead size/load, milling time, stabiliser ratio	↑ time → ↓ size; risk of over-milling	Industrial standard / bead erosion
Hot homogenisation / ultrasonication	SLN, NLC	Lipid type, surfactant HLB, sonication energy	Surfactant controls size and stability	No organic solvent / metal shedding (probe)
Solvent injection / self-emulsification	Lipid particles, nanoemulsions, SNEDDS	Oil:surfactant ratio, injection rate, mixing	Composition dominates droplet size	Low energy / mixing-sensitive at scale

PDI, polydispersity index; PVA, polyvinyl alcohol; HLB, hydrophilic–lipophilic balance. Based on references [12,14,18,20,23,26].

6.8. Scale-up and manufacturing reproducibility

Laboratory batches of 10–50 mL rarely behave the same at litre scale. Mixing time in nanoprecipitation, heat transfer in homogenisation and solvent removal all change with volume. Continuous methods, such as microfluidic or in-line mixing and continuous milling, and early definition of critical process parameters reduce the risk [34].

7. MECHANISMS OF BIOAVAILABILITY ENHANCEMENT

Fig. 4 summarises the routes by which nanoparticles can increase oral exposure. They differ greatly in how firmly they are supported by evidence.

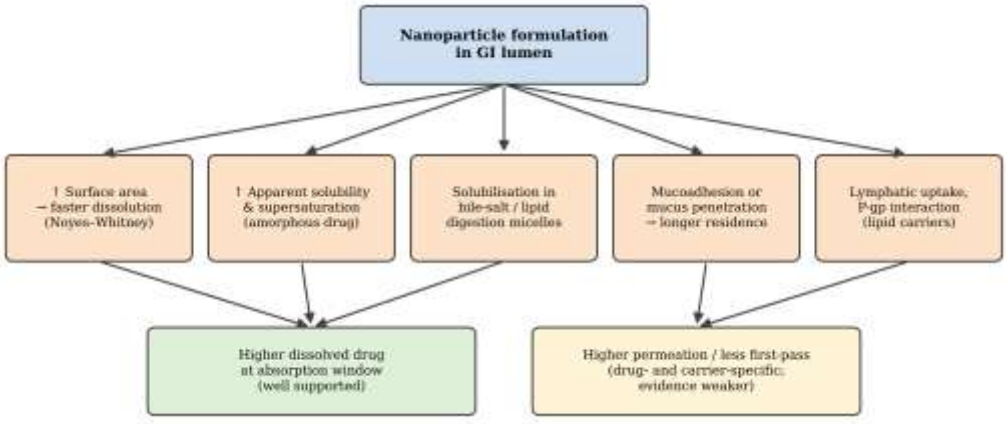


Fig. 4: Mechanisms by which nanoparticle formulations can enhance oral bioavailability, with relative strength of evidence

7.1. Increased surface area and faster dissolution

This mechanism is the best established. Going from 10 µm to 200 nm increases specific surface area about fifty-fold. Under sink conditions dissolution rate rises roughly in proportion, and for Class II drugs this brings dissolution within the absorption window [17,24].



7.2. Improved apparent solubility and maintenance of supersaturation

Amorphous drug in polymer matrices, and very small crystals, can produce concentrations above equilibrium solubility. Absorption benefits only if precipitation is delayed long enough, the so-called spring-and-parachute behaviour. Polymers such as HPMC and PVP often act as precipitation inhibitors [5].

7.3. Amorphization and changes in drug crystallinity

DSC and XRD often show that drug in PLGA, SLN or NLC is amorphous or molecularly dispersed. The higher free energy raises apparent solubility, but it brings a stability risk (Section 5.6).

7.4. Drug release and partitioning into gastrointestinal fluids

For carrier systems, the drug must leave the particle before it can be absorbed. A slow, "sustained" release over 12–24 h may look attractive in vitro, but it can lower total absorption if most of the drug is still inside the particles when they pass the absorptive region. For oral bioavailability enhancement, release should be fast enough to finish within small-intestinal transit.

