Available online on 15.02.2026 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Review Article

Green solvent-assisted emulsion solvent evaporation approaches for ethyl cellulose micro and nanospheres: Recent advances, formulation strategies, and future perspectives

Santosh Kumar Dash [1], Tusara Kanta Behera [1*], Abdul Sayeed Khan [1], Rudraksh Mohanty [1], Ram Shankar Naik [1], Swarupa Mayee Kalta [2], Srimanta Kumar Das [2], Tekchand Senapati [3], Siddheswar Patel [3]

[1] Department of Pharmaceutics, The Pharmaceutical College, Samleswari Vihar, Tingipali, Barpali, 768029

[2] Department of Pharmachemistry, The Pharmaceutical College, Samleswari Vihar, Tingipali, Barpali, 768029

[3] Department of Pharmacology, The Pharmaceutical College, Samleswari Vihar, Tingipali, Barpali, 768029

Article Info:

Article History:

Received 20 Nov 2025
Reviewed 04 Jan 2026
Accepted 25 Jan 2026
Published 15 Feb 2026

Cite this article as:

Dash SK, Behera TK, Khan AS, Mohanty R, Naik RS, Kalta SM, Das SK, Senapati T, Patel S, Green solvent-assisted emulsion solvent evaporation approaches for ethyl cellulose micro and nanospheres: Recent advances, formulation strategies, and future perspectives, Journal of Drug Delivery and Therapeutics. 2026; 16(2):22-28 *DOI: http://dx.doi.org/10.22270/jddt.v16i2.7547*

For Correspondence:

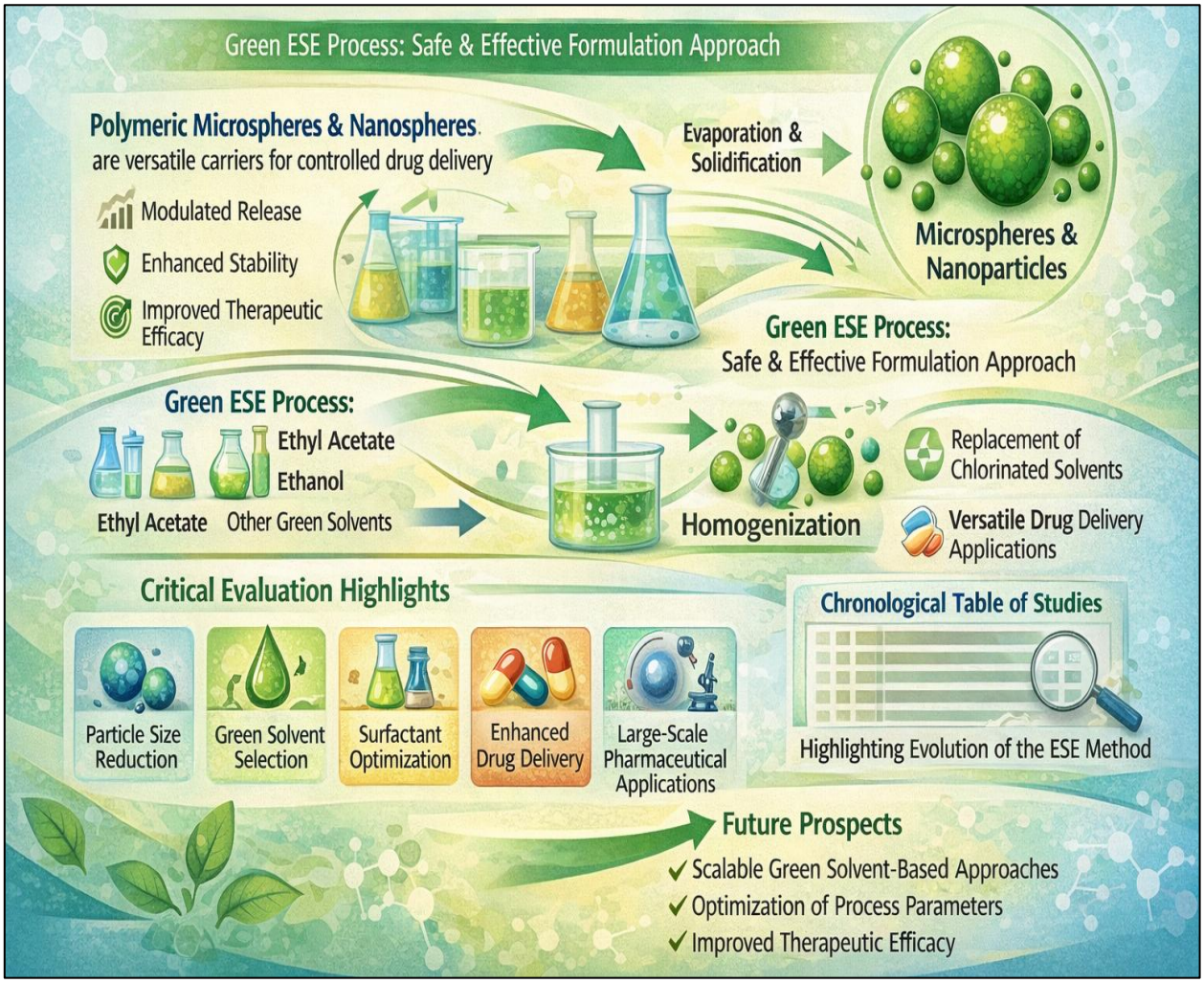
Tusara Kanta Behera, Department of Pharmaceutics, The Pharmaceutical College, Samleswari Vihar, Tingipali, Barpali, 768029

Abstract

Polymeric microspheres and nanospheres are versatile carriers for controlled drug delivery, as they can modulate release profiles, enhance stability, and improve therapeutic efficacy. Among fabrication techniques, the emulsion–solvent evaporation (ESE) method is widely used because of its simplicity, reproducibility, and adaptability to various polymers and drugs. Ethyl cellulose, a hydrophobic and chemically stable polymer, is frequently employed as a matrix-forming polymer. Recent trends emphasize the replacement of toxic chlorinated solvents with environmentally safer alternatives such as ethyl acetate and ethanol. High-energy homogenization is applied to achieve nanoscale particles with improved bioavailability. This review critically evaluates formulation strategies, process parameters, and solvent systems for the preparation of microspheres and nanospheres via ESE. Advances in particle size reduction, solvent selection, and surfactant optimization are discussed. A chronological table of previous studies highlights the evolution of this technique. Finally, current challenges, future prospects, and potential green solvent-based approaches for large-scale pharmaceutical applications are summarized.

Keywords: Controlled drug delivery, Emulsion-solvent evaporation, Polymeric microspheres

Graphical Abstract



1. Introduction

Controlled drug delivery systems (CDDS) have transformed pharmaceutical formulations by enabling precise modulation of drug release, reducing dosing frequency, and enhancing patient compliance[1]. Among various delivery carriers, polymeric microspheres and nanospheres have gained sustained attention due to their structural flexibility, drug encapsulation efficiency, and suitability for oral, parenteral, and targeted delivery[2]. Microspheres are generally defined as spherical polymeric particles with diameters ranging from 1 to 1000 µm, while nanospheres are colloidal particles below 500 nm[3]. The emulsion–solvent evaporation (ESE) technique is one of the most established methods for preparing polymeric particulate systems[4]. It involves dissolving the polymer and drug in a volatile organic solvent to form a dispersed phase, which is emulsified into an aqueous phase containing a stabilizer or surfactant[5]. Evaporation of the organic solvent results in polymer precipitation, producing solid microspheres or nanospheres[6]. This method is highly adaptable and reproducible, making it ideal for pharmaceutical applications[7]. Ethyl cellulose (EC) is widely employed in microsphere and nanosphere formulations due to its hydrophobicity, chemical stability, and sustained-release properties[8]. Its performance depends on polymer concentration, solvent composition, surfactant type, and processing parameters[9]. Traditionally, dichloromethane (DCM) was used as a solvent due to its high volatility and solubility for EC[10]. However, DCM is Class 2 toxic (ICH Q3C) and environmentally hazardous. To address these concerns, recent studies advocate green solvents such as ethyl acetate, ethanol, and isopropyl alcohol[11]. Ethyl acetate, in particular, is widely regarded as a green solvent due to its low toxicity (ICH Q3C Class 3)[12], rapid biodegradability in air, water, and soil, minimal environmental impact (no ozone depletion or persistence), compatibility with EC solubility and emulsion stability[31]. Using ethyl acetate instead of DCM enhances both safety and regulatory compliance, making formulations more sustainable. Mixed solvent systems (e.g., ethyl acetate with ethanol or isopropyl alcohol) further improve polymer solubility and droplet stability, enhancing encapsulation efficiency and uniform particle formation[13]. Surfactants are critical for stabilizing emulsion droplets during emulsion–solvent evaporation. Non-ionic surfactants like Tween 80 and Tween 20 are biocompatible and effective in reducing interfacial tension[14,15]. Higher surfactant concentrations typically result in smaller, more uniform particles[16]. The transition from microspheres to nanospheres is facilitated by high-shear homogenization, which

generates fine emulsion droplets that solidify into nanoscale particles[17,18]. Nanospheres offer enhanced dissolution, better cellular uptake, and potential for targeted delivery[19]. Recent optimization studies focus on homogenization speed, solvent choice, and polymer concentration to ensure reproducible nanoscale systems[20]. Despite advances, challenges remain in scale-up, solvent removal, long-term stability, and regulatory acceptance[21]. Addressing these issues is critical for translating laboratory-scale findings into clinically viable formulations[22].

2. Mechanism of Particle Formation by Emulsion–Solvent Evaporation

The emulsion–solvent evaporation technique is based on the principle of forming polymer droplets dispersed in a continuous aqueous phase, stabilized by surfactants[23]. The dispersed organic phase contains polymer (e.g., ethyl cellulose) and drug, dissolved in a volatile organic solvent such as ethyl acetate. Upon emulsification, mechanical stirring or high-shear homogenization creates droplets of varying sizes, which eventually solidify as the solvent evaporates[24,25].

Key mechanistic steps include:

a) *Droplet formation:* The dispersed phase forms droplets in the aqueous continuous phase. Surfactants like Tween 20 or 80 adsorb at the droplet interface to reduce interfacial tension and prevent coalescence[14,15].

b) *Solvent diffusion and evaporation*: Organic solvent diffuses into the aqueous phase or evaporates under stirring/heat, resulting in polymer precipitation[24]. The rate of evaporation influences particle size, porosity, and morphology[28].

c) *Solidification:* The polymer forms a solid matrix encapsulating the drug. Faster evaporation can lead to porous or hollow microspheres, while slower evaporation produces denser particles[24,25].

d) *Particle stabilization:* Surfactant concentration, type, and molecular weight determine particle stability, aggregation prevention, and size uniformity[16,26]. For nanospheres, high-energy homogenization creates smaller droplets, enhancing drug release control and cellular uptake[17,18,20].

Examples from literature:

- Lamprecht et al. (2004) demonstrated that adjusting surfactant type and concentration directly influenced nanosphere size and polydispersity[18].
- Patel et al. (2020) showed that replacing DCM with ethyl acetate maintainedparticle integrity and encapsulation efficiency, confirming solvent choice is critical[31].

3. Critical Formulation and Process Variables

Particle characteristics in emulsion–solvent evaporation are influenced by multiple interdependent variables:

a) *Polymer concentration:* Polymer concentration is a key factor that affects the formation and characteristics of microspheres and nanospheres. When the polymer content increases, the viscosity of the dispersed phase goes up. This makes it harder for droplets to break apart during emulsification, resulting in larger droplets and, ultimately, larger microspheres. On the other hand, a lower polymer concentration lowers the system's viscosity. This allows droplets to break apart more easily and encourages the creation of smaller droplets, leading to the formation of nanospheres with smaller particle sizes[26].

b) Solvent system: The solvent system significantly affects particle properties by influencing polymer solubility, emulsion stability, and the rate of solvent evaporation. Solvents like ethyl acetate, ethanol, or their mixtures impact how well the solvent diffuses into the external phase and regulate the solidification of the polymer. Additionally, solvent polarity directly affects drug–polymer affinity, which changes the drug loading capacity and shapes the drug release profile from the formed particles [12,13,31].

c) Surfactant type and concentration: Surfactant type and concentration are crucial for stabilizing the emulsion system and preventing droplet coalescence during particle formation. Non-ionic surfactants like Tween 20 and Tween 80 are often used because they lower interfacial tension, increase zeta potential, and boost encapsulation efficiency. However, not using enough surfactant can cause droplet aggregation and unstable particles. On the other hand, using too much surfactant may leave residues on the particle surface. This can affect purity, stability, and drug release behavior[14,15,16].

d) *Stirring and homogenization speed:* Stirring and homogenization speed greatly affect droplet size distribution and the final shape of particles. Moderate stirring speeds usually create microspheres that range from 1 to 1000 µm. In contrast, high shear forces above 8000 rpm cause significant droplet disruption, resulting in nanospheres smaller than 500 nm. Furthermore, homogenization conditions impact particle uniformity, surface features, and drug release rates by controlling how well droplets disperse and their stability[17,20,32].

e) *Temperature and solvent evaporation rate:* Temperature and the rate at which the solvent evaporates are important factors that affect how particles solidify. Higher temperatures speed up solvent removal, which can cause quick phase separation and create porous particles. On the other hand, slower solvent evaporation lets the polymer precipitate gradually, leading to dense, smooth, and uniform spheres with improved structural integrity[28].

f) *Drug–polymer interactions:* Drug-polymer interactions play a crucial role in how well drugs are captured and released. Hydrophobic interactions between the drug and the polymer matrix increase drug retention and allow for a sustained release. In

contrast, hydrophilic interactions can lead to quicker drug diffusion and a rapid initial release. Ultimately, these interactions shape the therapeutic performance and effectiveness of the microsphere or nanosphere delivery system[2,6,19].

Critical insight: Optimizing these variables allows tailoring of particle size, encapsulation efficiency, and controlled release, a key advantage of ESE for both micro- and nanospheres[7,9].

4. Green Solvent Integration and Regulatory Aspects

The shift from chlorinated solvents (DCM, chloroform) to green solvents (ethyl acetate, ethanol, IPA) addresses both regulatory and environmental concerns[12,31,32].

Advantages of green solvent use:

The use of green solvents in pharmaceutical and polymeric formulations offers several significant advantages over conventional organic solvents.

One of the main benefits is **reducing toxicity**. Solvents like ethyl acetate are classified under ICH Q3C as Class 3 solvents. This means they have low toxic potential and pose minimal risk to human health. In contrast, traditionally used solvents, such as dichloromethane (DCM), are in Class 2. These solvents are linked to higher toxicity and possible carcinogenic effects. Moving toward safer solvents improves occupational safety for workers. It also lowers the risk of harmful residual solvents in final products[12].

In terms of **environmental impact**, green solvents are usually biodegradable and have low ozone depletion potential. They also show minimal persistence in soil and water systems. Their quick breakdown and low bioaccumulation help lower long-term environmental pollution. This supports sustainable manufacturing practices and connects pharmaceutical production with environmental protection goals[31].

From a **regulatory perspective**, using green solvents helps meet Good Manufacturing Practice (GMP) guidelines and international regulations. Since these solvents are recognized as safe, their use makes regulatory paperwork easier, reduces scale-up issues, and speeds up the approval process for new formulations[32].

Additionally, green solvents contribute to improved **process efficiency**, particularly when used in mixed solvent systems such as ethyl acetate combined with ethanol. These combinations enhance polymer solubility and promote better droplet stability during emulsification, which in turn improves encapsulation efficiency and particle uniformity. As a result, green solvent systems not only offer safety and environmental benefits but also improve formulation performance and manufacturing reliability[13].

Literature examples:

- Rao et al. (2011) showed that ethyl acetate can replace DCM without altering particle size or drug release, demonstrating practical green formulation[13].
- Patel et al. (2020) prepared EC nanospheres using ethyl acetate and Tween 20 with high encapsulation efficiency and consistent particle morphology[31].
- Sharma et al. (2024) optimized green solvent-based nanospheres for scalable, eco-friendly drug delivery[33].

This demonstrates the feasibility of sustainable and safer micro/nanosphere formulations, a major focus of contemporary pharmaceutics.

5. Future Prospects

a) Sustainable green formulations: The increasing focus on sustainability in pharmaceutical manufacturing has led to more companies using green solvents like ethyl acetate, ethanol, and isopropyl alcohol in emulsion-solvent evaporation (ESE) processes. These solvents are less toxic, biodegradable, and better for the environment than traditional chlorinated or aromatic solvents. