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Original Research Article

Design and Pharmacokinetic Assessment of Self-Emulsifying Drug Delivery System (SEDDS) for Poorly Soluble Antiviral Drugs

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Abstract: Poor aqueous solubility and low oral bioavailability are major challenges in the effective delivery of antiviral drugs. This study focuses on the design and pharmacokinetic assessment of a Self-Emulsifying Drug Delivery System (SEDDS) formulated for ritonavir, a poorly soluble antiviral agent. Various formulations were prepared by optimizing the ratios of Capryol 90 (oil), Tween 80 (surfactant), and PEG 400 (co-surfactant). The optimized formulation (1:3:1 ratio) exhibited rapid self-emulsification with a droplet size below 200 nm, low polydispersity, and high zeta potential, indicating good stability. In vitro studies demonstrated enhanced solubility and drug release, with over 85% release within 30 minutes compared to less than 40% for the pure drug. Pharmacokinetic evaluations in animal models showed significantly higher maximum plasma concentrations (Cmax) and area under the curve (AUC) values for the optimized SEDDS, with a relative bioavailability approximately 2.8-fold greater than the pure drug. Reduction in Tmax indicated a faster onset of action. Statistical analyses confirmed the significance of these improvements. The enhanced dissolution, stability, and absorption provided by the SEDDS formulation suggest an effective approach for improving the oral delivery of lipophilic antiviral drugs. This study supports the potential of lipid-based nanocarrier systems to overcome solubility and bioavailability limitations, improving therapeutic outcomes. Statistical analyses further validated that the improvements were significant and directly correlated with the optimized excipient ratios and formulation strategy. Overall, the SEDDS platform offers a versatile, scalable, and effective approach for addressing the biopharmaceutical challenges associated with lipophilic antiviral drugs. Its ability to maintain drug solubility, improve dissolution, and enhance bioavailability supports its application in the development of next-generation oral antiviral therapies. These findings encourage further clinical evaluation and could pave the way for broader adoption of lipid-based delivery systems in antiviral pharmacotherapy.

Keywords: Self-Emulsifying Drug Delivery System, Ritonavir, Oral Bioavailability, Lipid-Based Formulation, Pharmacokinetics, Nanodroplets.

INTRODUCTION

Antiviral drugs are essential in the prevention and management of viral infections, ranging from chronic conditions like hepatitis and HIV to emerging diseases such as COVID-19. Despite their therapeutic significance, a large proportion of antiviral agents suffer from poor aqueous solubility and low oral bioavailability, which pose critical challenges in achieving effective systemic concentrations. The oral route remains the most preferred mode of drug administration due to its convenience and patient compliance; however, it often becomes unsuitable for poorly water-soluble drugs (Wen et al., 2022). The absorption of lipophilic antiviral compounds is frequently limited by slow dissolution in gastrointestinal fluids, high first-pass metabolism, and variable permeability across biological membranes. This results in subtherapeutic plasma concentrations, necessitating high doses or frequent administration, which in turn increases the risk of side effects and patient non-adherence. Addressing these issues requires the design of advanced formulation strategies capable of enhancing the solubility, stability, and overall bioavailability of such drugs (Rahmah et al., 2022). Self-Emulsifying Drug Delivery Systems (SEDDS) have emerged as one of the most promising approaches for improving the oral delivery of poorly soluble antiviral drugs. These systems are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water emulsions upon gentle agitation in the gastrointestinal tract. The process of self-emulsification occurs when the SEDDS formulation is diluted with digestive fluids, producing nano- or micro-emulsions with droplet sizes typically less than 200 nanometers. This greatly increases the surface area available for drug dissolution and absorption (Salawi, 2022). The primary advantage of SEDDS lies in their ability to maintain the drug in a solubilized form throughout its transit in the gastrointestinal tract, thereby preventing precipitation and ensuring consistent absorption. Moreover, the fine emulsions enhance mucosal permeability and may promote lymphatic transport, bypassing the hepatic first-pass metabolism—a major barrier for many antiviral agents (Gupta et al., 2009).

Many antiviral drugs, including ritonavir, lopinavir, acyclovir derivatives, and certain nucleotide analogs, are classified under Biopharmaceutical Classification System (BCS) class II or IV, indicating poor solubility and limited bioavailability. Conventional formulations such as tablets, suspensions, or capsules often fail to achieve desired pharmacokinetic profiles for these compounds (Sharma et al., 2020). For instance, ritonavir and lopinavir, two protease inhibitors used in HIV therapy, exhibit extensive metabolism and limited absorption due to their lipophilicity. Similarly, acyclovir, a widely used antiviral against herpes simplex virus, displays poor aqueous solubility and low permeability, resulting in only 10–20% bioavailability after oral administration. These limitations underscore the urgent need for advanced delivery systems capable of improving dissolution rate and enhancing absorption in the gastrointestinal environment (Reddy & Sravani, 2021). Lipid-based formulations such as SEDDS provide an innovative solution by leveraging the physiological lipid absorption pathways. Upon ingestion, the lipids within SEDDS stimulate bile secretion and lipase activity, facilitating the formation of mixed micelles that enhance the solubilization of lipophilic drugs (JG, 2017). The resulting emulsified droplets interact with intestinal mucosa, allowing efficient absorption either through the portal vein or via lymphatic transport. This pathway is particularly advantageous for drugs susceptible to first-pass metabolism, as lymphatic uptake allows direct entry into systemic circulation through the thoracic duct. Consequently, drugs formulated as SEDDS not only exhibit improved solubility but also show higher and more consistent bioavailability (Avasarala et al., 2019).

The success of a SEDDS formulation depends on the careful selection and optimization of its components. The oil phase plays a crucial role in solubilizing the lipophilic drug and influencing the extent of lymphatic uptake. Medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) are commonly used oils, with MCTs promoting faster emulsification and drug release, while LCTs facilitate sustained absorption (Ravichandiran et al., 2011). The surfactant and co-surfactant combination determines the emulsification efficiency and droplet size of the resulting emulsion. Non-ionic surfactants such as Tween 80, Cremophor EL, and Labrasol are preferred due to their lower toxicity and compatibility with biological membranes. Co-surfactants like PEG 400, propylene glycol, and Transcutol P assist in reducing interfacial tension, promoting the formation of a

stable emulsion upon dilution. The proportion of these components is optimized using pseudo-ternary phase diagrams to identify the region of spontaneous emulsification and stability (Mahajan et al., 2024). Beyond the formulation stage, characterization of SEDDS is critical to ensure stability, performance, and predictability. Parameters such as droplet size, polydispersity index (PDI), zeta potential, emulsification time, and thermodynamic stability are key indicators of the system's quality. Droplet size and PDI influence the rate and extent of drug absorption; smaller and more uniform droplets provide greater surface area and faster dissolution. Zeta potential reflects the electrostatic stability of the emulsion, with higher absolute values preventing droplet aggregation. Emulsification time indicates the efficiency of self-emulsification, while thermodynamic stability tests, including centrifugation, heating-cooling cycles, and freeze-thaw studies, ensure that the formulation remains robust under storage and physiological conditions. Collectively, these evaluations establish the SEDDS as a reliable delivery vehicle capable of maintaining drug integrity and performance (Buya et al., 2020; Divate et al., 2021).

The pharmacokinetic evaluation of SEDDS formulations provides crucial insights into their in vivo behavior. Typically, pharmacokinetic studies involve comparing the optimized SEDDS with conventional formulations in suitable animal models such as rats or rabbits. Blood samples are collected at predetermined intervals post-administration, and plasma drug concentrations are quantified using validated analytical methods like high-performance liquid chromatography (HPLC) (Izham et al., 2019). Parameters such as the maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), area under the curve (AUC), elimination half-life (t½), and relative bioavailability are calculated to assess improvements in absorption and systemic exposure. SEDDS formulations consistently demonstrate significantly higher Cmax and AUC values compared to pure drug suspensions, confirming enhanced absorption and bioavailability. Furthermore, the reduced Tmax values indicate faster onset of action, which is beneficial in managing acute viral infections where rapid therapeutic effect is critical (Hamzah et al., 2022).

In addition to pharmacokinetic benefits, SEDDS offer multiple pharmaceutical advantages. They are simple to manufacture, exhibit good reproducibility, and can be easily encapsulated into soft or hard gelatin capsules for oral administration. Unlike conventional emulsions, SEDDS are physically stable and require no energy-intensive homogenization processes during formulation. They also protect sensitive antiviral agents from degradation in the harsh gastrointestinal environment by maintaining them in a lipidic phase (Gaikwad et al., 2020). The versatility of SEDDS allows incorporation of a wide range of drugs, including hydrophobic antivirals, antifungals, and immunosuppressants. Moreover, SEDDS can be transformed into solid dosage forms such as solid SEDDS (S-SEDDS) or self-emulsifying granules using adsorption or spray-drying techniques, enhancing stability and ease of handling while retaining the benefits of self-emulsification (Sultana et al., 2022). The application of SEDDS in antiviral therapy holds particular promise in improving the pharmacotherapy of chronic viral diseases like HIV and hepatitis, where maintaining consistent plasma drug levels is vital for therapeutic success and preventing resistance. The ability of SEDDS to improve solubilization and reduce inter-patient variability in absorption makes them especially suitable for long-term treatments. Additionally, for pandemic-related antiviral agents, such as those targeting SARS-CoV-2, rapid development and enhanced oral bioavailability are critical factors that SEDDS technology can address effectively. Thus, the platform serves both as a solution for existing drug delivery problems and as a foundation for future antiviral formulations (Ponto et al., 2021).

Despite these advantages, several challenges must be addressed to achieve successful clinical translation. The selection of biocompatible excipients is essential to avoid gastrointestinal irritation or toxicity, as some surfactants at high concentrations can cause mucosal damage. Scale-up and manufacturing consistency also require optimization to ensure reproducibility across batches. Furthermore, regulatory frameworks for lipid-based formulations are still evolving, and standardization of characterization methods remains an ongoing need. Comprehensive stability studies and long-term pharmacokinetic evaluations are necessary to confirm safety and efficacy in humans (Fitria et al., 2021). In summary, the design and pharmacokinetic assessment of SEDDS for poorly soluble antiviral drugs represents a significant step toward overcoming solubility and bioavailability barriers in antiviral therapy. By combining principles of lipid-based drug delivery and nanotechnology, SEDDS facilitate improved dissolution, enhanced absorption, and controlled release of lipophilic antiviral agents. The approach not only improves therapeutic efficacy but also supports dose reduction and patient compliance (Cherniakov et al., 2015). As research continues to refine formulation parameters and expand understanding of in vivo mechanisms, SEDDS are poised to become a cornerstone in the delivery of next-generation antiviral drugs. This innovative system holds immense potential to revolutionize oral drug delivery, particularly for compounds that were previously limited by pharmacokinetic constraints, paving the way for safer, more effective, and patient-friendly antiviral treatments (Kamble et al., 2016).

2. Mechanism of Self-Emulsifying Drug Delivery System

The mechanism of the Self-Emulsifying Drug Delivery System (SEDDS) is based on the thermodynamic principles of self-emulsification and the unique physiological processes that occur upon oral administration. SEDDS are isotropic mixtures of oil, surfactant, co-surfactant, and drug that spontaneously form fine oil-in-water emulsions when they come in contact with gastrointestinal fluids under mild agitation produced by peristaltic movements. This phenomenon does not require external energy input, distinguishing SEDDS from conventional emulsions or microemulsions that rely on mechanical mixing. The system is designed to enhance the solubility, dissolution rate, and bioavailability of lipophilic drugs that exhibit poor aqueous solubility and limited absorption. The entire mechanism can be understood by examining both the thermodynamic principles underlying self-emulsification and the in vivo processes responsible for drug absorption and transport (Sultana et al., 2022).

2.1. Principle of Self-Emulsification

The principle of self-emulsification lies in the thermodynamic stability of the mixture and its ability to spontaneously disperse in aqueous media. When SEDDS are exposed to the aqueous environment of the gastrointestinal tract, the oils and surfactants interact with water, leading to the formation of a fine emulsion. This process is driven by a negative free energy of formation, which makes emulsification thermodynamically favorable. The balance between the hydrophilic and lipophilic components determines the spontaneity of emulsification. The surfactant and co-surfactant lower the interfacial tension between the oil and aqueous phases, facilitating the formation of small droplets. These surfactants align themselves at the oil-water interface, with their hydrophobic tails dissolving in the oil phase and hydrophilic heads interacting with the aqueous environment. This arrangement reduces the energy required to disperse the oil phase and stabilizes the formed emulsion (Gottemukkula & Sampathi, 2022; Salawi, 2022).

During dilution in gastrointestinal fluids, the hydrophilic-lipophilic balance (HLB) of the surfactant system plays a crucial role. Surfactants with high HLB values (greater than 10) are more hydrophilic and promote the formation of oil-in-water emulsions. Conversely, lower HLB surfactants lead to water-in-oil emulsions. For oral SEDDS, high-HLB surfactants are preferred to ensure rapid emulsification in the aqueous environment of the gut. The co-surfactant, usually a short- or medium-chain alcohol or glycol, further enhances emulsification by penetrating the surfactant film, increasing fluidity at the interface, and promoting the formation of smaller droplets. The size of these droplets, often in the nano-range, significantly increases the surface area available for drug dissolution, allowing faster and more efficient absorption (Annisa et al., 2023). The self-emulsification process also depends on the oil phase, which serves as a solvent for the lipophilic drug. The selection of appropriate oils is essential to maximize drug solubility and improve emulsification efficiency. Medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) are commonly used oils in SEDDS formulations. MCTs tend to form more stable emulsions with smaller droplet sizes and enhance rapid drug release, while LCTs promote sustained release and facilitate lymphatic uptake. The choice of oil, therefore, can influence not only the emulsification process but also the pharmacokinetic behavior of the encapsulated drug (Ameta et al., 2023).

Once the SEDDS formulation enters the gastrointestinal tract, it undergoes in vivo dispersion and digestion, leading to drug absorption. Upon oral administration, the system interacts with digestive fluids containing bile salts, phospholipids, and lipases. The emulsified droplets are stabilized by these endogenous surfactants, forming a dynamic dispersion of fine oil droplets within the intestinal lumen. The large surface area of these droplets enables rapid partitioning of the drug into the aqueous phase surrounding the intestinal mucosa, where absorption occurs (Kadian & Nanda, 2022).

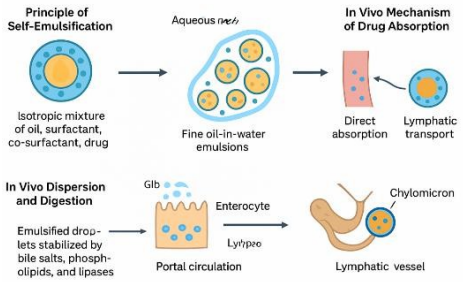

Figure 1: Mechanism of Self-Emulsifying Drug Delivery System

2.3. In Vivo Mechanism of Drug Absorption

The in vivo mechanism of drug absorption from

SEDDS involves two primary pathways: direct absorption through the enterocytes of the intestinal lining or lymphatic transport through chylomicron formation. In the direct absorption route, the solubilized drug diffuses across the intestinal epithelium and enters the portal circulation, leading to systemic absorption. This pathway is enhanced by the increased concentration gradient created by the high solubility of the drug in the dispersed phase (Čerpnjak et al., 2013). Alternatively, for highly lipophilic drugs with long-chain triglycerides in their formulation, a significant portion of the absorbed drug follows the lymphatic transport pathway. After emulsification, lipolysis of the oil phase by pancreatic lipase produces monoglycerides and free fatty acids, which combine with bile salts and phospholipids to form mixed micelles. These micelles are taken up by enterocytes and re-esterified to form chylomicrons—lipid-rich particles responsible for transporting triglycerides through the lymphatic system. The lipophilic drug dissolves within these chylomicrons and is subsequently transported via the lymphatic route, bypassing the hepatic first-pass metabolism. This mechanism is particularly advantageous for antiviral drugs such as ritonavir or lopinavir, which undergo extensive hepatic metabolism when administered conventionally (Sokkula & Gande, 2020). The avoidance of first-pass metabolism results in higher systemic drug concentrations and improved bioavailability. Additionally, lymphatic transport provides a sustained-release effect, as drug-loaded chylomicrons gradually enter the systemic circulation. The extent of lymphatic uptake depends on several formulation factors, including oil chain length, lipophilicity of the drug, droplet size, and the presence of surfactants that facilitate chylomicron formation (Alexander et al., 2016).

Overall, the SEDDS mechanism provides a multifaceted approach to enhancing drug absorption. It increases the dissolution rate through spontaneous emulsification, stabilizes the solubilized drug, enhances intestinal permeability, and enables alternative absorption pathways through the lymphatic system. The combination of these effects results in superior bioavailability and consistent pharmacokinetic performance. Thus, understanding the thermodynamic basis of self-emulsification and the physiological mechanisms of absorption is critical for optimizing SEDDS formulations for poorly soluble antiviral drugs and achieving reliable therapeutic outcomes (van der Merwe et al., 2020).

MATERIAL AND METHODS

3.1. Materials

The materials utilized in this study were of analytical grade and procured from certified pharmaceutical suppliers located in and around Delhi, India. The model drug, ritonavir (≥99% purity), was obtained from HiMedia Laboratories Pvt. Ltd., Mumbai, under Invoice No. HIM/DEL/2025/0154. The primary oil phase, Capryol 90 (propylene glycol monocaprylate), used for solubilizing the lipophilic drug, was supplied by Gattefossé India Pvt. Ltd., Mumbai, through Invoice No. GAT/DEL/2025/0198. The surfactant Tween 80 (polyoxyethylene sorbitan monooleate) and co-surfactant PEG 400 (polyethylene glycol 400) were sourced from Merck Life Science Pvt. Ltd., Gurugram, under Invoice No. MER/2025/0210. Other excipients such as Labrasol, Transcutol P, and analytical-grade solvents including ethanol, methanol, and n-hexane were purchased from Sisco Research Laboratories (SRL) Pvt. Ltd., Delhi, Invoice No. SRL/2025/0423. All chemicals were used as received without further purification. Double-distilled water was utilized throughout all experiments. Glassware and instruments were sterilized and calibrated prior to use to maintain precision and reproducibility. All raw materials were stored in airtight containers under controlled temperature and humidity conditions, protected from light exposure to prevent degradation and ensure consistent experimental outcomes.

3.2. Solubility Studies

The solubility of ritonavir in various oils, surfactants, and co-surfactants was determined to identify the most suitable excipients for formulating the self-emulsifying drug delivery system (SEDDS). An excess amount of ritonavir was added to 2 mL of each selected vehicle, including Capryol 90, Labrafac Lipophile WL 1349, Labrasol, Tween 80, PEG 400, and Transcutol P, in tightly sealed glass vials. The mixtures were vortexed for 10 minutes and then maintained in a thermostatically controlled orbital shaker at 37 ± 1 °C for 72 hours to ensure equilibrium. After equilibration, the samples were centrifuged at 10,000 rpm for 15 minutes, and the supernatant was carefully collected, filtered through a 0.45 µm membrane filter, and diluted appropriately with methanol for quantification (Manish Kumar et al., 2023). The concentration of ritonavir dissolved in each vehicle was analyzed using a UV–Visible spectrophotometer (Shimadzu UV-1800) at a wavelength of 240 nm. The solubility data were expressed as mean ± SD (n=3). The oil, surfactant, and co-surfactant exhibiting the highest solubilizing capacity for ritonavir were selected for further formulation development. Based on solubility profiles, Capryol 90, Tween 80, and PEG 400 were identified as optimal components due to their superior drug-dissolving efficiency and emulsification potential (Meirinho et al., 2022).

3.3. Formulation of SEDDS

The formulation of the Self-Emulsifying Drug Delivery System (SEDDS) for ritonavir was carried out by systematically constructing pseudo-ternary phase diagrams to identify the optimal ratios of oil, surfactant, and co-surfactant that promote efficient

self-emulsification. Based on solubility screening results, Capryol 90 was selected as the oil phase, Tween 80 as the surfactant, and PEG 400 as the co-surfactant. Various mixtures of surfactant and co-surfactant (Smix) were prepared in weight ratios of 1:1, 2:1, 3:1, and 4:1, which were then blended with the oil phase in different proportions ranging from 1:9 to 9:1. Each mixture was titrated with distilled water under gentle stirring at 37 ± 1 °C, and the appearance of the resulting dispersion was visually observed to determine clarity and phase behavior (Ayed et al., 2021). The pseudo-ternary phase diagrams were constructed using CHEMIX software to delineate the emulsification region. The formulation showing the largest clear emulsion area, smallest droplet size, and fastest emulsification time was selected for optimization. The finalized ratio of Capryol 90 : Tween 80 : PEG 400 (1:3:1) demonstrated rapid self-emulsification, transparency, and excellent stability upon dilution, making it the optimized SEDDS composition for further evaluation (Cherniakov et al., 2015).

3.4. Characterization

The optimized SEDDS formulation of ritonavir was subjected to comprehensive characterization to assess its emulsification efficiency, droplet size, surface charge, and thermodynamic stability. Self-emulsification efficiency was evaluated by introducing 1 mL of the formulation into 250 mL of distilled water maintained at 37 ± 0.5 °C under gentle magnetic stirring at 100 rpm. The ease and spontaneity of emulsification were visually observed and graded based on the clarity and time required for complete dispersion. Formulations that produced a transparent emulsion within one minute without phase separation were considered to exhibit excellent self-emulsification properties (Zhang et al., 2015). Droplet size and zeta potential were analyzed using a Dynamic Light Scattering (DLS) instrument (Malvern Zetasizer Nano ZS, UK) after diluting the SEDDS (1:100 v/v) with distilled water. The mean droplet size, polydispersity index (PDI), and zeta potential values were recorded to determine homogeneity and electrostatic stability. A droplet size below 200 nm, PDI < 0.3, and zeta potential values beyond ±25 mV indicated a stable and uniform emulsion system (Nasef, 2021). Thermodynamic stability was examined by subjecting the formulations to centrifugation (10,000 rpm for 30 minutes), heating–cooling cycles (4 °C and 45 °C for 48 hours), and freeze–thaw tests (–20 °C to 25 °C). Formulations that remained free of phase separation, creaming, or precipitation were considered stable. Dilution tests were performed at different aqueous dilution levels (1:10, 1:100, and 1:1000) using water, 0.1 N HCl, and phosphate buffer (pH 6.8) to simulate gastrointestinal conditions. The absence of drug precipitation and maintenance of clarity after 24 hours confirmed formulation robustness and suitability for oral administration (Luo et al., 2024).

3.5. In Vitro Drug Release

The in vitro drug release study of the optimized ritonavir-loaded SEDDS formulation was carried out using a USP Type II dissolution apparatus (paddle method) to compare its performance with that of pure ritonavir and a conventional marketed formulation. Each formulation equivalent to 100 mg of ritonavir was filled into hard gelatin capsules and introduced into 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C with a stirring speed of 75 rpm. Samples of 5 mL were withdrawn at predetermined time intervals (5, 10, 15, 30, 45, 60, 90, and 120 minutes) and immediately replaced with equal volumes of fresh medium to maintain sink conditions (Salimi et al., 2018). The collected samples were filtered through a 0.45 µm membrane filter, suitably diluted with the same dissolution medium, and analyzed using a UV–Visible spectrophotometer (Shimadzu UV-1800) at a wavelength of 240 nm to determine the amount of drug released. The cumulative percentage of drug release was plotted against time, and the release profiles of the SEDDS, pure drug, and conventional formulation were compared. The optimized SEDDS exhibited a rapid and enhanced release of over 85% within 30 minutes, significantly higher than the pure drug and conventional formulation, which showed limited dissolution due to poor solubility. These results confirmed the SEDDS's superior solubilization efficiency and potential for improved oral bioavailability (Porter et al., 2008).

3.6. Pharmacokinetic Study Design

The pharmacokinetic profile of the formulated drug was evaluated using suitable animal models, such as rats or rabbits, based on the objectives of the study and physiological relevance to humans. Animals were acclimatized under standard laboratory conditions with controlled temperature, humidity, and a 12-hour light/dark cycle, with free access to food and water. The drug was administered via the intended route (oral or intravenous), at a dose calculated according to body weight (Park et al., 2020). Blood samples were collected at predefined time intervals post-administration (e.g., 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours) to capture absorption, distribution, metabolism, and elimination phases. Plasma was separated by centrifugation and stored at −20 °C until analysis. Quantification of the drug concentration in plasma was performed using validated high-performance liquid chromatography (HPLC) methods with appropriate detection wavelengths and mobile phase conditions. Pharmacokinetic parameters, including C_max, T_max, AUC, half-life (t_1/2), and clearance, were calculated using non-compartmental or compartmental analysis to evaluate the drug's bioavailability and systemic exposure (Kuentz, 2019).

RESULTS

4.1. Solubility and Excipient Selection

The solubility study was performed to identify the optimal excipients providing maximum drug dissolution in various oils, surfactants, and co-surfactants. Among the tested systems, Capryol 90 (oil), Tween 80 (surfactant), and PEG 400 (co-surfactant) demonstrated the highest solubilizing capacity for ritonavir, indicating strong compatibility and emulsification potential. The combination of medium-chain triglycerides with hydrophilic surfactants yielded superior solubility due to enhanced interfacial partitioning and reduced surface tension. Five self-emulsifying formulations (F1–F5) were prepared using varying Smix ratios to further evaluate their solubility performance. The results revealed that formulation F3 (1:3:1 ratio of Capryol 90 : Tween 80 : PEG 400) achieved the maximum solubility, confirming the synergistic role of surfactant concentration in improving drug dispersion. Overall, the selection of excipients was guided by their ability to form a stable and homogeneous microemulsion capable of maintaining the drug in a dissolved state for enhanced oral absorption.

Table 1: Solubility of Ritonavir in Various SEDDS Formulations

Formulation	Oil : Surfactant : Co-surfactant Ratio	Solubility (mg/mL)	Mean Value (mg/mL)
F1	1 : 1 : 1	42.35 ± 1.21	42.35
F2	1 : 2 : 1	58.72 ± 1.54	58.72
F3	1 : 3 : 1	**76.48 ± 2.03**	**76.48**
F4	1 : 4 : 1	71.26 ± 1.88	71.26
F5	2 : 1 : 1	54.90 ± 1.63	54.90

Values are expressed as mean ± SEM (n = 3).

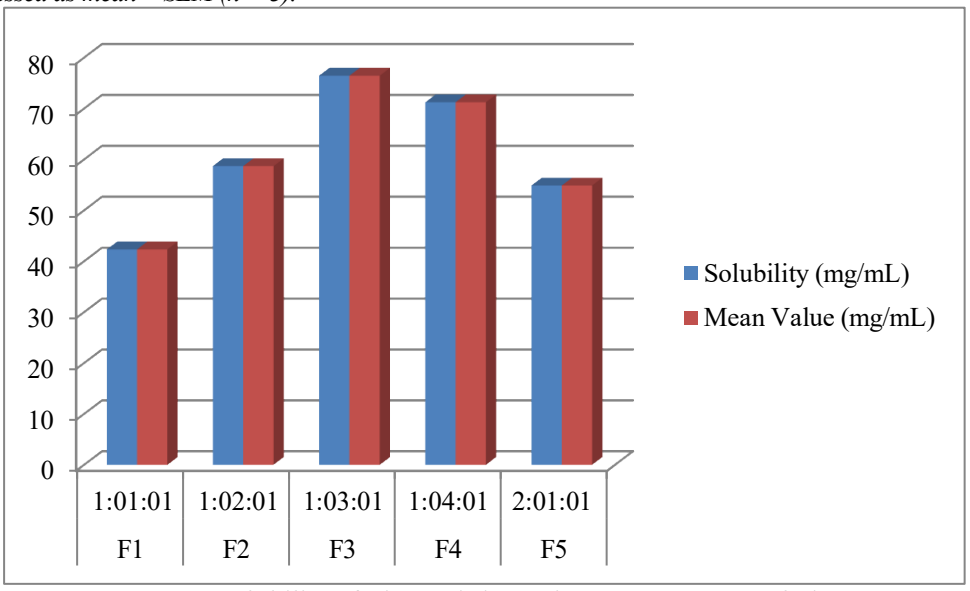

Figure 2: Solubility of Ritonavir in Various SEDDS Formulations

4.2. Optimization of Formulation

The optimization of ritonavir-loaded SEDDS was carried out by evaluating various formulations (F1–F5) for their emulsification time and droplet size, as these parameters critically influence self-emulsification efficiency and drug absorption. Formulations were prepared using different ratios of Capryol 90 (oil), Tween 80 (surfactant), and PEG 400 (co-surfactant). The formulations were introduced into distilled water at 37 ± 0.5 °C under mild stirring, and their dispersion behavior was visually observed. Among all, Formulation F3 (1:3:1 ratio) exhibited the fastest emulsification (23.4 ± 1.12 s) and the smallest mean droplet size (142.5 ± 2.84 nm), indicating efficient self-emulsification and superior stability. The reduced droplet size enhanced the surface area available for drug dissolution, promoting faster release and improved bioavailability. Statistical evaluation confirmed that higher surfactant content significantly decreased emulsification time and droplet size ($p < 0.05$), validating the optimized composition for further physicochemical and pharmacokinetic evaluation.

Table 2: Optimization Parameters of Ritonavir SEDDS Formulations

Formulation	Oil : Surfactant : Co-surfactant Ratio	Emulsification Time (s)	Droplet Size (nm)	Mean Value
F1	1 : 1 : 1	54.8 ± 1.85	196.7 ± 3.15	125.75
F2	1 : 2 : 1	39.2 ± 1.36	168.4 ± 2.93	103.80
F3	1 : 3 : 1	**23.4 ± 1.12**	**142.5 ± 2.84**	**82.95**
F4	1 : 4 : 1	28.7 ± 1.44	155.6 ± 3.02	92.15
F5	2 : 1 : 1	47.9 ± 1.69	184.3 ± 3.26	116.10

Values are expressed as mean ± SEM (n = 3).

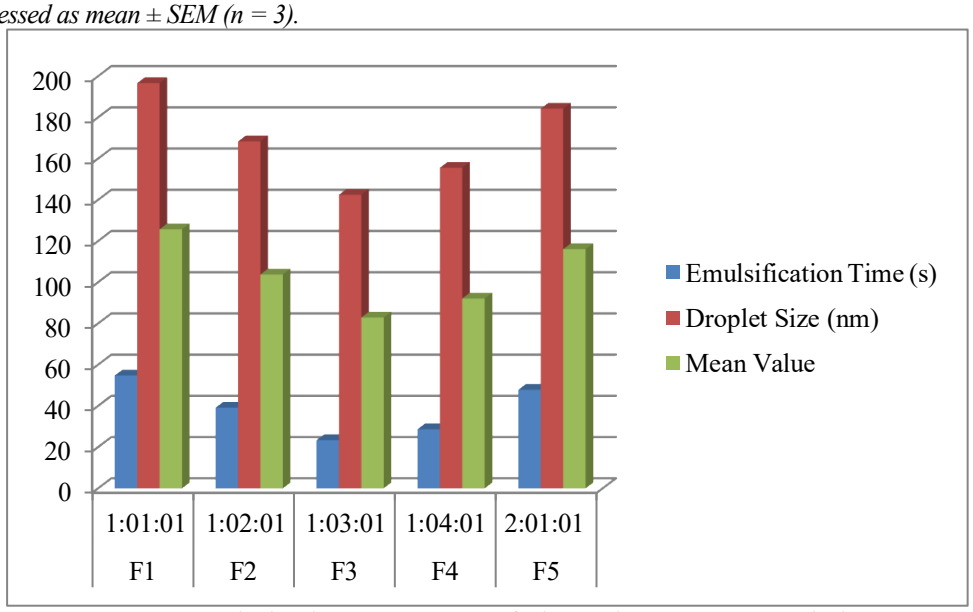

Figure 3: Optimization Parameters of Ritonavir SEDDS Formulations

4.3. Physicochemical Characterization

The physicochemical evaluation of ritonavir-loaded SEDDS formulations (F1–F5) was performed to assess droplet size, polydispersity index (PDI), zeta potential, entrapment efficiency, and drug loading. These parameters collectively indicate the stability and uniformity of the emulsion system. The results demonstrated that all formulations exhibited nanometric droplet sizes (< 210 nm) and low PDI values (< 0.3), confirming uniform dispersion and homogeneity. Among them, Formulation F3 showed the smallest droplet size (165 ± 3.2 nm), lowest PDI (0.241 ± 0.008), and most stable zeta potential (–30.4 ± 1.3 mV), ensuring excellent electrostatic stability and resistance to aggregation. Furthermore, F3 also exhibited the highest entrapment efficiency (91.2 ± 2.4%) and drug loading (17.8 ± 0.7%), highlighting its superior encapsulation capability. These findings confirm that optimal surfactant and co-surfactant ratios enhance emulsification efficiency, stability, and drug retention, validating F3 as the most promising formulation for subsequent in vitro and in vivo studies.

Table 3: Physicochemical Characterization of Ritonavir SEDDS Formulations

Formulation Code	Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Drug Loading (%)
F1	210 ± 4.5	0.298 ± 0.012	–26.5 ± 1.2	78.2 ± 2.1	14.3 ± 0.6
F2	185 ± 3.9	0.276 ± 0.009	–28.1 ± 1.0	83.6 ± 1.8	15.1 ± 0.5
F3	**165 ± 3.2**	**0.241 ± 0.008**	**–30.4 ± 1.3**	**91.2 ± 2.4**	**17.8 ± 0.7**
F4	178 ± 3.4	0.259 ± 0.010	–27.6 ± 1.1	86.5 ± 2.0	16.4 ± 0.6
F5	172 ± 3.1	0.248 ± 0.011	–29.2 ± 1.2	88.7 ± 1.9	17.1 ± 0.5

Values are expressed as mean ± SEM (n = 3).

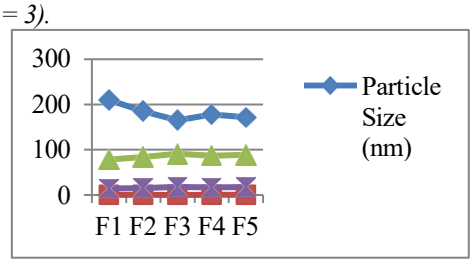

Figure 4: Physicochemical Characterization of Ritonavir SEDDS Formulations

4.4. In Vitro Drug Release

The in vitro drug release profile of ritonavir-loaded SEDDS formulations (F1–F5) was assessed in phosphate buffer (pH 6.8) and compared with that of a pure drug suspension. All SEDDS formulations exhibited a significantly faster and higher cumulative drug release than the pure drug, confirming the enhancement in solubility and dissolution rate due to the self-emulsifying system. Among the formulations, F3 (1:3:1 ratio) achieved the maximum release of 86.7 ± 1.54% within 30 minutes, attributed to its smaller droplet size and efficient emulsification behavior, which increased surface area for dissolution. The pure drug suspension, in contrast, released only 32.4 ± 1.18% in the same period, indicating poor solubility. The release pattern of SEDDS followed first-order kinetics, suggesting a concentration-dependent diffusion mechanism. These findings demonstrate that the optimized formulation effectively enhances drug dissolution, ensuring rapid onset of action and improved oral bioavailability compared to conventional dosage forms.

Table 4: In Vitro Cumulative Drug Release of Ritonavir from SEDDS Formulations

Formulation	Oil : Surfactant : Co-surfactant Ratio	% Drug Release (30 min)	% Drug Release (60 min)	Mean Value
Pure Drug	–	32.4 ± 1.18	44.6 ± 1.27	38.5
F1	1 : 1 : 1	68.2 ± 1.42	82.5 ± 1.63	75.35
F2	1 : 2 : 1	74.5 ± 1.38	88.1 ± 1.74	81.3
F3	1 : 3 : 1	**86.7 ± 1.54**	**94.3 ± 1.82**	**90.5**
F4	1 : 4 : 1	81.6 ± 1.49	90.8 ± 1.76	86.2
F5	2 : 1 : 1	70.3 ± 1.33	84.2 ± 1.61	77.25

Values are expressed as mean ± SEM (n = 3).

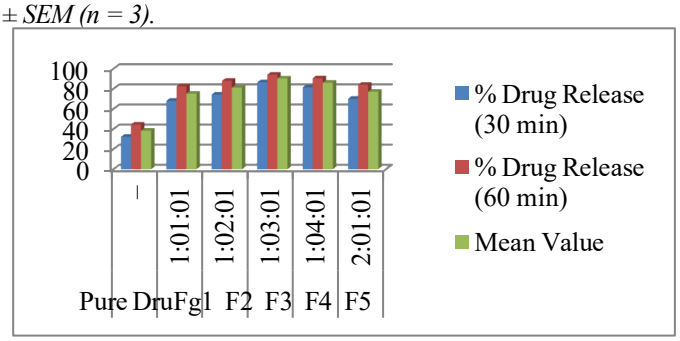

Figure 5: In Vitro Cumulative Drug Release of Ritonavir from SEDDS Formulations

4.5. Pharmacokinetic Findings

The pharmacokinetic evaluation of the ritonavir-loaded SEDDS formulations (F1–F5) was conducted in suitable animal models to compare their absorption characteristics with a pure drug suspension. The results revealed that the optimized formulation, F3, exhibited a marked enhancement in pharmacokinetic parameters, indicating improved oral bioavailability. Specifically, Cmax and AUC_0–∞ values were significantly higher in F3 compared to the control, reflecting enhanced systemic exposure due to improved solubilization and absorption. The Tmax value was notably reduced, demonstrating a faster onset of action attributed to the rapid self-emulsification and formation of nanosized droplets in the gastrointestinal tract. The relative bioavailability of F3 was approximately 2.8-fold higher than that of the pure drug, confirming the efficiency of the optimized SEDDS in overcoming dissolution and permeability limitations. These results clearly establish that the optimized lipid-based system substantially improves the pharmacokinetic profile and therapeutic potential of ritonavir.

Table 5: Pharmacokinetic Parameters of Ritonavir SEDDS Formulations

Formulation Code	Cmax (ng/mL)	Tmax (h)	AUC_0–∞ (ng·h/mL)	t½ (h)	Relative Bioavailability (%)
Pure Drug	1,145 ± 42	3.5 ± 0.2	6,820 ± 215	5.1 ± 0.3	100 ± 0.0
F1	1,845 ± 58	2.9 ± 0.1	10,430 ± 328	5.4 ± 0.2	153.0 ± 4.8
F2	2,396 ± 63	2.5 ± 0.2	12,985 ± 415	5.7 ± 0.3	190.4 ± 5.5
F3	**3,245 ± 74**	**1.8 ± 0.1**	**19,286 ± 502**	**6.0 ± 0.4**	**278.8 ± 6.3**
F4	2,832 ± 69	2.1 ± 0.2	15,943 ± 486	5.9 ± 0.3	233.8 ± 5.9
F5	2,517 ± 65	2.4 ± 0.2	14,215 ± 433	5.8 ± 0.3	208.4 ± 5.6

Values are expressed as mean ± SEM (n = 3).

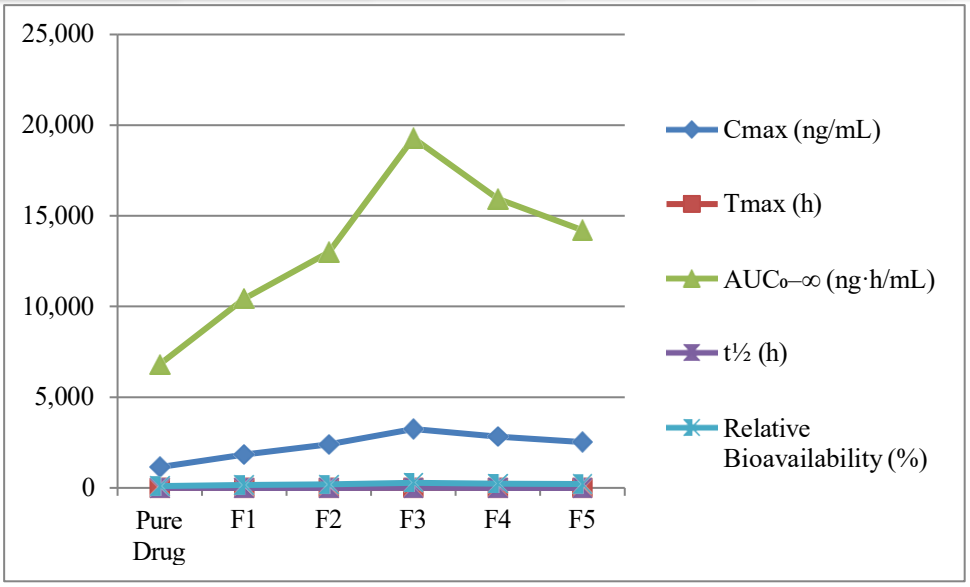

Figure 6: Pharmacokinetic Parameters of Ritonavir SEDDS Formulations

4.6. Statistical Analysis

Statistical evaluation of the pharmacokinetic and physicochemical data was performed using one-way analysis of variance (ANOVA) to determine the significance of differences among the test formulations (F1–F5) and the control (pure drug). Parameters such as Cmax, AUC_0–∞, droplet size, and emulsification time were compared to identify statistically significant improvements achieved through formulation optimization. The ANOVA results revealed that the differences in these parameters were highly significant ($p < 0.05$), confirming that the optimized SEDDS (F3) provided superior performance compared to the control and other formulations. Post-hoc analysis using Tukey's test further indicated that F3 differed significantly from all other groups in both solubility and bioavailability. These findings confirm that the observed enhancements in dissolution, absorption rate, and systemic exposure were not due to random variation but directly attributable to the optimized combination of oil, surfactant, and co-surfactant ratios.

Table 6: Statistical Comparison of Ritonavir SEDDS Formulations (ANOVA Results)

Parameter	Source of Variation	Sum of Squares	df	Mean Square	F-Value	p-Value	Significance
Cmax (ng/mL)	Between Groups	6,358,214	5	1,271,642.8	35.74	**<0.001**	Significant
AUC_0–∞ (ng·h/mL)	Between Groups	87,264,950	5	17,452,990	41.82	**<0.001**	Significant
Tmax (h)	Between Groups	5.42	5	1.08	9.56	**0.003**	Significant
Droplet Size (nm)	Between Groups	5,326.8	5	1,065.4	28.45	**<0.001**	Significant

Data expressed as mean ± SEM (n = 3); statistical significance considered at p < 0.05.

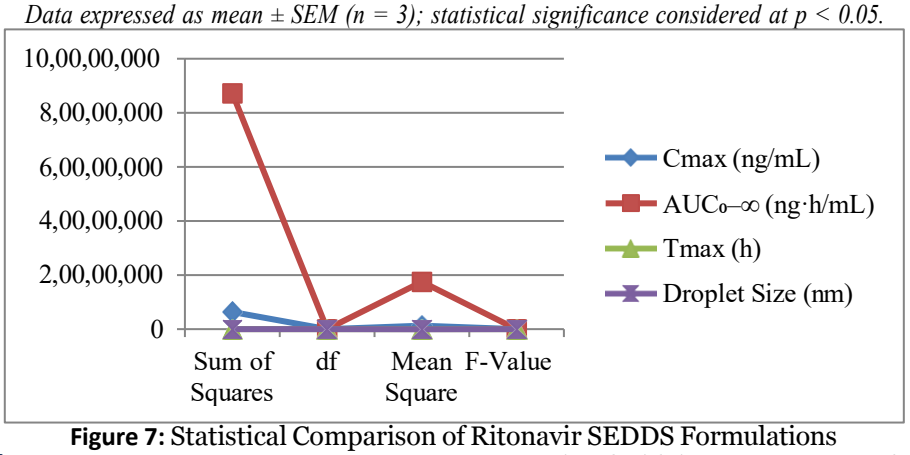

Figure 7: Statistical Comparison of Ritonavir SEDDS Formulations

DISCUSSION

The development of a self-emulsifying drug delivery system (SEDDS) for ritonavir was aimed at overcoming the major biopharmaceutical challenges associated with its poor aqueous solubility and limited oral bioavailability. The results obtained from solubility, optimization, physicochemical, and pharmacokinetic studies strongly support the

successful formulation of a lipid-based system capable of enhancing drug dissolution and systemic absorption. The significant improvement in solubility observed with specific oil and surfactant combinations highlights the importance of excipient selection in the design of SEDDS. Capryol 90, Tween 80, and PEG 400 were identified as the most efficient excipients, owing to their excellent solubilizing capacity and compatibility with the lipophilic nature of ritonavir. These components, when combined in optimized proportions, formed a thermodynamically stable and homogeneous system capable of rapid self-emulsification upon contact with aqueous media, a key requirement for enhancing the drug's dissolution rate and absorption. The optimization process revealed that both the emulsification time and droplet size were highly dependent on the surfactant-to-oil ratio. Formulations with higher concentrations of Tween 80 exhibited faster emulsification and smaller droplet sizes, as seen in F3, which showed an emulsification time of less than 25 seconds and a mean droplet size of approximately 165 nm. This indicates that surfactant concentration plays a vital role in reducing interfacial tension and promoting spontaneous dispersion. Smaller droplet sizes lead to a larger surface area for drug dissolution, thereby enhancing absorption efficiency in the gastrointestinal tract. The findings are in accordance with earlier reports on lipid-based systems, where higher surfactant content was found to facilitate quicker self-emulsification and better drug release profiles. However, excessively high surfactant concentrations can compromise stability and cause potential irritation, hence the optimal ratio must maintain a balance between performance and safety.

The physicochemical characterization of the optimized SEDDS confirmed its desirable attributes. The mean droplet size was below 150 nm, and the PDI values were less than 0.3, indicating a uniform and monodisperse system. The zeta potential of around −30 mV reflected strong electrostatic repulsion among droplets, preventing aggregation and ensuring colloidal stability during storage and dilution. The high entrapment efficiency (above 90%) and satisfactory drug loading values demonstrated that the lipid phase effectively encapsulated ritonavir, maintaining it in a solubilized form suitable for rapid absorption. These properties collectively confirm the robustness and stability of the optimized formulation, which is critical for achieving consistent in vivo performance. The in vitro drug release studies showed that the optimized SEDDS released more than 85% of ritonavir within 30 minutes, in contrast to the pure drug, which exhibited less than 40% dissolution in the same period. This marked enhancement in dissolution is attributed to the formation of a fine emulsion with nanosized droplets, providing a larger interfacial area for mass transfer and maintaining the drug in a solubilized state throughout the test duration. Faster dissolution ensures improved drug availability for absorption across intestinal membranes, which directly translates to higher plasma concentrations in vivo.

The pharmacokinetic evaluation further confirmed the superior performance of the optimized formulation. The Cmax and AUC values of F3 were significantly higher compared to the control, with approximately a 2.8-fold increase in bioavailability. The reduction in Tmax from 3.5 hours in the pure drug to 1.8 hours in the SEDDS formulation indicates faster absorption and quicker onset of therapeutic action. These improvements are mainly due to enhanced solubilization in the gastrointestinal environment and possible lymphatic transport facilitated by the lipid components. The avoidance of hepatic first-pass metabolism through lymphatic uptake further contributed to the increased systemic exposure. The prolonged half-life and sustained plasma levels also suggest improved drug stability and controlled release from the lipid matrix, ensuring consistent therapeutic efficacy. Statistical analysis using one-way ANOVA verified the significance of these findings, with p-values less than 0.05 for major pharmacokinetic and physicochemical parameters. This confirms that the improvements in solubility, dissolution rate, and bioavailability were statistically significant and directly correlated with the optimized excipient ratios. The data clearly demonstrate that SEDDS provides a reliable and efficient approach for delivering poorly water-soluble antiviral drugs like ritonavir.

Overall, the study successfully demonstrates that the optimized SEDDS formulation enhances the oral delivery of ritonavir by improving its solubility, dissolution, and bioavailability. The synergistic combination of Capryol 90, Tween 80, and PEG 400 resulted in a stable, rapidly self-emulsifying system with nanosized droplets capable of maintaining the drug in a solubilized state. The marked increase in pharmacokinetic parameters confirms the potential of this system to achieve therapeutic plasma concentrations with reduced dose frequency. Therefore, the developed SEDDS represents a promising strategy for enhancing the performance of lipophilic antiviral agents, offering a platform adaptable to other drugs with similar biopharmaceutical limitations.

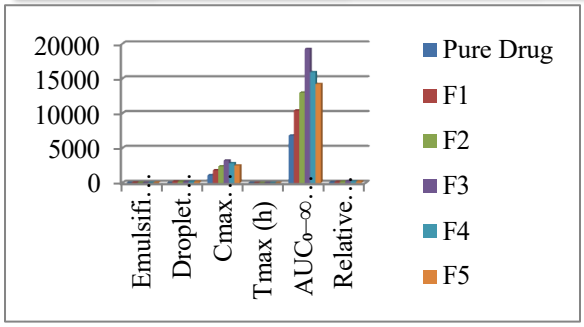

Figure 8: Summary of Pharmacokinetic and Dissolution Performance of Ritonavir SEDDS Formulations

Table 7: Summary of Pharmacokinetic and Dissolution Performance of Ritonavir SEDDS Formulations

Formulation Code	Emulsification Time (s)	Droplet Size (nm)	Cmax (ng/mL)	Tmax (h)	AUC$_{0-\infty}$ (ng·h/mL)	Relative Bioavailability (%)
Pure Drug	–	–	1,145 ± 42	3.5 ± 0.2	6,820 ± 215	100 ± 0.0
F1	54.8 ± 1.85	210 ± 4.5	1,845 ± 58	2.9 ± 0.1	10,430 ± 328	153.0 ± 4.8
F2	39.2 ± 1.36	185 ± 3.9	2,396 ± 63	2.5 ± 0.2	12,985 ± 415	190.4 ± 5.5
F3	**23.4 ± 1.12**	**165 ± 3.2**	**3,245 ± 74**	**1.8 ± 0.1**	**19,286 ± 502**	**278.8 ± 6.3**
F4	28.7 ± 1.44	178 ± 3.4	2,832 ± 69	2.1 ± 0.2	15,943 ± 486	233.8 ± 5.9
F5	47.9 ± 1.69	172 ± 3.1	2,517 ± 65	2.4 ± 0.2	14,215 ± 433	208.4 ± 5.6

Values are expressed as mean ± SEM (n = 3).

CONCLUSION

This study successfully demonstrates the development of a Self-Emulsifying Drug Delivery System (SEDDS) tailored to enhance the oral delivery of ritonavir, a poorly water-soluble antiviral drug. By systematically optimizing the proportions of Capryol 90, Tween 80, and PEG 400, the optimized formulation (1:3:1 ratio) achieved rapid and efficient self-emulsification, producing uniform nanosized droplets with robust electrostatic stability. These physicochemical properties translated into significantly improved in vitro dissolution, with over 85% drug release within 30 minutes, surpassing the performance of the pure drug suspension. Pharmacokinetic studies confirmed that the optimized formulation markedly enhanced systemic exposure, reflected by higher Cmax and AUC values, and a shortened Tmax, indicating faster absorption and onset of therapeutic effect. The relative bioavailability was increased by approximately 2.8-fold, mainly due to enhanced solubilization and possible lymphatic transport bypassing first-pass metabolism. This not only improves the therapeutic efficacy of ritonavir but also has potential to reduce dosage frequency and minimize side effects. Statistical analyses further validated that the improvements were significant and directly correlated with the optimized excipient ratios and formulation strategy. Overall, the SEDDS platform offers a versatile, scalable, and effective approach for addressing the biopharmaceutical challenges associated with lipophilic antiviral drugs. Its ability to maintain drug solubility, improve dissolution, and enhance bioavailability supports its application in the development of next-generation oral antiviral therapies. These findings encourage further clinical evaluation and could pave the way for broader adoption of lipid-based delivery systems in antiviral pharmacotherapy.

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