7.5. Interaction with bile salts and intestinal lipid digestion

Lipid carriers are digested by pancreatic lipase. The resulting monoglycerides and fatty acids join bile-salt micelles and vesicles, which keep lipophilic drug solubilised. This can reduce food effects, because the formulation supplies the lipid normally provided by a meal [25].

7.6. Mucus interaction and intestinal residence

Mucoadhesive (cationic, chitosan-coated) particles stick to the mucus layer and may lengthen local residence. Mucus-penetrating (dense PEG) particles cross it and reach the epithelium [11]. Either may help in particular cases, but mucus turnover limits how long mucoadhesion lasts.

7.7. Intestinal permeability and possible transporter interactions

Surfactants such as polysorbate 80 and some polymers can inhibit P-glycoprotein or loosen tight junctions in vitro. Intact uptake of particles by enterocytes and M cells does occur, but quantitative studies show that only a small fraction of an oral dose of particles is absorbed intact [9]. Claims of transporter-mediated benefit need direct evidence, such as bidirectional Caco-2 transport with and without inhibitors [2].

7.8. Lymphatic transport: opportunities and limitations

Highly lipophilic drugs (log P above about 5, with high triglyceride solubility) can enter chylomicrons and reach the systemic circulation through the thoracic duct, bypassing the liver [28]. For most antihypertensives this route carries only a small fraction of the dose. Lymphatic claims should be supported by lymph-cannulated or chylomicron-blocking (for example cycloheximide) studies, not assumed.

7.9. The distinction between improved dissolution and demonstrated bioavailability enhancement

A faster release curve in a dialysis bag shows only that drug left the bag faster. It does not show higher exposure. A bioavailability claim needs plasma concentration data compared with an appropriate reference. Many studies in this field, including our own, stop at the in vitro stage and should be reported as such.

8. CHARACTERIZATION AND EVALUATION OF NANOPARTICLE FORMULATIONS

8.1. Particle size, polydispersity index, and zeta potential

Dynamic light scattering gives the intensity-weighted hydrodynamic diameter (z-average) and PDI. Both should be reported with the dispersant, temperature and dilution used, and confirmed by a number-weighted or imaging method when the PDI is above 0.3 [7]. Zeta potential depends on pH and ionic strength, so it should be measured in a stated medium.

8.2. Morphology and surface characterization

SEM and TEM show shape, surface texture and aggregation. Image-derived sizes should be consistent with DLS values once drying artefacts are allowed for. AFM and XPS can probe surface coatings.

8.3. Drug loading and encapsulation efficiency, where applicable

Encapsulation efficiency is usually measured indirectly, from free drug in the supernatant after ultracentrifugation or ultrafiltration. A direct check, dissolving the washed particles and assaying total drug, prevents overestimation when free drug sticks to the particles or precipitates.

8.4. Differential scanning calorimetry and X-ray diffraction

DSC (loss or shift of the melting endotherm) and powder XRD (loss of Bragg peaks) show the physical state of the drug and lipid polymorphism. Repeating these measurements during stability studies is the most direct way to detect recrystallisation.

8.5. In vitro dissolution and drug-release studies

Dialysis-bag methods are common but can be limited by diffusion across the membrane, which disguises genuinely fast release. A freely soluble control drug should be run in the same bag to show this. Sample-and-separate methods (centrifugal ultrafiltration) and USP apparatus with in-situ fibre-optic analysis avoid the problem. Profiles should be compared with model-independent similarity factors (f2) and fitted to kinetic models (zero-order, first-order, Higuchi, Korsmeyer–Peppas) [6].



8.6. Solubility, supersaturation, and precipitation assessment

Apparent solubility should be measured on the formulation in biorelevant media. Transfer tests, from simulated gastric to simulated intestinal fluid, show whether supersaturation is kept or lost [5].

8.7. Simulated gastrointestinal digestion and biorelevant media

FaSSIF and FeSSIF contain bile salt and lecithin and predict food effects better than simple buffers. In vitro lipolysis models (pH-stat titration with pancreatin) show how lipid carriers behave during digestion and where the drug goes [25].

