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Formulation And Evaluation Of Self Emulsifying Drug Delivery System Of Lopinavir

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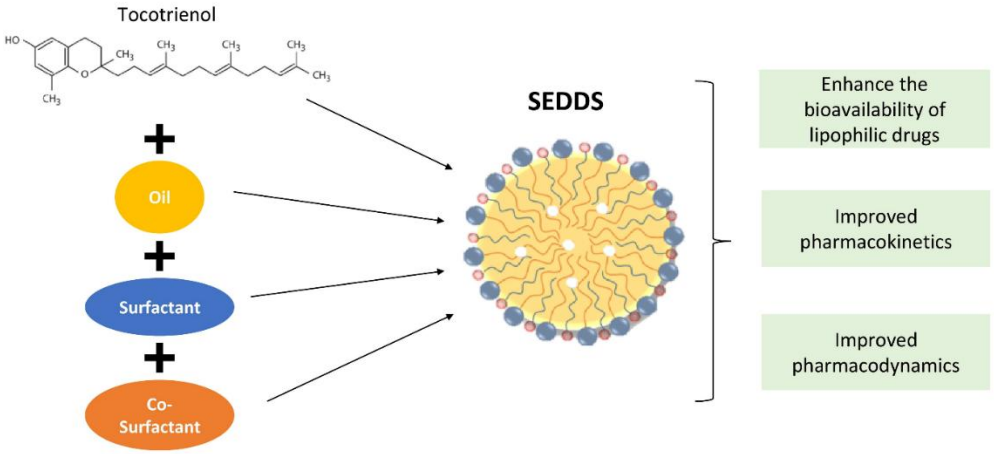
Abstract

Lopinavir, a protease inhibitor used in combination therapy for the treatment of HIV-1 infection, suffers from poor oral bioavailability due to its low aqueous solubility and extensive first-pass metabolism. These challenges necessitate innovative formulation strategies to improve its therapeutic efficacy. Self-Emulsifying Drug Delivery Systems (SEDDS) have gained attention as a promising lipid-based approach for enhancing the solubility and absorption of hydrophobic drugs like lopinavir. SEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water emulsions in the gastrointestinal tract, thereby improving drug dissolution and intestinal absorption.

This review provides a comprehensive overview of the formulation and evaluation strategies employed in the development of lopinavir-loaded SEDDS. It discusses the selection of excipients, phase diagram construction, emulsification behaviour, and formulation optimization techniques. Furthermore, the review highlights critical evaluation parameters such as droplet size, zeta potential, in vitro drug release, and stability studies. Recent advancements in nano-based self-emulsifying formulations, patent developments, and regulatory considerations are also examined. The findings underscore the potential of SEDDS to overcome the pharmacokinetic limitations of lopinavir and pave the way for improved oral delivery of antiretroviral drugs.



2. Introduction

Overview of HIV and role of Lopinavir

Human immunodeficiency virus (HIV) remains a major global health challenge. As of 2024, approximately 40.8 million people worldwide are living with HIV, with 1.3 million new infections and 630,000 AIDS-related deaths reported in that year[1]. Despite substantial advances in antiretroviral therapy (ART), HIV continues to cause significant morbidity and mortality. Lopinavir (LPV), a potent HIV-1 protease inhibitor, is a key component of many ART regimens. Administered typically in combination with ritonavir (RTV)—which inhibits CYP3A4-mediated metabolism—lopinavir helps suppress viral replication and maintain durable viral suppression[2].

Biopharmaceutical classification (BCS Class II) of Lopinavir

Lopinavir is classified as a Biopharmaceutics Classification System (BCS) Class II compound, characterized by high permeability but low aqueous solubility. Its solubility is around 3–4 µg/mL across physiological pH, and dissolution rate is the limiting factor in its oral absorption[3]. Drugs in this category are often hampered by erratic absorption and reduced oral bioavailability, making them suitable candidates for solubility-enhancing delivery systems.

Challenges in oral delivery

The oral bioavailability of lopinavir is compromised by multiple barriers. Its limited aqueous solubility results in poor dissolution in the gastrointestinal (GI) tract. In addition, first-pass metabolism by CYP3A4 significantly reduces systemic exposure[2]. To overcome this, lopinavir is co-administered with ritonavir, which can increase its bioavailability by up to 77-fold. However, this pharmacokinetic boosting strategy is associated with gastrointestinal side effects, drug–drug interactions, and concerns over long-term metabolic toxicity[3]. Even with boosting, plasma concentrations of lopinavir vary widely among patients due to differences in GI physiology, food intake, and enzyme expression.

Brief on lipid-based systems and intro to SEDDS

Lipid-based formulations have gained growing attention for enhancing the oral delivery of hydrophobic, poorly soluble drugs. Among these, Self-Emulsifying Drug Delivery Systems (SEDDS) are gaining prominence. SEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine emulsions—often nano-sized—upon dilution in GI fluids, under gentle agitation. This transformation enhances drug dissolution, maintains the drug in a solubilized state in the GI tract, and improves absorption and bioavailability.

SEDDS offer multiple benefits over conventional formulations. Their nano-sized droplets (<100 nm) provide a large interfacial surface area that enhances drug release and uptake. Lipid excipients can also stimulate bile secretion, further promoting solubilization. Additionally, potential lymphatic uptake may bypass first-pass metabolism[4]. These advantages make SEDDS attractive for solubility-challenged drugs like lopinavir, particularly where metabolic boosting strategies introduce adverse effects.

Literature reveals a growing body of studies supporting these benefits. For instance, self-nano-emulsifying systems (SNEDDS) for antiviral protease inhibitors, including lopinavir, have shown improved in vitro solubility and in vivo bioavailability in animal models[5]. Moreover, several antiviral drugs—ritonavir (Norvir®) and saquinavir (Fortovase®)—have been successfully formulated as commercial SEDDS products, demonstrating clinical viability[6].

Objective of the review

Given lopinavir's critical role in ART and its inherent delivery challenges, this review aims to provide a detailed examination of the use of SEDDS to improve its oral performance. Specifically, the review will:

1. **Characterize lopinavir's physicochemical and biopharmaceutical attributes**, elucidating factors that hinder its oral efficacy;
2. **Outline the principles and components of SEDDS**, including oils, surfactants, and co-surfactants, and classify them into SEDDS, self-micro emulsifying (SMEDDS), and self-nanoemulsifying (SNEDDS) systems;
3. **Survey formulation strategies** such as excipient screening, solubility testing, pseudo-ternary phase diagram construction, and Design of Experiments (DoE) approaches for optimizing lopinavir SEDDS;
4. **Assess evaluation parameters**, encompassing droplet size, polydispersity index (PDI), zeta potential, thermodynamic stability, in vitro release kinetics, and in vivo bioavailability studies;
5. **Highlight advancements and regulatory aspects**, including the development of solidified SEDDS (solid SNEDDS), patent landscapes, and considerations for scale-up and clinical translation;
6. **Identify challenges and future directions** in translating SEDDS for lopinavir into market-ready ART formulations, addressing stability, manufacturability, regulatory acceptance, and patient compliance.

By integrating cases from both liquid and solid SEDDS, in vitro and in vivo data, and emerging regulatory and industrial perspectives, this review will offer a comprehensive understanding of how SEDDS can enhance lopinavir delivery and optimize therapeutic outcomes in HIV management.

3. Self-Emulsifying Drug Delivery Systems (SEDDS): Fundamentals

3.1 Definition and Components

Self-emulsifying drug delivery systems (SEDDS) are *isotropic mixtures* of oils, surfactants, and co-surfactants/co-solvents that spontaneously form fine oil-in-water emulsions upon gentle agitation in gastrointestinal (GI) fluids—without the input of external energy such as sonication or high-shear mixing[7]. The essential components of a SEDDS formulation include:

- **Oils** (triglycerides like medium-chain triglycerides or long-chain fatty acids): act as carriers for lipophilic drugs, aid solubilization, and may promote lymphatic transport[8].
- **Surfactants** (e.g., non-ionic types like Cremophor®, Tween®, Labrasol®) reduce interfacial tension and stabilize the emulsion; typical concentrations can exceed 25–30 % w/w to ensure effective droplet formation[9].
- **Co-surfactants or co-solvents** (e.g., short-chain alcohols like ethanol or propylene glycol): boost surfactant efficiency, enhance drug loading, and modulate interfacial layers[10].

By carefully balancing the ratios of these components—often aided by pseudo-ternary phase

diagrams—SEDDS can be optimized for optimal emulsification performance and drug solubilization[7].

3.2 Mechanism of Emulsification

SEDDS rely on *low-energy self-emulsification* driven by spontaneous thermodynamic processes rather than external energy[11]. Upon dispersion in an aqueous environment such as stomach fluids with gentle agitation, surfactants and co-surfactants rapidly reduce surface tension. According to the *Bancroft rule*, surfactants that are more soluble in the continuous phase (typically water) form oil-in-water emulsions[12].

Co-surfactants further fluidize the interfacial film, enabling the generation of nano-sized droplets (often < 100 nm for SNEDDS)[10]. This leads to a high surface-area colloidal dispersion that maintains drugs in the solubilized state throughout GI transit. Furthermore, GI lipase-mediated digestion of lipid components can assist in sustained drug release and absorption[13].

3.3 Advantages and Disadvantages

Advantages

SEDDS offer multiple benefits for enhancing oral drug delivery:

- **Enhanced solubilization and dissolution**: Rapid formation of fine emulsions improves dissolution rates of poorly soluble drugs[7].
- **Improved oral bioavailability**: Increased droplet surface area and potential lymphatic uptake help bypass first-pass metabolism[7][14].
- **Reproducible absorption and reduced food effects**: Maintenance of drug in a dissolved form leads to consistent pharmacokinetics, often independent of food intake[7][15].
- **Thermodynamic stability**: Unlike emulsions that require energy-intensive production, SEDDS are stable due to their isotropic nature[7].
- **Ease of manufacture and scale-up**: SEDDS can be filled into capsules directly or solidified using carriers, facilitating industrial production[16].

Disadvantages

Despite these benefits, SEDDS face several challenges:

- **High surfactant loads** may cause GI irritation and raise toxicity concerns[6].
- **Stability issues** like phase separation, drug precipitation, and chemical degradation can occur during storage[6].
- **Low drug loading capacity** in conventional formulations limits their use with high-dose drugs[17].
- **Dependence on in vitro-in vivo correlation**: Proper profiling of formulation behavior under biorelevant digestion conditions is challenging[18].
- **Liquid SEDDS drawbacks**: Liquid formulations can leak from capsules and are unsuitable for moisture-sensitive drugs[6].

To address these issues, research has shifted toward **solid SEDDS** (S-SEDDS), where the liquid system is adsorbed onto or spray-dried with solid carriers. This hybrid form combines benefits of lipid solubilization with greater stability and dosage flexibility[16].

3.4 Classification: SEDDS, SNEDDS, SMEDDS

Lipid-based self-emulsifying systems are sub-categorized based on droplet size upon dispersion:

1. **SEDDS**: Droplet sizes typically >200 nm; generally produce coarse emulsions[15][7].
2. **SMEDDS (Self-Microemulsifying DDS)**: Produce microemulsions (~100–250 nm) with transparent appearance, thermodynamically stable[10].
3. **SNEDDS (Self-Nanoemulsifying DDS)**: Generate nano-emulsions (<100 nm) with rapid dispersion and superior absorption potential[19][7].

Classification depends on excipient composition, oil-to-surfactant/co-surfactant ratios, and the entropy of formulation[9]. Phase diagram mapping helps in identifying optimal formulations that yield the desired droplet size and mimic in vivo performance[19].

4.4 Justification for SEDDS Approach

Despite these advancements, many of these strategies face limitations such as scale-up complexity, stability concerns, and reliance on ritonavir boosting. **Self-Emulsifying Drug Delivery Systems (SEDDS)** offer a compelling alternative for improving lopinavir's oral delivery profile:

1. **Enhanced solubilization and dissolution**: Lipid-based SEDDS maintain lopinavir in a solubilized state in the GI tract, addressing its intrinsic solubility issues without the need for high doses of surfactants or solid carriers[21][20].
2. **Potential to bypass first-pass metabolism**: Lipid-drug complexes in SEDDS may be absorbed via the lymphatic pathway, reducing the drug's exposure to CYP3A4 and P-gp mediated metabolism[21].
3. **Elimination of ritonavir**: By improving bioavailability through physical-chemical enhancement, SEDDS may reduce or eliminate the need for ritonavir co-administration, thereby avoiding associated adverse effects and drug-drug interaction risks.
4. **Simplified manufacturing and dosage flexibility**: SEDDS can be delivered as liquid-filled soft gels or converted into solid form (S-SEDDS) by adsorption onto carriers—facilitating easy manufacturing and patient compliance[20].

