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REVIEW ARTICLE

Novel Nanocarriers for Rosuvastatin Calcium

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SUMMARY

Rosuvastatin calcium (RC), a statin drug, is commonly prescribed for the treatment of hyperlipidemia by lowering levels of low-density lipoprotein (LDL) cholesterol, triglycerides, and apolipoprotein B, while simultaneously increasing high-density lipoprotein (HDL) cholesterol. It has also shown effectiveness in managing conditions such as familial hypercholesterolemia, dyslipidemia, osteoporosis, atherosclerosis, benign prostatic hyperplasia, and Alzheimer's disease. However, its therapeutic potential is limited due to challenges like poor aqueous solubility, low intestinal absorption, reduced oral bioavailability, and significant first-pass metabolism. One strategy to overcome these issues is the reduction of drug particle size to the nanoscale, which enhances the dissolution rate of poorly water-soluble compounds. Numerous advanced formulation strategies have been explored to improve the solubility and dissolution of such drugs. These include nanocarrier systems, hydrogels, nanogels, amorphous solid dispersions, co-crystals, nanocrystals, liposomes, micronization, polymer-based nanoparticles, solid lipid nanoparticles, supercritical fluid techniques, nanosuspensions, nanoemulsions, surfactants, micellar solubilization, pH adjustment, co-solvents, hydrotropic agents, and cyclodextrin complexes. This review focuses on the development and application of nanocarrier-based systems to improve the solubility, dissolution rate, and overall bioavailability of RC. Furthermore, the physicochemical characteristics and pharmacological potential of RC in the context of nanocarrier-mediated delivery are discussed.

Keywords: *Rosuvastatin calcium, nanocarriers, oral drug delivery, bioavailability enhancement.*

Rosuvastatin Kalsiyum İçeren Yeni Nanotaşıyıcılar

ÖZ

Statin ilaç sınıfına ait olan rosuvastatin kalsiyum (RC), düşük yoğunluklu lipoprotein (LDL) kolesterol, trigliserit ve apolipoprotein B düzeylerini düşürürken aynı anda yüksek yoğunluklu lipoprotein (HDL) kolesterolü artırarak hiperlipidemi tedavisinde yaygın olarak reçete edilir. Ayrıca ailevi hiperkolesterolemi, dislipidemi, osteoporoz, ateroskleroz, iyi huylu prostat hiperplazisi ve Alzheimer hastalığı gibi durumların yönetiminde de etkili olduğu gösterilmiştir. Ancak, zayıf suda çözünürlük, düşük bağırsak emilimi, azalmış oral biyoyararlanım ve önemli ilk geçiş metabolizması gibi zorluklar nedeniyle terapötik potansiyeli sınırlıdır. Bu sorunların üstesinden gelmek için bir strateji, ilaç partikül boyutunu nanometre ölçeğine indirgemektir; bu, suda az çözünen bileşiklerin çözünme hızını artırır. Bu tür ilaçların çözünürlüğünü ve çözünmesini iyileştirmek için çok sayıda gelişmiş formülasyon stratejisi araştırılmıştır. Bunlar arasında nanotaşıyıcı sistemler, hidrojeller, nanojeller, amorf katı dispersiyonlar, ko-kristaller, nanokristaller, lipozomlar, mikronizasyon, polimer bazlı nanopartiküller, katı lipit nanopartiküller, süperkritik akışkan teknikleri, nanosüspansiyonlar, nanoemülsiyonlar, yüzey aktif maddeler, misel çözünürleştirme, pH ayarlaması, ko-çözücüler, hidrotropik ajanlar ve siklodekstrin kompleksleri yer almaktadır. Bu derleme, RC'un çözünürlüğünü, çözünme hızını ve genel biyoyararlanımını iyileştirmek için nanotaşıyıcı sistemlerin geliştirilmesi ve uygulanmasına odaklanmaktadır. Ayrıca, nanotaşıyıcı aracılı uygulama bağlamında RC'un fizikokimyasal özellikleri ve farmakolojik potansiyeli tartışılmaktadır.

Anahtar Kelimeler: *Rosuvastatin kalsiyum, nanotaşıyıcılar, oral ilaç uygulaması, biyoyararlanım artışı.*

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INTRODUCTION

Recent advancements in nanotechnology have significantly impacted the field of medicine, particularly in improving the diagnosis and treatment of various diseases. Nanomaterials possess unique physical and chemical properties due to their increased surface area at the nanoscale. In pharmaceutical sciences, one of the most promising applications of nanotechnology is the formulation of nanoscale drug delivery systems. These systems can enhance drug solubility and bioavailability, prolong drug release, and minimize adverse effects. Additional benefits include increased local drug concentration, reduced variability in gastrointestinal transit, minimized interpatient variability, prevention of dose dumping, and suitability for various routes of administration (oral, parenteral, inhalation). Furthermore, they are capable of encapsulating both hydrophilic and lipophilic drug molecules (Çetin & Şahin, 2016; Luo et al., 2021). In recent years, considerable attention has been devoted to the development of innovative delivery platforms for RC, particularly using nanoformulations such as solid dispersions (SDs), self-nanoemulsifying drug delivery systems (SNEDDS), nanoemulsions, and solid lipid nanoparticles (SLNs) (Balakumar et al., 2013).

Statins, first introduced in the 1970s as lipid-lowering agents, have become the most commonly prescribed class of antihyperlipidemic drugs worldwide (Al-Heibshy et al., 2019). In addition to lowering cholesterol, statins are also effective in reducing elevated triglyceride levels and increasing HDL cholesterol factors critical in reducing cardiovascular disease risk. Compared to other statins (e.g., lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and cerivastatin), RC has a comparatively lower potential for drug-drug interactions. Rosuvastatin, marketed as Crestor® by AstraZeneca, was the seventh statin to be approved by the U.S. FDA in August 2003 for treating primary hypercholesterolemia at doses up to 40 mg/day (Quirk et al., 2003; FDA, 2025). It was first launched in the Netherlands in November 2002, followed by Canada in February 2003. As of today, the drug has received approval in over 90 countries and has accumulated over 4 million patient-years of post-marketing use (FDA, 2025).

RC is widely used to manage hyperlipidemia and homozygous familial hypercholesterolemia by reducing LDL, triglycerides, and apolipoprotein B while increasing HDL levels. It is also prescribed to slow the progression of atherosclerosis and to prevent cardiovascular events (Al-Heibshy et al., 2020a; Vishwakarma et al., 2016). Among statins, it is considered one of the most potent in its class and is often referred to as a "super statin" due to its high efficacy (Ahmed, 2020; Zhou et al., 2013). Beyond its lipid-lowering capabilities, RC has been investigated for potential benefits in treating osteoporosis, benign prostatic hyperplasia, and Alzheimer's disease (Sarfraz et al., 2017; Zalak et al., 2012).