8.8. In vitro permeability and intestinal transport models

Caco-2 monolayers, co-culture models with mucus-producing or M-like cells, everted or non-everted gut sacs, Ussing chambers and in situ single-pass perfusion each answer different questions [2]. Ex vivo sac data, such as the roughly four-fold higher apparent permeability reported for olmesartan nanosuspension [3], are useful supporting evidence but do not replace pharmacokinetics.

8.9. Stability, redispersibility, and storage evaluation

Aqueous dispersions are prone to aggregation, Ostwald ripening, hydrolysis and drug leakage. Lyophilisation with cryoprotectants (trehalose, mannitol, sucrose) or spray-drying into tablets is usually needed. Size should be reported before and after drying and reconstitution, and under ICH storage conditions. Table 5 lists the main characterisation techniques and their critical quality attributes (CQAs).

Table 5: Characterization techniques and critical quality attributes

Critical quality attribute	Technique(s)	Typical target / remark
Particle size and PDI	DLS; laser diffraction; NTA	100–300 nm; PDI < 0.3 for oral dissolution enhancement
Surface charge	Electrophoretic light scattering (zeta potential)	≥ |20–30| mV, or steric stabilisation shown
Morphology	SEM, TEM, AFM	Spherical/discrete; sizes consistent with DLS
Drug loading / encapsulation	Ultracentrifugation or ultrafiltration + HPLC/UV	Report both direct and indirect methods
Solid state	DSC, PXRD, FTIR	Physical form of drug; carrier polymorphism; compatibility
In vitro release	Dialysis, sample-and-separate, USP II/IV	Discriminating, biorelevant; f2 and kinetic models
Apparent solubility / supersaturation	Shake-flask, transfer (pH-shift) tests	Duration of supersaturation in FaSSIF/FeSSIF
Behaviour during digestion	pH-stat in vitro lipolysis	Drug distribution between aqueous, oil and pellet phases
Permeability	Caco-2, Ussing chamber, gut sac, SPIP	Papp vs control; efflux ratio
Stability	ICH storage; size, assay, solid state over time	Redispersibility after lyophilisation/spray-drying

DLS, dynamic light scattering; NTA, nanoparticle tracking analysis; PXRD, powder X-ray diffraction; SPIP, single-pass intestinal perfusion. Based on references [2,5,6,7,25].

9. PHARMACOKINETIC EVALUATION AND EVIDENCE OF BIOAVAILABILITY ENHANCEMENT

9.1. In vivo study designs and comparator selection

Most nanoparticle studies use rats with oral gavage, and often compare the formulation only with a coarse aqueous suspension of the drug. That comparator makes almost any formulation look better. A fairer design also includes the marketed product or an optimised conventional formulation at the same dose, uses crossover designs where possible, includes enough animals for the expected variability, and uses a validated bioanalytical method.

9.2. Maximum plasma concentration (Cmax) and time to maximum concentration (Tmax)

A higher Cmax with an earlier Tmax is the expected signature of faster dissolution. For antihypertensives, a sharper peak is not always desirable. Reflex tachycardia with fast-acting dihydropyridines is a well-known example, so peak changes have to be read in pharmacodynamic terms.

9.3. Area under the concentration–time curve (AUC)

AUC0–t and AUC0–∞ measure the extent of exposure. Results should be reported with variability (CV%) and tested statistically, preferably on log-transformed data. For prodrugs (candesartan cilexetil, olmesartan medoxomil) and drugs with active metabolites (losartan and E-3174), both parent and metabolite should be measured.

9.4. Relative and absolute bioavailability

Relative bioavailability, Frel = (AUCtest/AUCref) × (Doseref/Dosetest), against a stated reference is the usual endpoint. Absolute bioavailability needs intravenous data and is rarely reported. A large Frel against a crude suspension says much less than a modest Frel against the marketed tablet.