5. **Improved pharmacokinetic reproducibility**: Compared to crystalline or amorphous solid systems, SEDDS often exhibit less intersubject variability and reduced food effect due to sustained solubilization and absorption behavior.

Initial proof-of-concept studies for lopinavir SEDDS demonstrate favorable outcomes: SNEDDS formulations produced droplet sizes under 60 nm, rapid dissolution (>95% in minutes), high entrapment efficiency, and significantly enhanced in vivo bioavailability compared to both pure drug and LPV/r formulations[23][22]. These findings support SEDDS as a powerful platform for enhancing lopinavir oral delivery.

5. Formulation Development of Lopinavir SEDDS

5.1 Selection of Excipients (Based on Solubility Studies)

Optimizing excipient selection is foundational to SEDDS development. In a key study by Patel et al., **Capmul® MCM C8 (medium-chain mono- and diglycerides)** was selected as the oil phase, **Cremophor® RH 40** as a surfactant, and **propylene glycol** as a co-surfactant. Solubility screenings showed that lopinavir had maximal solubility in Capmul MCM C8 among tested oils, and high drug loading was achieved using Cremophor RH 40 and propylene glycol.

The formulation achieved drug loading of approximately 160 mg per unit with optimized component ratios. The chosen surfactant and co-surfactant ensured both high solubilization and emulsification efficiency. This formulation was later transformed into a solid form via adsorption onto **Neusilin US2**, forming a solid SNEDDS (S-SNEDDS) system.

5.2 Pseudo-Ternary Phase Diagrams

To determine the optimal regions for self-emulsification, pseudo-ternary phase diagrams (SP-T diagrams) were constructed using the titration method. In the lopinavir SNEDDS study, six different phase diagrams were generated varying oil-to-surfactant/co-surfactant ratios. One optimized formulation (L-14) delivered droplet size of ~58 nm, dispersibility grade A (rapid clarity), and transmittance >85%, indicating an extensive nanoemulsifying region.

This mapping allowed identification of oil-surfactant mixtures that yield stable nanoemulsions and high entrapment efficiency (~98.9%). Such diagrams are central to selecting mixture ratios that balance drug loading, emulsification, and stability.

5.3 Emulsification Efficiency and Characterization

The optimized liquid SNEDDS (L-14) formulation produced globules of **58.18 ± 0.62 nm**, PDI ≈ **0.326**, zeta potential ≈ **−22.08 mV**, and entrapment efficiency ≈ **98.93 ± 1.18 %**. Transmission electron microscopy confirmed spherical droplets under 60 nm. Dissolution testing showed nearly **99 % of lopinavir released within 30 minutes**, significantly higher than suspension control in methylcellulose.

Solidification via adsorption onto Neusilin US2 retained nanoemulsion characteristics upon dispersion, with similar droplet sizes and zeta potentials, indicating preserved emulsification performance. In vitro and in vivo studies confirmed maintained performance of solid SNEDDS compared to liquid SNEDDS and commercial LPV/RTV formulations.

5.4 Optimization Techniques (DoE, Factorial Design)

Design-of-Experiments (DoE) strategies such as mixture designs were used by Patel et al. to optimize formulation variables. A **Scheffé mixture design** systematically explored the proportions of oil, surfactant, and co-surfactant, optimizing responses including droplet size, drug loading, and dissolution profile. The optimized liquid SNEDDS produced the smallest droplet size (~33 nm in rats study) with >95 % drug release in <15 min, and showed 2.97-fold and 1.54-fold increases in bioavailability over pure drug and LPV/RTV respectively.

Other studies using **central composite designs** for vitamin E-TPGS micelles of lopinavir (though not SEDDS) illustrate the broader utility of experimental design: optimizing parameters (e.g. TPGS:drug ratio, process speed) led to particle size ~91.7 nm, PDI 0.129, entrapment efficiency ~99.4 %, and ~3.17-fold improved bioavailability versus suspension control. This reinforces that DoE can guide excipient ratio choice and process conditions to maximize performance.

5.5 Solidification Strategies: S-SNEDDS and Platform Benefits

The transformation of optimized liquid SNEDDS into **solid S-SNEDDS** via adsorbent carriers (e.g. Neusilin US2) enables improved stability and handling while maintaining performance. Patel et al. reported that **amorphization of lopinavir** occurred in the adsorbed system, which improved dissolution rate and prevented crystallization. The resultant S-SNEDDS showed shelf life of ~2.85 years per ICH stability testing, and retention of globule size and zeta potential upon aqueous dilution.

Solid SNEDDS offer dose uniformity, reduced leakage risk, and easier scale-up and capsule filling, making them particularly attractive for commercial applications.

5.6 Comparative Performance: SEDDS vs Conventional and Other Platforms

Comparative evaluation highlights SEDDS advantages over other lopinavir delivery platforms.

Patel et al.'s S-SNEDDS achieved **nearly 3× bioavailability** (vs pure drug) and ~1.5× bioavailability over LPV/RTV tablets. Vitamin E-TPGS micelles improved relative bioavailability by ~3.17× over suspension. Solid dispersions using Soluplus improved bioavailability ~3.7× relative to pure drug. However, S-SNEDDS combine high entrapment, nano-size, fast dissolution, and long-term stability alongside elimination of ritonavir co-formulation.

Moreover, SEDDS development is scalable: liquid systems can be filled into soft-gels or encapsulated, and solid forms can be produced by spray-drying, extrusion, or adsorption—a clear advantage over micelles or solid dispersions that may require complex processing or stability control.