Although RC demonstrates strong therapeutic performance, its clinical effectiveness is limited by several unfavorable biopharmaceutical properties. These include low solubility in water, limited permeability through the intestinal wall, reduced oral bioavailability, and a substantial hepatic first-pass effect (Arun et al., 2020). As a Biopharmaceutics Classification System (BCS) Class II drug, RC typically shows around 20% bioavailability, primarily attributed to extensive hepatic metabolism and significant plasma protein binding (~88%). Furthermore, its crystalline structure further restricts its solubility in aqueous environments (Al-Heibshy et al., 2020b; Al-Shdefat et al., 2020; Martin et al., 2003). To address these challenges, innovative drug delivery platforms are necessary to enhance absorption, improve pharmacokinetic behavior, and minimize side effects. Approaches such as improving solubility and avoiding extensive hepatic metabolism are being explored to unlock RC's full therapeutic potential (Ashraf et al., 2023; Balakumar et al., 2013; Zalak et al., 2012; Zhou et al., 2013).

Particle size reduction at the nanoscale level has emerged as a promising strategy to improve solubility,

dissolution rate, and ultimately, bioavailability. This review investigates nanoformulation-based strategies designed to improve RC's biopharmaceutical profile and examines its relevant physicochemical and pharmacological attributes.

Physicochemical properties

RC is a synthetic statin with lipid-lowering effects and a strong affinity for hepatocytes. Chemically, it is defined as (3R,5S,6E)- 7- {4- (4- fluorophenyl)- 6- (1-methylethyl)- 2- [methyl (methylsulfonyl) amino] pyrimidin- 5- yl}- 3,5- dihydroxyhept- 6-enoic acid calcium salt (2:1) (Figure 1) (Cada et al., 2004; Sarfraz et al., 2018; USP 44-NF39, 2022).

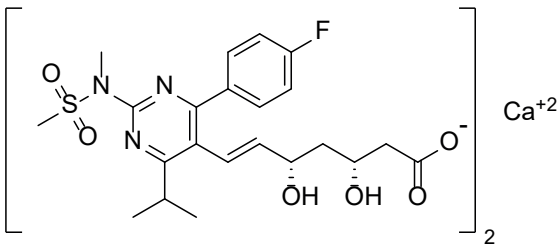

Figure 1. Chemical structure of RC (USP 44-NF39, 2022).

In its physical form, RC appears as a white to off-white hygroscopic powder with a molecular weight of approximately 1001 g/mol (Türk Farmakopesi, 2016). It exhibits limited solubility in water and methanol, is more readily soluble in methylene chloride, and is practically insoluble in anhydrous ethanol. Proper storage conditions include well-sealed containers, protected from light and moisture, at a controlled temperature of 20-25°C (Türk Farmakopesi, 2016; USP 44-NF39, 2022). Solubility of RC decreases at lower pH levels, and as a BCS Class II drug, it is characterized by poor aqueous solubility and high intestinal permeability (Alshora et al., 2019; Patil-Gadhe & Pokharkar, 2016; Ponnuraj et al., 2015; Sarfraz et al., 2017; Shoukat et al., 2024). It has a lipophilic nature with a log P value of 2.4 and low water solubility (0.00936 mg/mL) (Ahsan & Verma, 2017; Oza et al., 2020). Moreover, its partition coefficient in octanol/water is -0.33 at pH 7.4, further confirming its limited absorption and poor bioavailability in conventional oral forms (~20%) (Ahmed, 2020; Carswell et al., 2002; Thenmozhi et al., 2023).

Adverse effects

Statins, including RC, have been reported to cause mild elevations in liver enzyme levels (transaminases), although the clinical significance of these elevations remains uncertain. In general, minor increases do not suggest a substantial risk of hepatic injury during treatment (FDA, 2025; McKenney et al., 2006). Muscular symptoms such as soreness, pain, weakness, flu-like symptoms, headaches, and myalgia are also commonly reported, while serious conditions like rhabdomyolysis are rare (Carswell et al., 2002; McKenney et al., 2006). Clinical studies have shown that high doses of RC (80 mg/day) resulted in incidences of myopathy and rhabdomyolysis in 1.0% and 0.4% of patients, respectively (Thenmozhi et al., 2023). Due to these adverse outcomes, this dose was not approved for clinical use (FDA, 2025). Additionally, proteinuria was observed in approximately 12% of patients receiving the 80 mg dosage, leading to its exclusion from the market (Jones et al., 2003). Although proteinuria has been associated with other statins as well, its prevalence may be higher with more potent agents like RC (Bays, 2006). However, the FDA concluded in 2005 that proteinuria associated with statin therapy does not indicate renal damage or increased risk of kidney failure (FDA, 2025).

Pharmacokinetics properties

RC has an absolute bioavailability of around 20% (90% CI: 17.2–23.4), limited primarily by its poor solubility, low permeability, and significant hepatic metabolism, which includes processes like oxidation, glucuronidation, lactonization, and direct biliary secretion (Al-Heibshy et al., 2016; Thenmozhi et al., 2023; White, 2002). These pharmacokinetic drawbacks necessitate frequent (often thrice daily) dosing, increasing the risk of adverse effects and reducing patient adherence (Elsayed et al., 2020).

After oral administration, peak plasma concentrations (C_{max}) are typically reached within 3-5 hours. For instance, a median t_{max} of 5 hours has been reported (range: 0.5-6 hours), with C_{max} and area under the plasma concentration-time curve (AUC) values increasing in a dose-proportional manner over the 5-80 mg range (Culhane et al., 2005; Kanukula et al., 2021). Geometric mean C_{max} values for 20 mg, 40 mg, and 80 mg doses were found to be 9.7 ng/mL, 37 ng/mL, and 46.2 ng/mL, respectively. Corresponding AUC values were 81.7, 255.9, and 329 ng·h/mL, respectively (Warwick et al., 2000).

The AUC_{0-24} value on day 14, compared to a single dose, was 76%, suggesting mild accumulation over time (Kanukula et al., 2021). While food intake reduces the C_{max} by roughly 20%, it does not significantly alter the total drug absorption (White, 2002). RC's lipid-lowering efficacy remains unaffected by food or dosing time (morning vs. evening) (Culhane et al., 2005; Martin et al.,2002).

Following a single 20 mg dose, the C_{max} is approximately 6.1 ng/mL, achieved around 5 hours (t_{max}). At steady state, the C_{max} increases to about 9.7 ng/mL at 3 hours post-dose. Both C_{max} and AUC show a linear relationship across the dosage range of 5-80 mg, under both single and repeated dosing. The steady-state t_{max} ranges from 3 to 5 hours, which is longer than for many other statins that typically reach t_{max} in ≤3 hours (White, 2002). In three randomized, double-blind, placebo-controlled clinical trials conducted in healthy male participants, single oral doses of RC ranging from 20 to 80 mg exhibited a near-linear increase in both C_{max} and the average AUC over a 24-hour period (AUC_{0-24}) (Carswell et al., 2002). After daily administration of 40 mg RC for 7 consecutive days, steady-state levels revealed a C_{max} of 37.0 µg/L, with the time to reach this peak (t_{max}) recorded at 3 hours. The drug's mean elimination half-life was approximately 20.8 hours, and the AUC_{0-24} reached 256 µg·h/L (Carswell et al., 2002).

A bioequivalence study, conducted under fasting conditions in healthy adult subjects, assessed the pharmacokinetic comparability between two RC 20 mg tablet formulations (reference and test). The 90% confidence intervals of the geometric mean ratios (GMRs) for C_{max} (95.01-112.66), AUC_0-t (93.38–111.67), and AUC_0–∞ (93.65–111.29) fell within the standard bioequivalence acceptance limits of 80% - 125%, confirming the equivalence of the two formulations (Pena et al., 2024).

Following oral intake, RC undergoes significant first-pass hepatic metabolism and demonstrates a high plasma protein binding rate of approximately 88% (Al-Heibshy et al., 2019; Al-Heibshy et al., 2020b). At steady-state, the drug distributes extensively, with an average volume of distribution around 134 liters, and has a terminal half-life close to 19 hours. The primary route of elimination is via feces, with renal excretion contributing minimally. Unlike many other statins, RC is not extensively metabolized by the cytochrome P450 3A4 (CYP3A4) pathway. Instead, it is minimally metabolized by CYP2C9 and, to a lesser extent, by CYP2C19 (Culhane et al., 2005). Age and sex appear to have negligible influence on RC's pharmacokinetic behavior. In individuals with mild to moderate renal impairment, plasma concentrations remain stable after 14 days of 20 mg/day administration (Culhane et al., 2005). Using the Sheiner method, the average total body clearance (CL) following a single dose has been calculated to be 28.3 L/h (Kanukula et al., 2021).

Emerging evidence suggests that RC may have beneficial effects in pregnancies affected by fetal growth restriction, with no immediate adverse outcomes reported for neonates (Kasraeian et al., 2025). Current data do not support a definitive link between congenital anomalies and statin use during pregnancy. While findings to date suggest that statins are likely non-teratogenic, their use during pregnancy is still discouraged until further safety data becomes available (Karalis et al., 2016; Trakadis et al., 2009).

Hyperlipidemia and rosuvastatin calcium

RC is a highly effective lipid-lowering agent that works by inhibiting the activity of HMG-CoA reductase, the enzyme responsible for a critical step in cholesterol biosynthesis (Ahsan & Verma, 2017). Its primary therapeutic application is in managing hyperlipidemia, where it produces a strong, dose-dependent reduction in LDL cholesterol, while simultaneously increasing HDL cholesterol levels (Desavathu et al., 2020). It is also used in managing other lipid abnormalities, including familial hyperlipidemia, dyslipidemia, and elevated triglyceride levels. Additionally, RC has demonstrated potential benefits in conditions such as atherosclerosis, osteoporosis, benign prostatic hyperplasia, and neurodegenerative disorders like Alzheimer's disease (Balakumar et al., 2013; Karasulu et al., 2016; Shoukat et al., 2022).

Hyperlipidemia plays a major role in the development of cardiovascular disease, particularly acute coronary syndromes (ACS), which are a leading cause of morbidity and mortality worldwide (Darwish et al., 2022). Among lipids, LDL cholesterol is strongly linked with coronary artery disease risk, with numerous studies confirming a direct correlation between elevated LDL levels and increased cardiovascular events. As a result, LDL-C reduction remains a key therapeutic target in both the prevention and treatment of ACS (Al-Heibshy et al., 2020b).

Rosuvastatin calcium-loaded nanocarriers

Reducing drug particle size to the nanoscale significantly improves the dissolution rates of poorly soluble compounds, a principle supported by the Noyes–Whitney equation, which states that smaller particle sizes result in a greater surface area for dissolution (Rani et al., 2023; Song et al., 2021). Various formulation strategies have been devised to enhance solubility and bioavailability of drugs in BCS Class II and IV categories. These include the development of nanogels, hydrogels, nanocrystals, co-crystals, amorphous SDs, SLNs, liposomes, micronized forms, and supercritical fluids (SCFs) technologies. Additional techniques include the use of surfactants, nanosuspensions (NSs), nanoemulsions, micellar systems, hydrotropic agents, pH modulators, co-solvents, and cyclodextrin inclusion complexes (Grimaudo et al., 2019; Joshi et al., 2023; Shoukat et al., 2024). Several novel delivery platforms have also been tested for RC to increase its solubility, dissolution rate, and overall bioavailability. These include microemulsions, liquisolid systems, nanocrystals, SDs, inclusion complexes, both solid and liquid SNEDDS, SLNs and nanosponge-based carriers (Alshora et al., 2019; Al-Heibshy et al., 2020b; Anwar et al., 2025; Beg et al., 2019).

Polymer-based nanoparticles

Polymeric nanoparticles are submicron colloidal carriers, typically between 1 and 1000 nm in size that can be biodegradable or non-biodegradable (Thenmozhi et al., 2023). Their application in drug delivery is widely studied due to several advantages: they can encapsulate both water-soluble and lipophilic drugs, offer high drug-loading capacity, and provide formulation stability, particularly when lyophilized or appropriately stored. They are also compatible with diverse administration routes, including oral, nasal, and parenteral methods (Çetin & Şahin, 2016). Depending on their structure and composition, nanoparticles can be categorized into various types such as polymeric, lipid-based, carbon-based, ceramic, metallic, and semiconductor nanoparticles (Darwish et al., 2022). Among these, polymeric nanoparticles have received significant attention for their customizable properties and potential for targeted and controlled drug delivery.

Thenmozhi et al. (2023) designed and assessed polymeric nanoparticles to enhance the oral delivery of RC. These nanoparticles were synthesized through nanoprecipitation using varying ratios of Eudragit L100 and S100 polymers. By controlling the formulation parameters, particle sizes ranging from 100 to 250 nm were achieved, with drug entrapment efficiencies (EE) between 28% and 79%. *In vitro* release testing exhibited a biphasic release pattern: an initial burst

within the first two hours, likely aiding in early absorption, followed by a prolonged release phase consistent with the Higuchi model of diffusion-controlled release. The RC-loaded nanoparticles approximately doubled the drug's aqueous solubility in comparison to its unformulated state. Furthermore, permeability studies across rat intestinal tissues showed significantly improved transport of RC when encapsulated in Eudragit-based nanoparticles versus the free drug. Transmission electron microscopy (TEM) confirmed the spherical morphology of the particles. Overall, the results suggest that Eudragit-based polymeric nanoparticles are a promising system for improving RC's oral bioavailability by enhancing solubility and intestinal absorption (Thenmozhi et al., 2023).