9.5. Relationship between dissolution, permeability, and systemic exposure

For a Class II drug, faster dissolution should increase AUC until permeability or solubility in the absorption window becomes limiting. Beyond that point further size reduction gains little. For Class III or highly metabolised drugs, a gain in AUC requires a change in permeation or metabolism. Physiologically based absorption models can tell these situations apart before animal work begins [17].

9.6. Food effects, pharmacokinetic variability, and drug interactions

Reducing the difference between fed and fasted exposure, and between subjects, can matter as much clinically as increasing the mean AUC. Nanocrystal and lipid systems have reduced food effects for several drugs [13,25]. Surfactants that inhibit CYP3A4 or P-gp could, in principle, create interactions, and this deserves attention for polypharmacy patients.

9.7. Correlation between in vitro and in vivo performance

A Level A in vitro–in vivo correlation is the strongest link between a release test and plasma levels. It is seldom attempted for nanoparticles because release methods are not standardised and particle uptake complicates the picture. Even an approximate correlation, using biorelevant dissolution and deconvolution, would greatly strengthen the evidence.

9.8. Safety and therapeutic relevance of increased systemic exposure

Antihypertensives have dose-related adverse effects: hypotension, oedema, bradycardia, hyperkalaemia and renal impairment. A formulation that raises exposure should allow the dose to be reduced proportionately. Pharmacodynamic endpoints, such as blood pressure in spontaneously hypertensive or DOCA-salt rats, are needed to show that the extra exposure produces a useful, not excessive, effect [10,26].

10. COMPARATIVE ANALYSIS OF PUBLISHED STUDIES

10.1. Polymeric nanoparticle formulations of selected antihypertensive drugs

Felodipine is the clearest polymeric example. PLGA nanoparticles optimised by factorial design improved absorption and enhanced both antihypertensive and antianginal effects compared with the plain drug [26]. In our laboratory, losartan potassium was loaded into PLGA nanoparticles by nanoprecipitation/emulsification with polysorbate 80 (0.5–1.0% w/v) as stabiliser. Six batches (F1–F6) varied the drug and polymer amounts. The best batch, F3 (7.5 mg drug, 100 mg PLGA, 0.5% polysorbate 80), had a mean size of 186 ± 3.1 nm, a PDI of 0.264, a zeta potential of −28.6 mV and an encapsulation efficiency of 86.7%. It released 96.4% of the drug over 12 h in phosphate buffer pH 6.8, compared with 71.6% for a conventional losartan formulation (Fig. 5). Across the batches, higher polymer content and lower surfactant concentration went with smaller size and higher entrapment. These results describe a well-formed, reproducible PLGA system. Because losartan is a freely soluble BCS Class III drug, however, the faster release seen here cannot be read as evidence of higher bioavailability. Pharmacokinetic studies, together with measurement of the E-3174 metabolite, are needed to test whether the particles change permeation or first-pass metabolism.

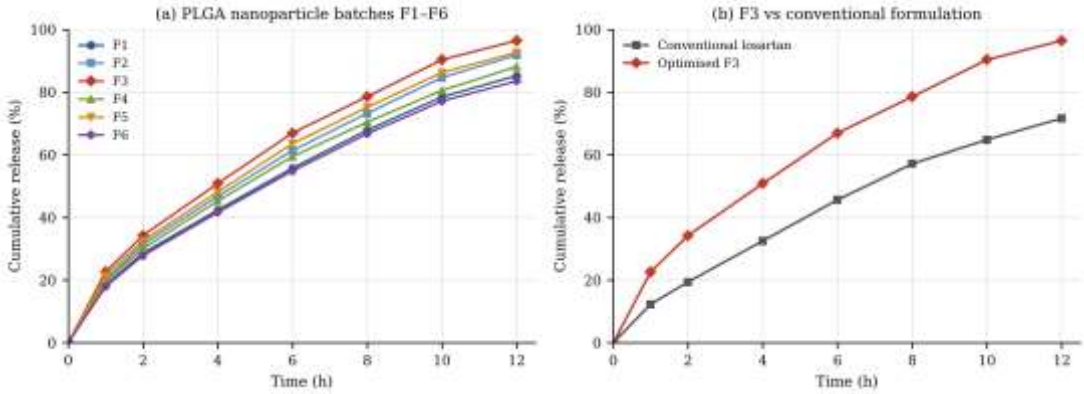


Fig. 5: In vitro release (dialysis bag, phosphate buffer pH 6.8, 37 ± 0.5 °C) of losartan potassium from PLGA nanoparticles: (a) batches F1–F6; (b) optimised F3 compared with a conventional formulation