5.7 Formulation Summary

Table

Development Step	Key Findings
Solubility screening	Capmul MCM C8 (oil), Cremophor RH 40, propylene glycol identify optimal solubilization
Pseudo-ternary phase mapping	Selected formulation region yields <60 nm droplets, high transmittance, good dispersibility
DoE Optimization	Mixture design (Scheffé) tunes excipient proportions to minimize droplet size, maximize drug loading and release
Solidification to S-SNEDDS	Neusilin US2 adsorption yields amorphous lopinavir, long stability (~2.85 years), maintained nanoemulsion properties
Performance vs controls	~3× bioavailability vs pure drug; ~1.5× vs LPV/RTV; near-complete release ≤30 min
Comparative platforms	S-SNEDDS outperform vitamin E-TPGS micelles and Soluplus dispersions in combining bioavailability, stability, scalability

6. Evaluation Parameters of Lopinavir-Loaded SEDDS

6.1 Thermodynamic Stability

Thermodynamic stability testing ensures that SEDDS remains homogeneous without phase separation or drug precipitation during storage and upon dilution. Patel et al. subjected their lopinavir SNEDDS (formulation L-14) to centrifugation, heating–cooling, and freeze–thaw cycles. The system retained clarity, no phase separation, and consistent droplet size and transmittance across tests—indicating high thermodynamic stability[24]. Stability of the adsorbed solid SNEDDS (S-SNEDDS) paralleled that of its liquid counterpart; according to ICH guidelines, it maintained physical and chemical integrity with an estimated shelf life of ~2.85 years[25].

6.2 Droplet Size, PDI, and Zeta Potential

Droplet size, polydispersity index (PDI), and zeta potential critically influence in vivo performance:

- **Droplet size:** In the optimized LPV-SNEDDS (L-14), mean droplet size was **58.18 ± 0.62 nm** by dynamic light scattering, with HRTEM confirming spherical droplets under 60 nm[24]. Such sub-100 nm droplets offer high surface area and enhanced absorption.
- **PDI:** The PDI of **0.326 ± 0.005** reflects a narrow and homogenous droplet distribution[26].
- **Zeta potential:** The optimized system had a negative surface charge of **–22.08 ± 1.2 mV**, which promotes electrostatic repulsion and colloidal stability in GI conditions[24].

Comparatively, in nanoparticulate lipid carriers (NLCs) freeze-dried with trehalose, particle size ranged from ~287 nm, PDI ~0.41, and zeta potential ~–48.6 mV. While the magnitude of charge was higher, droplet size was significantly larger (~5× than SNEDDS)[21].

6.3 In Vitro Drug Release Studies

In vitro dissolution profiles assess how quickly lopinavir is released from SEDDS:

- The LPV-SNEDDS formulation L-14 released **>95% of lopinavir within 15 minutes** in simulated gastrointestinal conditions—markedly faster than suspension controls (<30 % release)[25].
- Another evaluation of LPV-loaded SNEDDS confirmed **~99% release within 30 minutes**, significantly higher than the drug–methylcellulose suspension comparator[24].

These rapid release profiles are attributed to efficient emulsification, small droplet size, and high entrapment efficiency.

6.4 In Vivo Evaluation

In vivo pharmacokinetic data validate the bioavailability benefit of optimized SEDDS:

- Patel et al. demonstrated that S-SNEDDS improved lopinavir bioavailability **2.97-fold** compared to pure drug, and **1.54-fold** relative to the commercial LPV/RTV formulation in Wistar rats[20][25].
- In LPV-NLC studies, although not SEDDS, a freeze-dried nanoparticulate carrier enhanced bioavailability **~6.98-fold** compared to suspension; droplet size ~287 nm, PDI ~0.41, zeta potential ~–

48.6 mV—supporting lipid systems for enhancing absorption[21].

Additionally, Caco-2 cellular uptake assays showed significantly increased intracellular lopinavir levels with SNEDDS compared to free drug, suggesting improved potential for intestinal absorption[24].

6.5 Comparative Studies with Conventional and Alternative Formulations

Comparisons across different platforms illustrate the relative strengths of SEDDS:

- **vs LPV/RTV tablets:** S-SNEDDS delivered ~1.54× greater bioavailability than the marketed combination, without ritonavir, reducing drug–drug interaction risk[25].
- **vs NLCs:** While NLCs yielded ~6.98× bioavailability enhancement, their larger size and complexity differ from the simpler SEDDS approach; still, SNEDDS showed superior size and faster release profiles[21].
- **vs solid dispersions/micelles:** Systems like Soluplus dispersions achieved ~3.7× relative bioavailability and vitamin E-TPGS micelles ~3.17× improvement; SNEDDS combine faster dissolution, smaller droplet size, and design flexibility for scale-up[21][22].

6.6 Additional Characterization and Quality Attributes

Some general studies on other SEDDS emphasize stability and dispersion quality:

- Notably, in quetiapine-loaded SEDDS, droplet size ~145 nm, PDI ~0.327, zeta potential ~–28 mV, and stable after centrifugation and freeze–thaw, reinforcing typical benchmarks of good nanoemulsions (stability and homogenous distribution)[26].

Summary

- **Thermodynamic stability** validated by stress tests ensures SEDDS durability and absence of phase changes.
- **Droplet size < 60 nm, PDI ≈ 0.3, and zeta potential around –20 mV to –30 mV** support high colloidal stability and bioavailability.
- **Rapid in vitro drug release (>95% within minutes)** correlates with efficient drug solubilization.
- **In vivo studies** confirm clear bioavailability enhancement versus pure drug and LPV/RTV formulation.
- **Comparative assessments** show SEDDS outperform other platforms on speed of release, droplet size, and scalable design, while offering potential reduction or elimination of ritonavir use.

These collective evaluation parameters provide compelling support for the utility of SEDDS in enhancing oral delivery of lopinavir, highlighting both mechanistic rationale and translational promise.

7. Recent Advances and Patents

7.1 Novel Lipids and Surfactant Systems

Recent research has focused on identifying innovative lipids and surfactants to enhance SEDDS performance. For instance, chemistries such as *vitamin E-TPGS* (D-α-tocopheryl polyethylene glycol succinate) have been utilized as surfactant/co-surfactant to enhance solubilization and permeability. A central composite design study with LPV-TPGS micelles (~92 nm size, ~3.2-fold bioavailability increase) showcases the benefit of surfactants that combine solubilizing and P-gp inhibitory functions[27].

Additionally, there is growing interest in **silica-lipid hybrid (SLH) microparticles**, where porous silica is coated with a lipid blend to offer controlled release and enhanced stability. While not yet applied to LPV, SLH technologies have improved loading and release of other lipophilic drugs, indicating promise for next-generation SEDDS[14].

