

Advanced Nanocarrier-Based Drug Delivery for PCOS Management**Abhishek Buda¹, Durgesh Dangi², Mahendra Chandana³, Kiran Joshi⁴, Dr. Sandhya Suresh⁵**¹⁻²⁻³Student B. Pharm, Sunrise College of Pharmacy, Umarda, Udaipur, Rajasthan, India⁴Assistant Professor, Sunrise College of Pharmacy, Umarda, Udaipur, Rajasthan, India⁵Associate Professor, Sunrise College of Pharmacy, Umarda, Udaipur, Rajasthan, India

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Abstract:

Polycystic ovary syndrome (PCOS), also referred to as polyendocrine metabolic ovarian syndrome (PMOS), is a common endocrine and metabolic disorder characterized by hyperandrogenism, insulin resistance, chronic inflammation, oxidative stress, and reproductive dysfunction. Conventional treatments primarily target individual symptoms but may be limited by poor bioavailability, adverse effects, and variable therapeutic response. Nanocarrier-based drug delivery systems offer promising strategies for improving drug solubility, stability, bioavailability, controlled release, and targeted delivery. This review summarizes major nanocarrier systems, therapeutic targets, preclinical evidence, and emerging approaches for PCOS management. It also discusses safety concerns, translational challenges, and future prospects for the clinical application of nanomedicine in PCOS.

Keywords: Polycystic ovary syndrome; Polyendocrine metabolic ovarian syndrome; Nanocarriers; Nanomedicine; Targeted drug delivery; Insulin resistance; Hyperandrogenism; Oxidative stress; Controlled release.

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Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine condition characterised by androgen excess, ovulatory dysfunction and polycystic ovarian morphology, together with metabolic and psychological consequences. Depending on the diagnostic criteria applied, its reported prevalence in women of reproductive age ranges from roughly 4% to 21% (4,5). It is the leading cause of anovulatory infertility and carries a long-term risk of obesity, dyslipidaemia, type 2 diabetes and cardiovascular disease (6)

The clinical management of PCOS is guided by the 2023 international evidence-based guideline, which contains 254 recommendations and practice points covering diagnosis, lifestyle, psychological features, non-fertility features and infertility [1]. The guideline development team noted that, although the evidence base has improved over the past five years, much of it remains of low to moderate quality, which underlines how many treatment questions are still open. In 2026 a global consensus process involving patients and health professionals from all world regions renamed the condition polyendocrine metabolic ovarian syndrome (PMOS), stating that it affects about one in eight women and that the old name wrongly implied a disorder of ovarian cysts [2,3].

Current pharmacotherapy is symptom-directed. Insulin sensitisers, ovulation-induction agents and hormonal treatments each address only part of the syndrome, and many patients experience side effects, incomplete response or discontinuation. Many promising bioactive compounds, especially plant-derived polyphenols, cannot be used effectively in their native form because of poor solubility, low oral bioavailability and rapid metabolism [15]. Nanotechnology-based delivery systems have therefore attracted growing interest.

The aim of this article is to provide an organised overview of nanocarrier-based drug delivery for PCOS. We first outline the pathophysiological processes that can be targeted, then describe the limitations of conventional therapy, review the principal classes of nanocarriers and the evidence supporting each, discuss targeting and stimulus-responsive strategies, and finally consider safety, translational challenges and future directions.

Pathophysiology and Therapeutic Targets of PCOS: PCOS is mainly associated with hyperandrogenism, insulin resistance, chronic inflammation, and oxidative stress. These mechanisms are interconnected and contribute to reproductive and metabolic abnormalities.

Hyperandrogenism: Excess androgen production by ovarian theca cells leads to irregular ovulation, follicular arrest, and hormonal imbalance. Therefore, restoring androgen–estrogen balance and normal follicular development is an important therapeutic target.