10.2. Lipid-based formulations and their performance

Polymer-coated SLN of carvedilol increased oral bioavailability in rats compared with a carvedilol suspension, and the coating removed the need for intraduodenal administration in the animal model [30]. Candesartan cilexetil SLN improved oral bioavailability and gave a longer blood-pressure-lowering effect in hypertensive rats than the drug suspension [10]. These results fit the lipid-digestion and solubilisation mechanisms described in Section 7.5.

10.3. Nanocrystals and nanosuspensions

Nifedipine nanocrystals made by high-pressure homogenisation showed higher saturation solubility and a much faster dissolution rate than the unprocessed drug [14]. Olmesartan medoxomil nanosuspension (about 470 nm, −19.1 mV, Poloxamer 407) produced roughly four-fold higher apparent permeability across rat duodenal sacs than the coarse drug [3]. Neither study measured plasma pharmacokinetics in humans. The broader nanocrystal literature does show consistent AUC gains for Class II drugs in vivo [13].



Table 4: Published studies on nanoparticle-based oral delivery of antihypertensive drugs

Drug	Nanocarrier and method	Key physicochemical findings	Main outcome	Ref.
Felodipine	PLGA nanoparticles; factorial-design optimisation	Nanoscale, optimised for size and entrapment	Enhanced absorption; improved antihypertensive and antianginal effects in vivo	[26]
Carvedilol	Polymer-coated solid lipid nanoparticles	Coating stabilised SLN in gastric conditions	Higher oral bioavailability than suspension in rats; avoided intraduodenal dosing	[30]
Candesartan cilexetil	SLN; hot homogenisation + ultrasonication	Nanoscale lipid particles with good entrapment	Improved oral bioavailability and longer BP reduction in hypertensive rats	[10]
Olmesartan medoxomil	Nanosuspension; ball milling + probe sonication (Poloxamer 407)	469.9 nm, PDI 0.439, −19.1 mV; reduced crystallinity on DSC	~4-fold higher apparent permeability (rat duodenal sac)	[3]
Nifedipine	Nanocrystals; high-pressure homogenisation	Sub-micron crystals retaining crystallinity	Higher saturation solubility and faster dissolution than unmilled drug	[14]
Losartan potassium	PLGA nanoparticles; nanoprecipitation/emulsification, polysorbate 80	F3: 186 nm, PDI 0.264, −28.6 mV, EE 86.7%	96.4% vs 71.6% release in 12 h (in vitro only)	Present work

BP, blood pressure; EE, encapsulation efficiency; SLN, solid lipid nanoparticles.

10.4. Comparative dissolution and pharmacokinetic outcomes

Table 6 compares the outcomes and grades each according to what it actually demonstrates. Dissolution gains are consistent across all platforms. In vivo exposure gains have been reported mainly in rats, and almost always against suspensions of unprocessed drug. Pharmacodynamic confirmation exists for felodipine and candesartan.

Table 6: Comparative pharmacokinetic outcomes of nanoparticle and conventional formulations

Drug / system	Comparator	Model	Reported outcome	Level of evidence
Felodipine PLGA NPs	Plain felodipine	Rats (PK + PD)	Improved absorption; greater and longer antihypertensive and antianginal effect	In vivo PK/PD, animal
Carvedilol coated SLN	Carvedilol suspension	Rats (oral)	Significantly higher AUC than suspension	In vivo PK, animal
Candesartan cilexetil SLN	Drug suspension	Rats (PK + PD)	Higher relative bioavailability; prolonged BP lowering	In vivo PK/PD, animal
Olmesartan medoxomil nanosuspension	Coarse drug	Rat duodenal sac	~4-fold ↑ apparent permeability	Ex vivo only
Nifedipine nanocrystals	Unmilled drug	Dissolution testing	Faster dissolution; ↑ saturation solubility	In vitro only
Losartan PLGA NPs (F3)	Conventional losartan	Dialysis, pH 6.8	96.4% vs 71.6% cumulative release at 12 h	In vitro only; BCS III drug

AUC, area under the curve; PD, pharmacodynamics; PK, pharmacokinetics. Sources: [3,10,14,26,30] and present work.

10.5. Limitations of the available experimental evidence

Several weaknesses recur: small animal numbers; comparisons only with plain suspension; dialysis-bag release without diffusion controls; no stability data beyond a few weeks; no measurement of active metabolites; and a tendency to attribute results to lymphatic uptake or P-gp inhibition without testing either. Studies that use a drug of the wrong biopharmaceutical class as the model, so that nanosizing could not be expected to raise exposure through dissolution, make interpretation harder still.

10.6. Lessons for future formulation development

The most informative studies match the platform to the drug's limiting factor, use a design-of-experiments approach, characterise solid state and biorelevant behaviour, and test pharmacokinetics and pharmacodynamics against a clinically relevant comparator. Fewer, better-designed studies would move the field further than many in vitro reports.

11. SAFETY, REGULATORY, AND TRANSLATIONAL CONSIDERATIONS

11.1. Excipient toxicity and gastrointestinal tolerability

Oral nanoparticles made from established excipients are generally well tolerated. Daily intake of surfactants, effects on the epithelial barrier with long-term use, residual solvents and the fate of any particles absorbed intact still need to be considered for lifelong therapy.

11.2. Reproducibility, stability, and manufacturing scale-up

Batch-to-batch variation in size, loading and residual solvent is a frequent cause of failure. Conversion of liquid dispersions into stable solid dosage forms (lyophilised powders, spray-dried granules, layered pellets) is usually required, and redispersion of the original particles has to be shown [34].



11.3. Regulatory considerations for nanomedicines

FDA guidance on drug products containing nanomaterials asks sponsors to characterise particle size distribution, surface properties, physical and chemical stability, and in vitro release using methods suited to the nanomaterial, and to link these attributes to performance [29]. Comparable reflection papers from the EMA take a similar case-by-case approach.

11.4. Bioequivalence and quality control

A nanoparticle product with a different exposure from the reference cannot rely on standard bioequivalence. It needs its own dose justification and, in most cases, clinical data. Release specifications should include particle size (D50, D90 or z-average with PDI), assay, related substances, solid-state form, residual solvent and a discriminating dissolution test.

Table 7: Translational barriers and strategies for improving clinical applicability

Barrier	Consequence	Strategy
Wrong model drug (not solubility-limited)	No exposure gain despite better dissolution	Classify by BCS/BDDCS before formulating [1,33]
Weak comparators	Inflated relative bioavailability	Compare with marketed product at equal dose
Non-discriminating release tests	Misleading in vitro claims	Biorelevant media, diffusion controls, f2 [6]
Physical instability	Aggregation, recrystallisation, shorter shelf life	Solidification, steric stabilisers, ICH stability
Scale-up variability	Batch-to-batch differences in size and loading	QbD, DoE, continuous processing, PAT [34]
Excipient load for lifelong use	Tolerability and regulatory questions	Use established excipients within inactive-ingredient limits
Regulatory uncertainty	Long development, higher cost	Early dialogue; follow FDA nanomaterial guidance [29]
Lack of human data	Uncertain clinical benefit	Small crossover PK/PD studies in patients

BDDCS, Biopharmaceutics Drug Disposition Classification System; DoE, design of experiments; PAT, process analytical technology; QbD, quality by design.

11.5. Clinical evidence and commercialization barriers

To our knowledge, no nanoparticle formulation of an antihypertensive has been approved as a new product with a nanotechnology-based claim, and controlled human pharmacokinetic studies are rare. Cost, manufacturing complexity and the availability of cheap generics with adequate efficacy are real commercial obstacles [15].

11.6. Implications of altered exposure for chronic antihypertensive therapy

Because antihypertensive response is graded and long-term, a formulation that changes Cmax, Tmax or AUC changes the dose–response relationship. Any new formulation must be re-titrated against blood pressure and safety. A smoother 24-hour profile and lower variability are more useful clinically than a higher peak.

12. FUTURE PERSPECTIVES

12.1. Rational selection of nanoparticle platforms using biopharmaceutical data

Dose number, pH–solubility, permeability, metabolic route and solid-state data should determine whether nanotechnology is needed and which platform to use. Nanocrystals suit high-dose, high-melting Class II drugs. Lipid carriers suit very lipophilic, low-melting drugs. Polymeric carriers suit drugs that benefit from amorphous stabilisation or modified release [16,32].

12.2. Hybrid nanocarriers and multifunctional formulations

Lipid–polymer hybrids and fixed-dose combination nanocarriers (for example, a CCB with an ARB) could support single-pill combination therapy, which guidelines already encourage [31]. Their added complexity must be justified by a measurable benefit.

12.3. Predictive dissolution and absorption modeling

Physiologically based biopharmaceutics modelling, combined with biorelevant dissolution, can predict whether nanosizing will increase AUC, estimate food effects and reduce animal use [17,32].

12.4. Quality-by-design and process analytical technologies

Defining a quality target product profile and critical quality attributes, and using design of experiments and in-line particle sizing, can make nanoparticle manufacture reproducible and acceptable to regulators [34].

12.5. Patient-centered oral dosage forms

Orodispersible films, mini-tablets and once-daily formats containing nanoparticles could help elderly patients and those who struggle to swallow tablets. These are common in hypertension, where adherence is the main cause of poor control.

12.6. Priorities for clinical translation

The main priorities are as follows. Model drugs should be selected on biopharmaceutical grounds. Comparators should be clinically relevant. Active metabolites should be measured. Long-term stability should be shown in the final dosage form. Pharmacodynamic studies in validated hypertensive models should be included. Small, well-controlled human pharmacokinetic studies should follow for the most promising candidates [22].



13. CONCLUSION

Nanoparticle formulations reliably speed up dissolution and raise the apparent solubility of poorly soluble antihypertensives. The strongest evidence of improved oral exposure comes from BCS Class II drugs: dihydropyridines such as felodipine and nifedipine, carvedilol, and lipophilic sartan prodrugs such as candesartan cilexetil and olmesartan medoxomil. For these drugs, polymeric, lipid and nanocrystal systems have produced higher AUC and, in some cases, better blood-pressure control in animal models. Claims of increased permeation, lymphatic transport and avoidance of first-pass metabolism remain preliminary and depend on the drug. Our PLGA work on losartan potassium shows that a stable, well-entrapped nanoparticle with faster release can be made easily. It also shows why such results must be read in light of the drug's biopharmaceutical class: for a freely soluble, first-pass-limited drug, only in vivo data can show a benefit. To demonstrate clinical value, the field now needs a mechanism-based choice of drugs, biorelevant and pharmacokinetic endpoints against realistic comparators, solid-dosage stability, scalable manufacture, and controlled studies in patients.

ACKNOWLEDGEMENT

The authors thank the management and Principal of Sardar Patel College of Pharmacy, Gorakhpur, for providing facilities for this work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

This work received no specific grant from any funding agency.