7.2 Nano-based and Hybrid Approaches

Beyond conventional liquid and solid SEDDS, **hybrid nanoparticles** are generating interest:

- **In situ self-assembly nanoparticles (ISNPs)**: A subcutaneous LPV/RTV formulation that self-assembles into injectable nanoparticles achieved sustained plasma **AUC ~384 µg·h/mL** for LPV compared to ~10 µg/mL C_{max}, demonstrating longer half-life profiles[27].
- **Electrospun amorphous solid dispersions (ASDs)**: Fibers containing LPV/RTV have been fabricated by electrospinning; this approach enhances dissolution and stability and offers precise dose control, although it requires further biopharmaceutic evaluation for oral SEDDS[28].

These nano-enabled strategies aim to combine improved pharmacokinetics with solid oral dosage forms, potentially serving as orally administered S-SEDDS with advanced release characteristics.

7.3 Key Patents for Lopinavir SEDDS and Lipid Formulations

Patent landscaping reveals several filings involving LPV formulation advancements:

- **US20140066468A1** describes methods for creating *amorphous lopinavir* (and ritonavir) via solvent antisolvent precipitation — an enabling technology for high-energy drug forms with better solubility[29][30][31].
- **CA2403635A1** discloses the crystalline forms of lopinavir used in combination with ritonavir in fixed-dose regimens such as Kaletra/Aluvia[32].

- **US20220076137A1** encompasses claims around molecule-optimization frameworks (e.g., LPV, cinanserin) but focuses on lead optimization rather than SEDDS.

While direct patents on LPV SEDDS are limited—likely proprietary to industry—the development of amorphous APIs, lipid-surfactant blends and hybrid nanocarrier systems have patent coverage.

7.4 Patent and Technological Trends

Recent patent reviews in lipid drug delivery show an uptick in **solid lipid nanoparticles (SLNs)** and **self-nanoemulsifying oral lipid systems (SNOLS)**, with patents filed for increased stability, controlled release, and targeted delivery[33][14]. Though not LPV-specific, these technologies are directly translatable to developing improved SEDDS for lopinavir.

Furthermore, innovation in **solid oral combination therapies**, including LPV/RTV, continues with patents covering crystal polymorphs, ASD formulations, and stability improvements[30]. While these primarily protect ritonavir forms, they are relevant to SEDDS optimization in combination ARV regimens.

7.5 Summary of Technological Landscape

Innovation Category	Highlights
Novel surfactants	Vitamin E-TPGS micelles with dual solubility and P-gp inhibition[34]
Silica-lipid hybrids	SLH systems promise controlled release and stability[14]
ISNP injectable systems	Prolonged exposure LPV/RTV via self-assembling nanoparticles[27]
Amorphous solid dispersions	Electrospun LPV/RTV fibers for enhanced dissolution[28]
Patents for amorphous LPV	US20140066468A1 covers methods to generate amorphous lopinavir[31]
ARV fixed-dose formulations	CA2403635A1 details crystalline LPV/RTV for oral therapy[32]
Trend in lipid formulation patents	Increased SLNs, SNOLS, and polymorph patents[35]

8. Challenges, Limitations & Future Perspectives

◆ 8.1 Scale-up Issues

While laboratory-scale SEDDS formulations demonstrate excellent performance, scaling up to industrial production poses several challenges:

- **Manufacturing reproducibility**: At large scales, maintaining consistent droplet size, PDI, and zeta potential requires tightly controlled mixing, temperature, and shear conditions. Batch-to-batch variability may increase without stringent process controls. Experimental scale-up of polymeric and lipid nanoparticles has highlighted the need for precise equipment calibration and design adjustments during scale-up[36].
- **Solidification hurdles**: Converting liquid-SNEDDS into solid dosage forms (e.g. solid-SEDDS) through adsorption, spray drying, or hot-melt extrusion often leads to challenges such as drug crystallization or loss of nanoemulsion properties. Optimization of carrier and process parameters is essential to retain drug loading and release characteristics, yet is difficult to replicate on a manufacturing scale.
- **GMP-compliant production**: Good Manufacturing Practice (GMP) mandates require validated manufacturing processes, clean systems, and controlled environments. Lipid phases and surfactants must be handled to avoid contamination, and final dosage forms—particularly soft-gel capsules—must meet strict fill-weight and seal integrity specifications, increasing production complexity and costs.

◆ 8.2 Regulatory Barriers

Regulatory agencies such as the FDA and EMA pose significant expectations for novel delivery systems:

- **IND/NDA expectations**: Before human trials, Investigational New Drug (IND) applications require comprehensive characterization—physicochemical properties, stability, bioavailability, and reproducibility—often in large-animal models under GLP conditions[6]. CM&C elements such as composition, dissolution performance, and batch consistency must align with ICH Q8/Q9/Q10 guidelines.
- **Unclear classification**: Hybrid SEDDS, particularly solidified ones, may fall between novel excipient and drug delivery categories, complicating the regulatory pathway. Agencies may require additional data showing that nanoemulsion characteristics are retained post-manufacturing and in-use.
- **Analytical and safety data**: Regulators demand detailed stability studies—shelf-life predictions, lipid oxidation, and excipient-drug interaction data. Surfactants at high concentrations may pose gastrointestinal safety concerns; hence, specific toxicology studies might be required for components like Cremophor RH 40 or vitamin E-TPGS.

- **Patient compliance and dosage form**: Transitioning from liquid to solid (capsules/tablets) is preferred for patient acceptability, but involves validation of spray-drying or extrusion parameters, as outlined in SEDDS reviews[6].

◆ 8.3 Need for Human Trials

Despite encouraging preclinical data, human clinical trials are essential but currently limited:

- **Feasibility unmet**: Early-phase clinical studies (Phase I) have not yet evaluated lopinavir-loaded SEDDS, though LPV/RTV combination trials exist in other therapeutic areas like COVID-19[37]; SEDDS-based formulations require initial safety and pharmacokinetic bridging studies.
- **Design challenges**: Lopinavir bioavailability must be demonstrated against benchmark formulations (e.g. Kaletra®). Adaptive clinical trial designs may optimize sample sizes and endpoints, but phase-appropriate planning—bioequivalence vs. superiority—is necessary[38].
- **Clinical endpoints and compliance**: For ART, consistency in trough concentrations (C_min) and AUC is critical to viral suppression. SEDDS must show not just enhanced bioavailability, but also therapeutic equivalence or superiority with acceptable tolerability.
- **Patient populations**: Data must be obtained in both healthy volunteers and HIV-positive patients, including special populations (pediatrics, pregnancy), reflecting real-world use and varying GI conditions.