In another study, Alshora et al. (2019) utilized a planetary ball mill technique to prepare RC nanoparticles aimed at enhancing dissolution and systemic bioavailability. The optimized formulation showed a 1.3-fold increase in dissolution rate and a twofold rise in plasma concentration compared to raw RC ($P < 0.05$). Stability assessments conducted under long-term storage conditions (30°C and 60% relative humidity) indicated excellent formulation stability. Follow-up experiments involved refining both the formulation and stabilization strategies through wet milling with 0.1 mm milling media at 800 rpm for three 10-minute cycles. Among the resulting NSs, those stabilized with 10% polyvinylpyrrolidone (PVP) displayed the smallest particle size and highest stability. This optimized batch exhibited a particle size of 461.8 ± 16.68 nm and a zeta potential (ZP) of −31.8 ± 7.22 mV, compared to the unprocessed RC with a size of 618 μm. Dissolution studies demonstrated that 72% of RC from the nanoparticle formulation dissolved within one hour, significantly outperforming the 58.25% from the pure drug ($P < 0.05$). *In vivo* pharmacokinetic evaluation confirmed a marked enhancement in drug absorption, with C_{max} increasing to 82.35 ng/mL at 2 hours post-administration, compared to just 9.2 ng/mL for the unformulated drug (Alshora et al., 2019).

Hirpara et al. (2018) formulated long-circulating PEGylated chitosan nanoparticles to improve RC's pharmacokinetic and therapeutic profile. PEGylation was achieved using a carbodiimide-mediated reaction involving PEG carboxylic acid derivatives. Two optimized formulations were produced, each with particle sizes under 200 nm and EE around 14%. *In vitro* release testing over 120 hours showed cumulative drug releases of 14.07 ± 0.57% and 22.02 ± 0.81%, indicating a controlled and extended release behavior. TEM analysis revealed that the nanoparticles were predominantly spherical. In pharmacokinetic studies, the formulations provided a prolonged drug release profile lasting up to 72 hours. Additionally, pharmacodynamic assessments in hyperlipidemic rat models demonstrated significantly improved lipid-lowering activity of the PEGylated formulation compared to the free drug, underscoring the system's potential for enhanced therapeutic efficacy (Hirpara et al., 2018).

Parameswaran et al. (2022) developed RC-loaded chitosan nanoparticles via the solvent evaporation method, employing a 2^3 factorial design for optimization. The optimized formulation exhibited a particle size of 159.9 ± 16.1 nm, contributing to improved dissolution, permeability, and surface area. The formulation's ZP was 33.5 ± 1.54 mV, indicating favorable colloidal stability, while the polydispersity index (PDI) of 0.587 ± 0.16 suggested a relatively uniform particle distribution. EE and percentage yield were high, measured at 94.20 ± 2.46% and 96.80 ± 2.08%, respectively. *In vitro* release studies showed a maximum drug release of 96.54 ± 2.02% within 24 hours, following a controlled zero-order release pattern and a non-Fickian diffusion mechanism. The release exponent ($n = 0.5–0.8$) from the Peppas model indicated drug transport was governed by both diffusion and polymer relaxation. *In vivo* pharmacokinetic studies showed a significant increase in $AUC_{0-\infty}$, confirming the enhanced bioavailability of RC from the chitosan nanoparticle system (Parameswaran et al., 2022).

Bhokare et al. (2020) successfully created sustained-release, biodegradable chitosan nanoparticles

loaded with the drug RC. They utilized a modified ionotropic gelation method, optimized through a 3^2 full factorial design, to prepare the nanoparticles. The *in vitro* release analysis indicated a two-phase pattern: an initial burst effect followed by a significantly slower drug release. This research confirms that the modified ionic gelation technique presents a promising strategy for the effective delivery hydrophobic drugs using chitosan nanoparticles (Bhokare et al., 2020).

In their 2020 research, Mujtaba and Alotaibi created chitosan-alginate nanoparticles for the drug RC. Their method involved the ionotropic pre-gelation of an alginate core, which was then followed by chitosan polyelectrolyte complexation. The researchers fine-tuned the formulation by optimizing the concentrations of the two biopolymers and the crosslinker. The resulting nanoparticles showed a two-stage drug release pattern: an initial fast release over the first two hours, succeeded by a slower, more gradual release spanning the full 24-hour period. Overall, the findings indicate that this novel chitosan-alginate nanoparticle system for RC is a promising approach for boosting the drug's solubility and, consequently, its therapeutic efficacy. The authors concluded that this new nanosystem also holds significant potential for the oral delivery of other hydrophobic compounds (Mujtaba & Alotaibi, 2020).

In a 2022 study, Saadallah and Hamid explored the creation, characteristics, *in vitro* release, and *ex vivo* permeability of RC-loaded Eudragit® L100 nanoparticles, which they produced using a nanoprecipitation method. Their *in vitro* release data showed that the Eudragit® L100 polymeric nanoparticles were capable of delivering RC with a sustained and pH-dependent release profile. Furthermore, the *ex vivo* permeability study revealed a 1.6-fold increase in the amount of RC that successfully penetrated the skin. These results suggest that Eudragit® L100 polymeric nanoparticles have a strong potential for successful use in both dermal and transdermal drug applications (Saadallah & Hamid, 2022).

Nanoparticle formulations were developed using Poloxamer 407 and lecithin via the thin-film hydration method. The particles had a size range of 167-408 nm, a PDI value between 0.15 and 0.37, and a ZP of -20 to -53 mV. An increase in the lecithin ratio was observed to decrease the release percentage. The optimized formulation was coated with silver, and its effect on wound healing was investigated. Histopathological studies and serum levels of tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) confirmed that the silver-coated RC nanoparticle-loaded gel formulation was more effective in wound healing compared to gentamicin ointment (Salem et al., 2021).

In a study, chitosan-coated silver nanoparticles were prepared using the solvent evaporation method with a 2^3 factorial design. The nanoparticles, with a size range of 211-223 nm and a PDI value of 0.254, were measured to have a ZP of -35.3 mV. Mucoadhesion studies revealed that chitosan increased the binding of the nanoparticles to mucin proteins through hydrogen bonds and other interactions. Release studies were conducted in dissolution media with different pH values. For the ideal formulations, it was determined that the release kinetics followed the Higuchi model, regardless of the media's pH. Furthermore, a lower release rate was observed at lower pH values, which confirmed that the solubility of RC is directly proportional to the pH. In addition, cytotoxicity studies reported that the optimized formulation had the lowest IC50 value and the strongest anticancer activity (Mahmoud et al., 2025).

In another study, RC-loaded Poloxamer® 188 nanoparticles were produced using the homogenization method. The nanoparticles, with a particle size of 183.4 nm, were compared to a commercially available tablet formulation. The nanoparticles, which had a PDI value of 0.241 and a ZP of -26.6 mV, demonstrated a faster drug release than the tablets. Within 5 minutes, while the pure RC suspension reached 13% and the commercial formulation reached 26% release, the Poloxamer nanoparticles achieved nearly 90% release. Furthermore, the half-life from the pharmacokinetic

parameters was determined to be 14.7 hours for the nanoparticles, compared to 8.9 hours for the commercial formulation. Pharmacodynamic studies also showed that the nanoparticle formulation was more effective (Dudhipala et al., 2021).

The effectiveness of any pharmaceutical compound is critically tied to its bioavailability. When the particle size of a drug is reduced, its dissolution rate in biological fluids and its overall bioavailability within the body are significantly improved. Najafi et al. (2021) employed the Gas Anti-Solvent (GAS) method to decrease the size of RC particles. Their analysis confirmed the success of this technique, showing that the RC particles produced by the GAS process (measuring 60.3 nm) were substantially smaller than the original particles (which measured 45.8 μm) (Najafi et al., 2021).

El-Salamouni et al. (2025) developed a sustained-release nanoformulation of RC co-precipitated with calcium carbonate, intended for local application directly into the bone of osteoporotic rats. The researchers created these nano-formulations using a coprecipitation method, systematically varying the concentrations of polyvinyl alcohol stabilizer (at 0.2, 0.4, or 0.6%) and equimolar ratios of calcium chloride and calcium carbonate (at 0.1, 0.3, or 0.5 M). The optimized formula demonstrated a satisfactory nanosize range, good homogeneity, and remained stable throughout the six-month study period. Crucially, the local administration of these calcium carbonate nanoparticles enabled a prolonged release of RC, confirming it as an intelligent strategy for quickly promoting the healing of bone defects associated with osteoporosis (El-Salamouni et al., 2025).

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC)

SLNs, with sizes ranging between 1-1000 nm, are widely studied nanocarriers known for their biocompatibility, non-toxicity, and scalability (Beg et al., 2017a; Singh et al., 2018). Compared to polymeric carriers, SLNs offer advantages such as low cost, ease of fabrication, high drug loading for both hydrophilic and lipophilic molecules, controlled release behavior, and good physical stability (Beg et al., 2017a). As a more advanced system, NLCs integrate liquid lipids into the solid lipid matrix, enhancing drug loading capacity and minimizing drug expulsion during storage (Amin & Ahmad, 2017). NLCs also display improved dispersibility, reduced water content in formulations, and enhanced biopharmaceutical performance (Darwish et al., 2022; Patil-Gadhe & Pokharkar, 2016).

Al-Heibshy et al. (2020) investigated SLNs for RC delivery, using stearic acid and tripalmitin as the lipid core materials. The SLNs were prepared through a hot homogenization process followed by ultrasonication. Particle sizes ranged from 134.37 ± 0.91 nm to 351.13 ± 1.39 nm, with narrow size distribution (PDI < 0.5), indicating uniform formulation. ZP measurements revealed negative surface charges (−17.03 ± 0.53 to −40.80 ± 1.2 mV), consistent with the presence of anionic lipids and suggestive of good dispersion stability. *In vitro* drug release studies showed that pure RC released ~75.8% of the drug within 2 hours, reaching 95.5% by 6 hours. In contrast, SLN formulations provided a more sustained release profile over 24 hours, with a noticeable initial burst phase in the first 6 hours. Permeation studies confirmed improved RC transport across biological membranes from SLNs compared to the unformulated drug. Pharmacokinetic analysis demonstrated significant enhancements in C_{max} (1.4-fold) and AUC_{last} (8.5-fold) for the SLN formulation, suggesting substantial improvement in systemic bioavailability (Al-Heibshy et al., 2020b).

Dudhipala and Veerabrahma (2017) formulated RC-loaded SLNs using different lipid matrices stearic acid, glyceryl behenate, and glyceryl trilaurate through a hot homogenization technique followed by ultrasonication. These formulations were evaluated for particle size, PDI, ZP, EE, drug content, and *in vitro* drug release. Among the tested lipids, glyceryl trilaurate produced the most favorable results, yielding nanoparticles with an average size of 67.21 ± 1.71 nm, a PDI of 0.25 ± 0.01, ZP of -28.93 ± 0.84 mV,

and EE of 93.51 ± 0.34%. The physical stability of the optimized SLNs was maintained over a 90-day period under both refrigerated and ambient conditions. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) analyses showed no significant drug–excipient interactions. Morphological assessment via scanning electron microscopy (SEM) and TEM revealed that the nanoparticles were nearly spherical. *In vitro* release testing indicated a slower release from SLNs (65–80%) over 24 hours, compared to nearly complete release (96%) from an RC suspension. Pharmacokinetic studies demonstrated a 4.6-fold increase in oral bioavailability for the SLNs. Additionally, pharmacodynamic evaluations in hyperlipidemic rat models showed prolonged lipid-lowering activity for 36 hours with the SLNs, while the drug suspension showed efficacy for only 24 hours (Dudhipala & Veerabrahma, 2017).

In a separate investigation, Singh et al. (2018) developed RC-loaded SLNs using stearic acid through a modified solvent emulsification-diffusion technique. The nanoparticles were characterized for their size, surface charge, drug loading, and release behavior. The optimized formulation exhibited a particle size of 115.49 ± 2.97 nm, PDI of 0.456, ZP of -18.40 mV, and an EE of 97.16%, with drug loading reaching 60.34%. *In vitro* drug release followed a sustained pattern, with 88.70 ± 3.59% of the drug released within 12 hours, conforming to the Higuchi model (R^2 = 0.9905). TEM analysis showed spherical particle morphology. The pharmacokinetic profile indicated a 4.44-fold enhancement in bioavailability over a plain RC suspension. Stability testing over 180 days at 25 ± 2°C and 60 ± 5% RH confirmed long-term stability of the formulation (Singh et al., 2018).

Darwish et al. (2022) explored the comparative performance of SLNs and NLCs for improving the solubility and oral bioavailability of RC. The nanoparticles were prepared using Apifil (solid lipid) and Maisine (liquid lipid) through high-speed homogenization combined with ultrasonication. The resulting nanoparticles were lyophilized and encapsulated into oral dosage forms. Particle sizes reached up to 180.3 nm, and EE values varied from 40.77% to 91.67%, depending on formulation parameters. Clinical testing in six healthy volunteers revealed that NLC-based formulations demonstrated superior pharmacokinetic performance. Specifically, the NLC-loaded RC achieved a C_{max} of 8.92 ng/mL, compared to 2.56 ng/mL for the marketed RC product, translating to a ~349% relative increase in bioavailability. Additionally, NLC capsules exhibited better formulation stability than their SLN counterparts (Darwish et al., 2022).

In another study, an NLC formulation of RC was developed using melt emulsification followed by ultrasonication, optimized via a Box–Behnken statistical design. The lipid matrix consisted of 3% w/v glyceryl monostearate (solid lipid) and capmul MCM EP (liquid lipid), with poloxamer 188 and Tween 80 as surfactants. The final optimized formulation had a particle size of 150.3 ± 4.67 nm, a PDI of 0.175 ± 0.022, ZP of -32.9 ± 1.36 mV, and an EE of 84.95 ± 5.63%. *In vitro* release studies in simulated intestinal fluid (pH 6.8) indicated that the NLCs released the drug more effectively than a suspension of the active pharmaceutical ingredient (API). Confocal laser scanning microscopy showed enhanced penetration into intestinal tissues relative to a rhodamine B dye control. Pharmacokinetic studies in female Wistar rats revealed a 5.4-fold improvement in relative bioavailability for the NLCs. Furthermore, lipid-lowering efficacy was significantly improved in hyperlipidemic rats ($p < 0.01$), highlighting the therapeutic potential of the optimized NLC system (Amin & Ahmad, 2017).

Patil-Gadhe and Pokharkar formulated a dry powder inhaler (DPI) system containing RC-loaded NLCs aimed at targeted pulmonary delivery. The NLCs were lyophilized using 5% mannitol as a cryoprotectant and carrier. Particle deposition and aerodynamic properties were evaluated using an 8-stage cascade impactor, revealing a mass median aerodynamic diameter (MMAD) below 3 μm and a fine particle fraction (FPF) exceeding 90% at a 60 L/min flow rate. Use of L-leucine as an anti-static agent further improved

dispersibility and aerosolization. *In vivo* pulmokinetic studies in Wistar rats showed enhanced pharmacokinetic outcomes, including a 1.14-fold increase in C_{max}, a fivefold extension in half-life, and a dramatic 35-fold rise in AUC_{0-1}, suggesting a substantial increase in systemic exposure. The combination of lipid-based composition and small particle size likely facilitated macrophage evasion, resulting in improved lung targeting. This delivery platform holds promise for managing pulmonary conditions such as chronic obstructive pulmonary disease (COPD) (Patil-Gadhe & Pokharkar, 2016).

Self-nanoemulsifying drug delivery systems (SNEEDS)

Given RC's extensive hepatic metabolism through oxidation, lactonization, and glucuronidation pathways, improving oral bioavailability requires strategies that increase solubility and reduce first-pass metabolism (Phan et al., 2024). SNEDDS have emerged as a promising approach to address these challenges (Desavathu et al., 2020). SNEDDS are isotropic mixtures comprising lipids, surfactants, and cosurfactants, forming nano-sized oil-in-water emulsions (typically <250 nm) upon contact with gastrointestinal fluids (Kulkarni et al., 2015). These systems improve bioavailability by enhancing solubility, promoting membrane permeation, and facilitating lymphatic transport, thereby bypassing hepatic metabolism (Vishwakarma et al., 2016). Their small droplet size and lipidic composition contribute to improved absorption and more predictable plasma drug profiles (Karasulu et al., 2018). However, liquid SNEDDS are often thermodynamically unstable, leading to the development of solid SNEDDS formulations to enhance stability and practicality for pharmaceutical applications (Arun et al., 2020; Kulkarni et al., 2015).

Phan et al. (2024) developed a SNEDDS formulation of RC using Capryol 90, Cremophor RH40, and PEG 400 as the oil, surfactant, and co-solvent, respectively. The primary aims of the study were to compare the oral absorption of the RC-SNEDDS with the pure drug and to establish a Level A *in vitro–in vivo* correlation (IVIVC). The pharmacokinetics of both formulations were assessed in beagle dogs following oral administration. Results indicated that the RC-SNEDDS improved oral bioavailability by 1.7 times and C_{max} by 2.1 times compared to the raw drug. A robust IVIVC was demonstrated by correlating the *in vitro* fraction of drug remaining to dissolve with the *in vivo* fraction of drug remaining to be absorbed. Optimal dissolution conditions were determined to be at pH 6.6 in a 900 mL medium, yielding the strongest linear relationship ($R^2 = 0.996$) and the lowest Akakike Information Criterion (AIC) value (506.9), supporting the predictability of the IVIVC model (Phan et al., 2024).

Using an optimized experimental design, Arun et al. (2020) formulated several RC-SNEDDS and evaluated them for emulsification time, ZP, globule size, PDI, and *in vitro* release. The optimized formulation contained 15% isopropyl myristate (lipid), 75% Tween 20 (emulsifier), and 10% ethanol (co-solvent). This composition enabled rapid emulsification in 150 seconds and yielded globules of 68 nm with a ZP of +27 mV. More than 85% of the drug was released within 30 minutes. *In vivo* pharmacokinetic studies in rats showed substantial enhancement in systemic exposure, with approximately 4.89- and 4.45-fold increases in C_{max} and $AUC_{0-24}h$, respectively ($p < 0.0001$), and a reduction in t_{max} by 0.98-fold ($p < 0.05$). These results suggest that the rapid drug release and enhanced intestinal absorption contributed to bypassing hepatic first-pass metabolism, thus improving bioavailability (Arun et al., 2020).

Desavathu et al. (2020) developed and characterized SNEDDS formulations using the aqueous titration method. The selected system, comprising cinnamon oil (oil), Cremophor RH40 (surfactant), and Transcutol P (co-surfactant) in a 1:5 oil-to-Smix ratio, yielded the smallest droplet sizes and demonstrated high thermodynamic stability. The SNEDDS formulations were encapsulated in hard gelatin capsules, making them suitable for drugs with low dose or high solubility requirements. Physical characteriza-

tion confirmed uniform droplet size distribution and stability based on ZP analysis. *In vitro* drug release studies demonstrated significantly enhanced dissolution rates compared to a marketed RC product. The optimized SNEDDS achieved a cumulative release of 97.70 ± 0.25%, significantly surpassing the marketed formulation's release of 63.5 ± 0.28%. These outcomes confirm the potential of SNEDDS in enhancing RC solubility and bioavailability (Desavathu et al., 2020).

Oza et al. (2020) formulated SNEDDS for RC using a simplex lattice design approach. Formulations were prepared using Peceol and ethyl oleate as oil components (in a 1:1 ratio), along with Labrasol and Cremophor EL as surfactants. The optimal SNEDDS contained 15% oil, 50% Labrasol, and 35% Cremophor EL. Physicochemical characterization showed globule sizes ranging from 22.90 ± 1.50 nm to 43.90 ± 1.40 nm, with no significant changes after 3 months of stability testing. High transparency (95.40 ± 1.40% to 99.50 ± 1.10%) and rapid drug diffusion (63.65 ± 1.51% to 93.72 ± 1.46% within 10 minutes) were observed. These data highlight the potential of SNEDDS to significantly improve the aqueous solubility and delivery efficiency of RC (Oza et al., 2020).

Karasulu et al. (2018) designed an RC-SNEDDS consisting of 12.8% oleic acid, 11% Labrafil M, 3.3% Labrasol, and 4.4% Transcutol HP. The resultant nanoemulsion had droplet sizes in the 200–250 nm range and showed excellent physical stability. Permeation studies demonstrated a fourfold increase in drug transport compared to the marketed Crestor® 20 mg tablet. Pharmacokinetic analysis in Yorkshire pigs confirmed higher bioavailability for the SNEDDS formulation. Correspondingly, pharmacodynamic studies revealed superior lipid-lowering effects: triglycerides and total cholesterol were reduced by 37% and 19%, respectively, compared to only 6% and 2% reductions with the commercial formulation. These findings emphasize the formulation's potential to enhance therapeutic outcomes by improving both absorption and efficacy (Karasulu et al., 2018).

To improve the dissolution and antihyperlipidemic activity of RC, Ahsan and Verma (2017) formulated a solid SNEDDS (S-SNEDDS). The solid form demonstrated good flow characteristics, with compatibility studies confirming the absence of interactions between drug and excipients. Electron microscopy revealed spherical, nanosized droplets (~100 nm) without aggregation. Dissolution testing showed a significant improvement: S-SNEDDS achieved 95% release within 60 minutes, compared to 51.89% from the raw drug. *In vivo* evaluations over 14 days indicated notable lipid-lowering benefits, with cholesterol and triglycerides reduced by 33.47% and 40.77%, respectively, and atherogenic index decreased by 81.28%. Additionally, HDL levels increased by 118.43%. These results suggest that the S-SNEDDS platform can substantially improve both the dissolution rate and therapeutic effectiveness of RC (Ahsan & Verma, 2017).

A Quality by Design (QbD) approach was employed to develop liquid SNEDDS (L-SNEDDS) of RC using long-chain lipophilic excipients. Solubility screening revealed Peceol (lipid), Tween 80 (surfactant), and Transcutol HP (co-solvent) as optimal components. Pseudoternary phase diagrams indicated the most extensive nanoemulsion region at a 1:1 S_{mix} ratio. Using a D-optimal mixture design, the optimized L-SNEDDS achieved rapid emulsification (~131 seconds), sub-100 nm droplet size, and >80% drug release within 15 minutes. Permeability studies showed significant enhancement: over 70% drug permeation across rat intestinal tissue *ex vivo* and 1.8- to 2.1-fold increases in *in situ* permeability and absorptivity versus plain drug suspension. *In vivo* pharmacokinetics demonstrated 1.8-fold and 5.7-fold increases in AUC_{o-t} and C_{max}, respectively, along with a 66% reduction in t_{max}. Over 21 days, the optimized L-SNEDDS led to substantial lipid-lowering effects: reductions in total cholesterol (52%), LDL (45%), and triglycerides (35%), outperforming both the marketed formulation and pure drug. Notably, HDL levels rose by 128% ($p < 0.0001$) (Beg et al., 2017b).

Kulkarni et al. (2015) developed S-SNEDDS of RC using a lipid blend of LAS/Capryol 90 and Maisine 35-1, combined with a S_{mix} of Tween 20 and Lutrol E400. The liquid formulation was solidified using Aerosil 200 (1:0.25 w/w ratio). Characterization revealed nano-sized droplets (119.8–228.9 nm), rapid self-emulsification within ~60 seconds, and high transmittance (~100%). *In vitro* release demonstrated a fourfold increase in dissolution within 10 minutes compared to raw RC. Pharmacodynamic studies using a Triton-induced hyperlipidemia model showed improved bioavailability and therapeutic response (Kulkarni et al., 2015).

Another investigation developed RC-loaded S-SNEDDS using Capmul MCM (oil), Tween 20 (surfactant), and PEG 200 (co-surfactant). The optimized liquid SNEDDS was adsorbed onto porous polystyrene spheres, yielding a solid system with good flowability and preserved droplet size post-reconstitution. Dissolution testing showed 98.92% drug release within 60 minutes, significantly higher than the 38.6% release from raw RC. Pharmacokinetic assessments showed a remarkable ~8-fold increase in both C_{max} and AUC_{0-t} over the pure drug, validating the effectiveness of S-SNEDDS in enhancing bioavailability (Panner Selvam et al., 2015).

Rokad et al. (2014) formulated S-SNEDDS using Capmul MCM, Cremophor ELP, and propylene glycol. The optimized system, encapsulated in hard gelatin capsules, showed a ZP of -22.11 mV, particle size of 10.59 nm, and rapid self-emulsification. Drug release was highly efficient, reaching 97.7%, exceeding even the marketed RC product. This study emphasized the benefits of transitioning from liquid to solid SNEDDS for enhanced solubility, stability, and reduced drug precipitation (Rokad et al., 2014).

Balakumar et al. evaluated SNEDDS containing cinnamon oil (30%), Labrasol (60%), and Capmul MCM C8 (10%). The formulation showed consistent droplet size (<200 nm), robust self-emulsification, and high stability across various pH levels. It exhibited a ZP of -29.5 ± 0.63 mV and an average particle size of 122 nm. *In vitro* studies showed improved dissolution, while *in vivo* analysis indicated a 2.45-fold enhancement in bioavailability compared to the plain suspension. The pharmacokinetics followed a one-compartment model, as analyzed using PKSolver 2.0. (Balakumar et al., 2013).

Vesicular nanocarriers

Vesicular carriers including liposomes, niosomes, and chitosomes consist of lipid bilayers or surfactant-based membranes encapsulating drugs. These systems enable targeted delivery and sustained release, improving both pharmacokinetics and pharmacodynamics.

Niosomes

Niosomes are bilayer vesicles composed of non-ionic surfactants and cholesterol. Unlike liposomes, they avoid phospholipids and exhibit greater physical stability (Shrivastava et al., 2025). Salih et al. formulated RC-loaded niosomes using the thin-film hydration method. Span 60-based formulations demonstrated higher drug entrapment and sustained release over 7 hours. TEM showed spherical vesicles ~150 nm in size (Salih et al., 2013).

Chitosomes and liposomal nanoparticles

Ahmed (2020) compared chitosan-coated lipid vesicles (chitosomes) with negatively charged liposomal nanoparticles. Chitosomes demonstrated enhanced cytotoxicity (lower IC_{50}) and broader therapeutic indices, while liposomal formulations showed higher intestinal cell compatibility. These findings suggest chitosomes may be more suitable for targeted delivery in hyperlipidemia, while liposomes are advantageous for cardiovascular therapeutic applications (Ahmed, 2020).

Other nanocarriers

RC, a BCS Class II compound, suffers from low aqueous solubility, which significantly limits its oral bioavailability (Shoukat et al., 2024). To address this challenge, numerous advanced drug delivery systems have been explored to enhance its solubility and dis-

solution. These include nanogels (NGs), nanocrystals (NCs), inclusion complexes, NSs, SDs, and vesicular systems. Below is a summary of key strategies, excluding emulsion-based carriers.

Nanogels (NGs)

NGs are nanoscale hydrogel systems (10–500 nm) that combine high water content with the responsiveness of polymer networks. Their ability to swell, retain water, and provide sustained release makes them suitable for enhancing the solubility of hydrophobic drugs like RC (Gallo et al., 2025; Shoukat et al., 2022). A recent study fabricated interpenetrating polymer network (IPN) NGs using chitosan (CS) and beta-cyclodextrin (β-CD). These NGs significantly improved RC solubility and release compared to conventional formulations. In hyperlipidemic rabbit models, RC-loaded NGs demonstrated marked reductions in LDL-C and increases in HDL, confirming superior therapeutic performance (Shoukat et al., 2022; Shoukat et al., 2024).

Nanocrystals (NCs)

NCs, existing between crystalline and amorphous states, enhance solubility by increasing surface area and reducing particle size. This transformation often involves partial amorphization, increasing surface energy and dissolution rate (Wang et al., 2012). Palani, et al. (2015) developed RC NCs via top-down and bottom-up techniques. The resulting tablets showed a 36% improvement in dissolution and 1.87-fold increase in bioavailability over micronized RC formulations (Palani et al., 2015).

Inclusion complexes with cyclodextrins

Cyclodextrins (CDs) form host-guest inclusion complexes with hydrophobic drugs, thereby enhancing aqueous solubility. Their hydrophobic interior accommodates drug molecules, while the hydrophilic exterior interacts with water (Anjani et al., 2022). Al-Heibshy et al. (2020) prepared RC inclusion complexes using methyl-β-cyclodextrin (M-β-CD) and sulfobutylether-β-cyclodextrin (SBE-β-CD; Captisol®) via kneading and lyophilization. These complexes achieved drug EE up to 105%, 3.7–4.1-fold solubility enhancement, and comparable dissolution to pure RC. Caco-2 cell assays confirmed biocompatibility, and the apparent permeability coefficient (Papp) reached 3.08×10^{-7} cm/s, indicating enhanced intestinal permeation (Al-Heibshy et al. 2020a).

Nanosuspensions (NSs)

NSs consist of pure drug particles dispersed in a liquid medium and stabilized by surfactants or polymers. Particle size reduction into the nanometer range drastically increases surface area and dissolution rate (Jacob et al., 2025). Rani et al. (2023) formulated an RC-NSs using PVP K-30 and Tween 80 via high-pressure homogenization. A 3-factor factorial design optimized particle size (92.79 nm), and PDI (0.201). *In vitro* studies showed significantly improved dissolution compared to pure RC (Rani et al., 2023). Joshi et al. (2023) successfully developed and evaluated transdermal patches loaded with an RC NSs. To enhance the drug's dissolution profile, a NSs was prepared using a precipitation-ultrasonication technique. This method involved blending various water-soluble, film-forming polymers, specifically hydroxyl propyl methyl cellulose (HPMC K4M) and Eudragit. The researchers concluded that these transdermal patches are potentially suitable for sustained drug release, thereby improving patient compliance (Joshi et al., 2023).

Solid dispersions (SDs)

SDs distribute drug molecules within inert hydrophilic carriers in the solid state, usually via melting or solvent techniques (Mhaske et al., 2025). Arjun et al. (2020) prepared RC-SDs via melt fusion and NSs using high-shear homogenization. Tablets made from both forms exhibited enhanced drug release in pH 6.8 buffer within 60 minutes, outperforming both the control and a marketed RC tablet (Arjun et al., 2020).

Nanosponges (NSPs)

NSPs are hyper-cross-linked polymeric nanoparticles characterized by colloidal size and nanoscale porous cavities. β-CD-based NSPs are particularly

attractive for drug delivery due to their ability to sustain drug release, enhance stability, achieve high drug loading, and encapsulate both hydrophilic and hydrophobic agents. These features contribute to improved bioavailability through modulation of pharmacokinetic profiles (Sampathi et al., 2025). Satya Lakshmi et al. (2021) prepared β-CD-based RC-NSPs using the emulsion solvent diffusion method. The resulting RC-loaded NSPs were formulated into extended-release tablets. Release kinetics predominantly followed first-order models, while some formulations aligned with Higuchi or Korsmeyer-Peppas models. Notably, erosion was identified as the dominant mechanism driving drug release in most formulations, rather than diffusion (Satya Lakshmi et al., 2021).

Nanofibers (NFs)

NFs are solid fibers with diameters typically below 100 nm, offering high surface area, exceptional porosity, flexibility, and favorable mechanical properties. These characteristics make nanofibers ideal drug delivery systems for precisely controlling release rate, duration, and site, thereby enhancing therapeutic efficacy and safety (Alijaniha et al., 2025). Mohammed & Al-Gawhari (2024) developed and optimized RC nanofibers and cyclodextrin inclusion complex nanofibers via electrospinning. Pharmacokinetic studies revealed significantly enhanced drug absorption, faster release, and superior bioavailability compared to pure RC and marketed formulations. The nanofibers demonstrated increased AUC and C_{max} values alongside reduced t_{max}, indicating more rapid and efficient systemic uptake (Mohammed & Al-Gawhari, 2024). Additionally, orodispersible films co-loaded with amlodipine besylate and RC were fabricated using electrospinning, achieving rapid dissolution (>90% release within 5 minutes). This method notably improved RC solubility and shows promise for scalable industrial production of fixed-dose combination films (Muratoğlu et al., 2024).

CONCLUSION

Statins, first discovered in the 1970s, remain the most widely prescribed class of antihyperlipidemic agents worldwide. RC, often termed the "super-statin," is distinguished by its potent lipid-lowering efficacy and broad global approval. However, RC's low aqueous solubility and limited permeability result in modest oral bioavailability (~20%) when administered via conventional dosage forms. To overcome these challenges, diverse nanocarrier-based delivery systems have been developed, including polymeric nanoparticles, SLNs, NLCs, SNEDDS, NGs, NCs, NSs, niosomes, NSPs, and NFs. Collectively, these approaches have significantly enhanced RC's solubility, dissolution rate, and pharmacokinetic profile, leading to improved oral bioavailability and therapeutic outcomes. These advancements underscore the considerable potential of nanotechnology-driven delivery platforms as promising strategies for optimizing the oral delivery of RC.

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AUTHOR CONTRIBUTION STATEMENT

Conception (MD), Literature research and writing (KA, MD), Reviewing the text (KA, MD), Supervision (MD).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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