REFERENCES

1. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413-20.
2. Artursson P, Karlsson J. Correlation between oral drug absorption in humans and apparent drug permeability coefficients in human intestinal epithelial (Caco-2) cells. Biochem Biophys Res Commun. 1991;175(3):880-5.
3. Attari Z, Bhandari A, Jagadish PC, Lewis S. Enhanced ex vivo intestinal absorption of olmesartan medoxomil nanosuspension: preparation by combinative technology. Saudi Pharm J. 2016;24(1):57-63.
4. Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. Biomedicines. 2022;10(9):2055.
5. Brouwers J, Brewster ME, Augustijns P. Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? J Pharm Sci. 2009;98(8):2549-72.
6. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13(2):123-33.
7. Danaei M, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, et al. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics. 2018;10(2):57.
8. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA-based nanoparticles: an overview of biomedical applications. J Control Release. 2012;161(2):505-22.
9. des Rieux A, Fievez V, Garinot M, Schneider YJ, Préat V. Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach. J Control Release. 2006;116(1):1-27.
10. Dudhipala N, Veerabrahma K. Candesartan cilexetil loaded solid lipid nanoparticles for oral delivery: characterization, pharmacokinetic and pharmacodynamic evaluation. Drug Deliv. 2016;23(2):395-404.
11. Ensign LM, Cone R, Hanes J. Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. Adv Drug Deliv Rev. 2012;64(6):557-70.
12. Fessi H, Puisieux F, Devissaguet JP, Ammoury N, Benita S. Nanocapsule formation by interfacial polymer deposition following solvent displacement. Int J Pharm. 1989;55(1):R1-4.
13. Gao L, Liu G, Ma J, Wang X, Zhou L, Li X. Drug nanocrystals: in vivo performances. J Control Release. 2012;160(3):418-30.
14. Hecq J, Deleers M, Fanara D, Vranckx H, Amighi K. Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. Int J Pharm. 2005;299(1-2):167-77.
15. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B. 2015;5(5):442-53.
16. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. Int J Pharm. 2011;420(1):1-10.
17. Kesisoglou F, Panmai S, Wu Y. Nanosizing—oral formulation development and biopharmaceutical evaluation. Adv Drug Deliv Rev. 2007;59(7):631-44.
18. Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles based drug delivery systems. Colloids Surf B Biointerfaces. 2010;75(1):1-18.
19. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2001;47(2-3):165-96.
20. Merisko-Liversidge E, Liversidge GG. Nanosizing for oral and parenteral drug delivery: a perspective on formulating poorly-water soluble compounds using wet media milling technology. Adv Drug Deliv Rev. 2011;63(6):427-40.
21. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020;16(4):223-37.



22. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021;20(2):101-24.

23. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the state of the art. Eur J Pharm Biopharm. 2000;50(1):161-77.

24. Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc. 1897;19(12):930-4.

25. 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):231-48.

26. Shah U, Joshi G, Sawant K. Improvement in antihypertensive and antianginal effects of felodipine by enhanced absorption from PLGA nanoparticles optimized by factorial design. Mater Sci Eng C Mater Biol Appl. 2014;35:153-63.

27. Sica DA, Gehr TWB, Ghosh S. Clinical pharmacokinetics of losartan. Clin Pharmacokinet. 2005;44(8):797-814.

28. Trevaskis NL, Kaminskas LM, Porter CJH. From sewer to saviour—targeting the lymphatic system to promote drug exposure and activity. Nat Rev Drug Discov. 2015;14(11):781-803.

29. U.S. Food and Drug Administration. Drug products, including biological products, that contain nanomaterials: guidance for industry. Silver Spring (MD): FDA; 2022.

30. Venishetty VK, Chede R, Komuravelli R, Adepu L, Sistla R, Diwan PV. Design and evaluation of polymer coated carvedilol loaded solid lipid nanoparticles to improve the oral bioavailability: a novel strategy to avoid intraduodenal administration. Colloids Surf B Biointerfaces. 2012;95:1-9.

31. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. J Am Coll Cardiol. 2018;71(19):e127-248.

32. Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, et al. Strategies to address low drug solubility in discovery and development. Pharmacol Rev. 2013;65(1):315-499.

33. Wu CY, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res. 2005;22(1):11-23.

34. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, et al. Understanding pharmaceutical quality by design. AAPS J. 2014;16(4):771-83.