◆ 8.4 Future Perspectives

- **Process analytical technology (PAT)**: Incorporating real-time monitoring of droplet size and lipid content (using NIR or Raman spectroscopy) during manufacturing can support consistency and regulatory compliance.
- **Standardization and excipient guidelines**: Clear guidance from ICH or pharmacopeial chapters on nano-emulsions and lipid-based systems (e.g., a Q&A clarifying classification under GCP/GMP frameworks) could help developers meet filing requirements efficiently.
- **Clinical adoption**: If SEDDS formulations can eliminate ritonavir while maintaining therapeutic exposure, the safety and interaction profiles of ART regimens could significantly improve, enhancing patient quality of life.
- **Filing strategy**: Nanotechnology-based pharmaceuticals may follow the FDA's Nanotechnology Regulatory Science Research Plan, incorporating nonclinical bridging studies for structure-function demonstration.

9. Conclusion

The delivery of poorly water-soluble drugs like Lopinavir poses a significant challenge in oral antiretroviral therapy due to limitations in aqueous solubility, variable bioavailability, and extensive first-pass metabolism. Traditional formulations, even when co-administered with pharmacokinetic enhancers such as Ritonavir, often result in suboptimal and inconsistent therapeutic outcomes. These limitations have driven the exploration of advanced drug delivery technologies—particularly Self-Emulsifying Drug Delivery Systems (SEDDS).

SEDDS have emerged as a promising platform for enhancing the solubility and systemic availability of hydrophobic drugs. By forming fine oil-in-water emulsions or nanoemulsions upon mild agitation in gastrointestinal fluids, SEDDS facilitate rapid and consistent drug release, improve solubilization in vivo, and may even promote lymphatic absorption. For Lopinavir, these mechanisms offer the potential to bypass hepatic first-pass metabolism, reduce the dependence on Ritonavir, and achieve more stable plasma drug levels. Multiple preclinical studies have demonstrated that SEDDS formulations significantly enhance Lopinavir's in vitro dissolution and in vivo pharmacokinetics compared to conventional dosage forms.

Moreover, the modular nature of SEDDS formulation—where components such as oils, surfactants, and co-surfactants can be tuned—enables the design of highly optimized drug delivery systems tailored to Lopinavir's unique physicochemical characteristics. Current research also supports solid SEDDS development, which overcomes limitations of liquid formulations and improves patient compliance.

Looking forward, the incorporation of SEDDS in antiretroviral therapy could transform the landscape of HIV treatment by offering potent oral formulations with improved tolerability, reduced dosing frequency, and enhanced efficacy. If SEDDS can replace the need for pharmacokinetic boosters like Ritonavir, it would significantly lower the risk of drug–drug interactions and metabolic side effects—particularly beneficial in long-term HIV management.

However, regulatory acceptance, scale-up feasibility, and clinical validation remain crucial for translation. Robust human trials and quality-by-design manufacturing frameworks will be necessary to bring Lopinavir SEDDS from lab to clinic. With continued innovation, SEDDS-based delivery systems have the potential to reshape the pharmacotherapy of HIV and support the development of more effective and patient-friendly antiretroviral regimens.

References

1. Walmsley S, Christian MD. The role of lopinavir/ritonavir (Kaletra) in the management of HIV infected adults. Expert Rev Anti Infect

Ther. 2003 Oct;1(3):389-401. doi: 10.1586/14787210.1.3.389. Erratum in: Expert Rev Anti Infect Ther. 2004 Feb;2(1):164. PMID: 15482136. (https://pubmed.ncbi.nlm.nih.gov/15482136/)

2. Fayed ND, Arafa MF, Essa EA, El Maghraby GM. Lopinavir-menthol co-crystals for enhanced dissolution rate and intestinal absorption. J Drug Deliv Sci Technol. 2022 Aug;74:103587. doi: 10.1016/j.jddst.2022.103587. Epub 2022 Jul 11. PMID: 35845293; PMCID: PMC9272570. (https://pmc.ncbi.nlm.nih.gov/articles/PMC9272570/)
3. Salim M, Ramirez G, Clulow AJ, Hawley A, Boyd BJ. Implications of the Digestion of Milk-Based Formulations for the Solubilization of Lopinavir/Ritonavir in a Combination Therapy. Mol Pharm. 2023 Apr 3;20(4):2256-2265. doi: 10.1021/acs.molpharmaceut.3c00072. Epub 2023 Mar 14. PMID: 36919249; PMCID: PMC10074382. (https://pmc.ncbi.nlm.nih.gov/articles/PMC10074382)
4. Zaslavsky, J., Allen, C. A dataset of formulation compositions for self-emulsifying drug delivery systems. *Sci Data* **10**, 914 (2023). https://doi.org/10.1038/s41597-023-02812-w https://doi.org/10.1038/s41597-023-02812-w
5. Peng Zi, Cheng Zhang, Caoyun Ju, Zhigui Su, Yusheng Bao, Jie Gao, Juan Sun, Jiannan Lu, Can Zhang, Solubility and bioavailability enhancement study of lopinavir solid dispersion matrixed with a polymeric surfactant - Soluplus, European Journal of Pharmaceutical Sciences, Volume 134, 2019, Pages 233-245, ISSN 0928-0987, https://doi.org/10.1016/j.ejps.2019.04.022. (https://www.sciencedirect.com/science/article/pii/S0928098719301666)
6. Uttreja P, Karnik I, Adel Ali Youssef A, Narala N, Elkanayati RM, Baisa S, Alshammari ND, Banda S, Vemula SK, Repka MA. Self-Emulsifying Drug Delivery Systems (SEDDS): Transition from Liquid to Solid—A Comprehensive Review of Formulation, Characterization, Applications, and Future Trends. *Pharmaceutics*. 2025; 17(1):63. https://doi.org/10.3390/pharmaceutics17010063
7. kanjani, Brajesh & Garg, Ashish & Garg, Sweta. (2016). A review on Self Emulsifying Drug Delivery System. Asian Journal of Biomaterial Research. 2. (https://www.researchgate.net/publication/313438437_A_review_on_Self_Emulsifying_Drug_Delivery_System)
8. Review Article www.ajphr.com 2020, Volume 8, Issue 1 ISSN: 2321–3647 (https://ajphr.com/ajphrfiles/uploaddir/AJPHR_810072.pdf)
9. J. Fac. Pharm. Ankara / Ankara Ecz. Fak. Derg., 47(2): 705-718, 2023 Doi: 10.33483/jfpau.1244378 (https://dergipark.org.tr/tr/download/article-file/2925519)
10. A REVIEW ON SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEMS Nur alom Mondal, G. Lakshmi Devi*, Koruboyina shiva, Mangali mahender, Jvc sharma February 2021 IJSDR | Volume 6 Issue 2ISSN: 2455-2631 (https://www.ijsdr.org/papers/IJSDR2102035.pdf)
11. Cholakova, D., Vinarov, Z., Tcholakova, S., & Denkov, N. D. (2022). Self-emulsification in chemical and pharmaceutical technologies. Current Opinion in Colloid &Amp; Interface Science, 59, 101576. (https://doi.org/10.1016/j.cocis.2022.101576)
12. Bancroft, WD (1915). "The Theory of Emulsification, VI". *The Journal of Physical Chemistry*. **19** (6): 275–309. doi:10.1021/j150157a002.
13. Joyce P, Dening TJ, Meola TR, Schultz HB, Holm R, Thomas N, Prestidge CA. Solidification to improve the biopharmaceutical performance of SEDDS: Opportunities and challenges. Adv Drug Deliv Rev. 2019 Mar 1;142:102-117. doi: 10.1016/j.addr.2018.11.006. Epub 2018 Dec 4. PMID: 30529138. (https://pubmed.ncbi.nlm.nih.gov/30529138/)
14. Salawi A. Self-emulsifying drug delivery systems: a novel approach to deliver drugs. Drug Deliv. 2022 Dec;29(1):1811-1823. doi: 10.1080/10717544.2022.2083724. PMID: 35666090; PMCID: PMC9176699. (https://pmc.ncbi.nlm.nih.gov/articles/PMC9176699)
15. Review on Self Emulsifying Drug Delivery System: Novel Approach for Solubility Enhancement Patel Nitesh N.*1 , Rathva Sunil R1 ., Mr. Shah Viral H1 , Dr. Upadhyay Umesh M1 , Sigma institute Of Pharmacy1 , Department Of Pharmaceutics, Vadodara, Gujarat, INDIA Volume 1, issue 3 (2012), 1-12 , ISSN 2277-3657 International Journal of Pharmaceutical Research & Allied Sciences, (https://ijpras.com/storage/models/article/GoEdKr9ExtwCDD7w0u2YgVfanWi0222oCbkq5cpoOZoPaSD3fYmYmNBtrvxd/review-on-self-emulsifying-drug-delivery-system-novel-approach-for-solubility-enhancement.pdf)
16. Raman Kallakunta V, Dudhipala N, Nyavanandi D, Sarabu S, Yadav Janga K, Ajjarapu S, Bandari S, Repka MA. Formulation and processing of solid self-emulsifying drug delivery systems (HME S-SEDDS): A single-step manufacturing process via hot-melt extrusion technology through response surface methodology. Int J Pharm. 2023 Jun 25;641:123055. doi:

10.1016/j.ijpharm.2023.123055. Epub 2023 May 18. PMID: 37207857; PMCID: PMC10429704. (https://pmc.ncbi.nlm.nih.gov/articles/PMC10429704)