Insulin Resistance: Insulin resistance causes hyper-insulinemic, which increases ovarian androgen production and further worsens insulin resistance. The PI3K/AKT–GLUT4 pathway is an important target for improving glucose metabolism and ovarian function.

Chronic Inflammation: Low-grade inflammation and increased TNF- α and other pro-inflammatory cytokines contribute to insulin resistance, abnormal follicular development, and ovulatory dysfunction. Thus, reducing inflammation is an important therapeutic strategy.

Oxidative Stress: Excess ROS causes oxidative damage, mitochondrial dysfunction, impaired steroidogenesis, and granulosa-cell injury. Because ROS levels are elevated in PCOS ovaries, they can also be exploited as a trigger for controlled drug release from ROS-responsive nanoparticles.

Limitations of Conventional Pharmacotherapy: Metformin is widely used as an insulin sensitiser in PCOS. However, it frequently causes gastrointestinal effects such as nausea, diarrhoea, abdominal pain and a metallic taste, which reduce adherence and limit long-term benefit [4]. Metformin used alone has also shown conflicting efficacy across studies [12]. Ovulation-induction agents and hormonal therapies act on separate parts of the syndrome and do not correct the underlying metabolic and inflammatory drivers.

They show antioxidant, anti-inflammatory and insulin-sensitising properties in experimental PCOS, yet poor solubility, chemical instability and low oral bioavailability restrict their clinical usefulness [13,15]. Nano-sized carriers can encapsulate hydrophobic molecules, improve their solubility and absorption, and protect them from degradation and metabolism in the body [9]. Compared with conventional dosage forms, delivery systems can also give higher local drug concentrations, lower inter-individual variability and reduced side effects [8].

Nanocarrier Platforms Investigated for PCOS: Nanocarriers, generally ranging from 1–1000 nm, have emerged as promising systems for improving drug solubility, stability, bioavailability, controlled release, and targeted delivery [10]. In PCOS, different nanocarrier platforms have been investigated, including polymeric, lipid-based, inorganic, phytochemical-loaded, and biomimetic systems [21,23].

Polymeric Nanoparticles: Chitosan is widely investigated because of its biodegradability, biocompatibility, and drug-loading capacity [6]. Metformin-loaded chitosan nanoparticles improved testosterone levels, insulin sensitivity, ovarian morphology, and AKT/GLUT4 signalling in letrozole-induced PCOS rats compared with free metformin [12]. Similarly, modified chitosan nanoparticles containing curcumin reduced LH, prolactin, testosterone, and insulin levels and improved ovarian morphology and ovulatory function [11].

Lipid-Based Nanocarriers: Lipid-based systems, including liposomes, niosomes, transethosomes, solid lipid nanoparticles, and nanoemulsions, can enhance drug stability, cellular uptake, and bioavailability (9). Liposomal formulations of resveratrol derivatives have shown beneficial effects on ovarian granulosa-cell steroidogenesis. Hyaluronic acid-coated liposomes containing linagliptin improved insulin sensitivity and lipid profiles in PCOS rats, suggesting potential for targeted delivery [18]. Metformin-loaded niosomes and progesterone-loaded transethosomes have also been investigated for vaginal delivery, with progesterone transethosomes progressing to clinical evaluation in women with anovulatory PCOS [16,17].

Inorganic Nanoparticles: Selenium nanoparticles (SeNPs) have demonstrated antioxidant and insulin-sensitising properties. In experimental PCOS, SeNPs improved glucose metabolism, insulin sensitivity, lipid profile, hormonal balance, inflammatory markers, oxidative stress, and mitochondrial function. Their combination with metformin produced greater improvements than either treatment alone [4]. Other metal and metal-oxide nanoparticles have also been explored for therapeutic and diagnostic applications, although dose-dependent toxicity and immune responses require further investigation [21,22].

Nano-formulated Phytochemicals: Phytochemicals such as curcumin, quercetin, daidzein, and genistein possess antioxidant, anti-inflammatory, and insulin-sensitizing activities but are often limited by poor solubility and bioavailability. Nano formulation can improve their stability, absorption, and pharmacological effects [14]. Daidzein- and genistein-loaded nanoparticles demonstrated greater efficacy than free compounds in a letrozole-induced PCOS model, highlighting their potential for multi-target PCOS therapy [15].

Biomimetic and Vesicular Systems: Biomimetic systems, including exosomes and cell-membrane-coated nanoparticles, provide opportunities for enhanced biocompatibility and targeted delivery. Mesenchymal stem cell-derived exosomes may reduce inflammation and granulosa-cell apoptosis [5]. ROS-responsive macrophage membrane-coated quercetin nanoparticles have shown controlled re-

lease and preferential delivery to the oxidative ovarian environment [19]. Artesunate-containing hybrid nanovesicles have also demonstrated reduc-

tions in cystic follicles and inflammatory responses in experimental PCOS [20].

Table 1: Representative nanocarrier systems evaluated for PCOS/PMOS

Nanocarrier	Payload	Model	Main reported findings	References
Chitosan nanoparticles	Metformin	Letrozole rat	Lower testosterone, HOMA-IR and cystic follicles; more corpora lutea; restored pAKT and GLUT4; better than metformin alone	12
Arg-CS-NACHis self-assembled nanoparticles	Curcumin	Rat	Reduced LH, prolactin, testosterone and insulin; improved ovarian morphology; ovulation and fertility recovery comparable to metformin	6, 11
Selenium nanoparticles (80 nm)	Selenium $\pm$ metformin	Letrozole + high-fat diet rat	Improved insulin sensitivity, lipids, hormones, TNF- α , oxidative and mitochondrial markers; PI3K/Akt up-regulated; combination best	4
Hyaluronic acid-coated liposomes	Linagliptin	PCOS rat	AI-optimised encapsulation; improved insulin sensitivity and lipid profile; ovarian targeting	18
Liposomes (glycerophospholipid)	DMU-212 (resveratrol derivative)	Ovarian granulosa cells	Increased oestradiol and progesterone secretion	6
Cationic niosomes in thermosensitive gel	Metformin	In vitro / in vivo, vaginal	Intravaginal delivery developed for PCOS	16
Transethosomes	Progesterone	Women with anovulatory PCOS	Enhanced vaginal permeation; clinical evaluation performed	17
Daidzein–genistein nanoparticles	Isoflavones	Letrozole rat	Outperformed plain compounds; efficacy comparable to clomiphene citrate	15
Macrophage membrane-cloaked ROS-responsive nanoparticles	Quercetin	PCOS model	Low toxicity, ROS-triggered release, relatively targeted delivery to ovarian lesion	19

Targeting and Stimulus Responsive Strategies:
Targeted nanoparticles improve ovarian delivery using ligands such as hyaluronic acid. ROS-responsive systems enable drug release in the

oxidative PCOS environment. Vaginal delivery and AI/ML-based formulation design can improve efficacy and reduce treatment burden.

Table 2: Therapeutic targets in PCOS and corresponding nano-strategies

Target	Role in PCOS	Nano-strategy	References
Hyperandrogenism / LH–FSH imbalance	Anovulation, cystic follicles, low oestradiol	Selenium and chitosan nanoparticles; isoflavone nanoparticles; liposomal steroid-modulating agents	15
Insulin resistance (PI3K/AKT, GLUT4)	Hyperinsulinaemia, androgen excess, dyslipidaemia	Metformin-loaded chitosan nanoparticles; SeNP + metformin; HA-coated liposomal linagliptin	12, 18
Chronic inflammation	Impaired folliculogenesis; raised TNF- α	Hybrid nanovesicles with artesunate; MSC exosomes; membrane-coated carriers	5, 20
Oxidative stress / ROS	Granulosa cell damage, steroidogenic dysfunction	Antioxidant SeNPs; ROS-responsive quercetin nanocarriers; curcumin nanoparticles	13, 19
Mitochondrial dysfunction	Reduced ATP, membrane potential, complex I activity	SeNPs (alone or with metformin) restoring mitochondrial parameters	4
Poor drug bioavailability / adherence	Limits phytochemicals and metformin	Encapsulation of hydrophobic drugs; vaginal niosomes and transethosomes	15-17