17. Park H, Ha ES, Kim MS. Current Status of Supersaturable Self-Emulsifying Drug Delivery Systems. Pharmaceutics. 2020 Apr 16;12(4):365. doi: 10.3390/pharmaceutics12040365. PMID: 32316199; PMCID: PMC7238279. (https://pmc.ncbi.nlm.nih.gov/articles/PMC7238279)
18. Fatouros DG; Nielsen FS; Douroumis D; Hadjileontiadis LJ; Mullertz A (August 2008). "In vitro-in vivo correlations of self-emulsifying drug delivery systems combining the dynamic lipolysis model and neuro-fuzzy networks". *Eur J Pharm Biopharm*. **69** (3): *887–98*. *doi*:*10.1016/j.ejpb.2008.01.022*. *PMID 18367386*. (https://www.sciencedirect.com/science/article/abs/pii/S0939641108000283?via%3Dihub)
19. Kadian R, Nanda A. A Comprehensive Insight on Self Emulsifying Drug Delivery Systems. Recent Adv Drug Deliv Formul. 2022;16(1):16-44. doi: 10.2174/2667387815666211207112803. PMID: 34875995. (https://pubmed.ncbi.nlm.nih.gov/34875995/)
20. Ravi PR, Vats R, Dalal V, Murthy AN. A hybrid design to optimize preparation of lopinavir loaded solid lipid nanoparticles and comparative pharmacokinetic evaluation with marketed lopinavir/ritonavir coformulation. J Pharm Pharmacol. 2014 Jul;66(7):912-26. doi: 10.1111/jphp.12217. Epub 2014 Feb 18. PMID: 24697749. (https://pubmed.ncbi.nlm.nih.gov/24697749/)
21. Khan AA, Mudassir J, Akhtar S, Murugaiyah V, Darwis Y. Freeze-Dried Lopinavir-Loaded Nanostructured Lipid Carriers for Enhanced Cellular Uptake and Bioavailability: Statistical Optimization, in Vitro and in Vivo Evaluations. Pharmaceutics. 2019 Feb 25;11(2):97. doi: 10.3390/pharmaceutics11020097. PMID: 30823545; PMCID: PMC6410192. (https://pmc.ncbi.nlm.nih.gov/articles/PMC6410192/)
22. Patel GM, Shelat PK, Lalwani AN. QbD based development of proliposome of lopinavir for improved oral bioavailability. Eur J Pharm Sci. 2017 Oct 15;108:50-61. doi: 10.1016/j.ejps.2016.08.057. Epub 2016 Aug 30. PMID: 27586019. (https://pubmed.ncbi.nlm.nih.gov/27586019/)
23. Klein CE, Chiu YL, Awni W, Zhu T, Heuser RS, Doan T, Breitenbach J, Morris JB, Brun SC, Hanna GJ. The tablet formulation of lopinavir/ritonavir provides similar bioavailability to the soft-gelatin capsule formulation with less pharmacokinetic variability and diminished food effect. J Acquir Immune Defic Syndr. 2007 Apr 1;44(4):401-10. doi: 10.1097/QAI.0b013e31803133c5. PMID: 17224848. (https://pubmed.ncbi.nlm.nih.gov/17224848/)
24. Khan AA, Akhtar S, Yadav Y, Atiya A, Alelwani W, Bannunah AM, Mahmood S. Lopinavir-Loaded Self-Nanoemulsifying Drug Delivery System for Enhanced Solubility: Development, Characterisation and Caco-2 Cell Uptake. Curr Drug Deliv. 2023;20(10):1474-1486. doi: 10.2174/1567201819666220817111054. PMID: 35980056. (https://pubmed.ncbi.nlm.nih.gov/35980056/)
25. Patel G, Shelat P, Lalwani A. Statistical modeling, optimization and characterization of solid self-nanoemulsifying drug delivery system of lopinavir using design of experiment. Drug Deliv. 2016 Oct;23(8):3027-3042. doi: 10.3109/10717544.2016.1141260. Epub 2016 Feb 16. PMID: 26882014. (https://pubmed.ncbi.nlm.nih.gov/26882014/)
26. Ayed OBH, Lassoued MA, Bahloul B, Sfar S. Self-emulsifying Drug Delivery System for Improved Dissolution and Oral Absorption of Quetiapine Fumarate: Investigation of Drug Release Mechanism and *In-vitro* Intestinal Permeability. Iran J Pharm Res. 2021 Summer;20(3):381-398. doi: 10.22037/ijpr.2021.114785.15032. PMID: 34903996; PMCID: PMC8653647. (https://pmc.ncbi.nlm.nih.gov/articles/PMC8653647/)
27. Tanaudommongkon I, Tanaudommongkon A, Dong X. Development of In Situ Self-Assembly Nanoparticles to Encapsulate Lopinavir and Ritonavir for Long-Acting Subcutaneous Injection. *Pharmaceutics*. 2021; 13(6):904. https://doi.org/10.3390/pharmaceutics13060904
28. Łyszczarz E, Sosna O, Srebro J, Rezka A, Majda D, Mendyk A. Electrospun Amorphous Solid Dispersions with Lopinavir and Ritonavir for Improved Solubility and Dissolution Rate. *Nanomaterials*. 2024; 14(19):1569. https://doi.org/10.3390/nano14191569
29. Anuj G. Agrawal, Ashok Kumar, Paraag S. Gide, Self emulsifying drug delivery system for enhanced solubility and dissolution of glipizide, Colloids and Surfaces B: Biointerfaces, Volume 126, 2015, Pages 553-560, ISSN 0927-7765, https://doi.org/10.1016/j.colsurfb.2014.11.022. (https://www.sciencedirect.com/science/article/pii/S0927776514006456)
30. WIPO Publication No. 946/1E ISBN 978-92-805-2162-7 (https://www.wipo.int/edocs/pubdocs/en/patents/946/wipo_pub_946.pdf)
31. United States Patent Application Publication Pub. No.: US 2014/0066468 A1 US 20140.066468A1 Parthasaradhi Reddy et al. Pub. Date: Mar. 6, 2014

AMORPHOUS FORM OF LOPINAVIR AND RITONAVIR, MIXTURE (https://patents.google.com/patent/US20140066468A1/en)\

32. INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT), World Intellectual Property Organization International Bureau WIPO OMp, International Publication Date 11 October 2001 (11.10.2001) PCT International Publication Number WO 01/74787 A3 (https://patents.google.com/patent/CA2403635A1/en)
33. IJRPC 2011, 1 Sunitha et al. ISSN: 2231–2781 828 INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY Available online at www.ijrpc.com NOVEL SELF-EMULSIFYING DRUG DELIVERY SYSTEM- AN APPROACH TO ENHANCE BIOAVAILABILITY OF POORLY WATER SOLUBLE DRUGS R. Sunitha1*, D. Satya Sireesha1 and M.V. L. Aparna (https://www.ijrpc.com/files/000012.pdf)
34. INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT), World Intellectual Property Organization International Bureau, International Publication Number, International Publication Date 27 August 2015 (27.08.2015), WO 2015/125082 Al (https://patentimages.storage.googleapis.com/92/7d/01/912c63de5397ad/WO2015125082A1.pdf)
35. Khatak, Dr & Dureja, Harish. (2015). Recent Techniques and Patents on Solid Lipid Nanoparticles as Novel Carrier for Drug Delivery. Recent Patents on Nanotechnology. 9. 150-177. 10.2174/1872210510999151126105754. (https://www.researchgate.net/publication/287108838_Recent_Techniques_and_Patents_on_Solid_Lipid_Nanoparticles_as_Novel_Carrier_for_Drug_Delivery)
36. Yedi Herdiana, Nasrul Wathoni, Shaharum Shamsuddin, Muchtaridi Muchtaridi, Scale-up polymeric-based nanoparticles drug delivery systems: Development and challenges, OpenNano, Volume 7, 2022, 100048, ISSN 2352-9520, https://doi.org/10.1016/j.onano.2022.100048. (https://www.sciencedirect.com/science/article/pii/S2352952022000111)
37. Alhumaid S, Al Mutair A, Al Alawi Z, Alhmeed N, Zaidi ARZ, Tobaiqy M. Efficacy and Safety of Lopinavir/Ritonavir for Treatment of COVID-19: A Systematic Review and Meta-Analysis. *Tropical Medicine and Infectious Disease*. 2020; 5(4):180. https://doi.org/10.3390/tropicalmed5040180 (https://www.mdpi.com/2414-6366/5/4/180)
38. Maharana, Rajib & Swain, Surya Kanta & Mahapatra, Santosh & Jena, Bikash Ranjan. (2024). Self-Emulsifying Drug Delivery Systems: Concept to Applications, Regulatory Issues, Recent Patents, Current Challenges and Future Directions. Current pharmaceutical biotechnology. 25. 10.2174/0113892010296223240612050639. (https://www.researchgate.net/publication/381660705_Self-Emulsifying_Drug_Delivery_Systems_Concept_to_Applications_Regulatory_Issues_Recent_Patents_Current_Challenges_and_Future_Directions)