Safety, Biocompatibility and Toxicological Considerations: Any carrier proposed for women of reproductive age must be safe for the reproductive system as well as for the whole body. Nanocarriers built from biodegradable and biocompatible polymers, such as chitosan, are generally considered favourable in this respect, and the preprint review mentioned above reports that in-vivo reproductive toxicity studies showed no adverse effects on oestrous cyclicity, fertility indices or offspring viability [24]. This claim needs confirmation in the peer-reviewed literature.

For inorganic particles the picture is less settled. Silver, copper and other metal nanoparticles can interact with granulosa cells and alter steroid secretion, which may be therapeutic at one dose and harmful at another [6]. High concentrations of nanoparticles may impair drug efficacy, cause unexpected effects or trigger immune responses [7].

Challenges to Clinical Translation

Despite encouraging data, several obstacles separate the current literature from clinical use.

- Reliance on animal models. Most studies use letrozole-induced rats or mice. Letrozole reproduces hyperandrogenism and polycystic ovarian changes but lacks metabolic changes, which is why it is often combined with a high-fat diet [4]. Differences between models make cross-study comparison difficult, and findings may not transfer to the heterogeneous human syndrome.
- Limited mechanistic resolution. Many reports measure whole-tissue endpoints, so it remains unclear which cell types are affected and whether biochemical improvements are the cause or the consequence of restored ovarian histology [4].
- Inconsistent reporting and comparators. Doses, particle characterisation, treatment duration and comparator drugs (metformin, clomiphene, free compound) differ widely between studies [12,13,15], which complicates meta-analysis.

Future Perspectives: Several developments are likely to shape the field. First, the move to the PMOS nomenclature and the recognition of PCOS as a multisystem condition may encourage delivery platforms that address metabolic, inflammatory and reproductive targets together rather than in isolation [2,3]. Combination nano-formulations, such as selenium nanoparticles with metformin, already show that co-delivery can be more effective than single agents [4].

Second, targeted and biomimetic carriers are expected to gain importance. Ligand-modified liposomes, cell-membrane cloaks and engineered exosomes may permit selective action on the ovary

or on specific immune populations, lowering the systemic dose required [5,18-20]. Third, artificial intelligence and statistical design-of-experiments approaches can accelerate formulation optimisation and predict properties such as encapsulation efficiency [17,18].

Fourth, green synthesis and food-grade materials may offer safer and cheaper routes, particularly in low-resource settings, but require rigorous standardisation [14,22]. Finally, the field needs harmonised preclinical protocols, longer follow-up with fertility and offspring endpoints, and early-phase clinical trials that include patient-reported outcomes. Non-oral routes such as vaginal delivery deserve particular attention because they may improve adherence [16,17].

Conclusion

Nanocarrier-based drug delivery is a promising strategy for PCOS because it addresses recognised weaknesses of existing therapy: poor bioavailability of active compounds, systemic side effects and lack of tissue specificity. Preclinical studies with chitosan, selenium, liposomal, niosomal, phytochemical and biomimetic systems consistently report improvements in hormonal balance, insulin sensitivity, oxidative stress, inflammation and ovarian histology, often exceeding the effect of the free drug. However, the evidence is largely limited to short-term rodent studies with heterogeneous designs, and reproductive safety data and human trials are lacking. Progress will depend on standardised models, comprehensive toxicology, scalable manufacturing and carefully designed clinical studies. If these gaps are closed, nanomedicine could become a valuable addition to personalised, multi-target management of PCOS

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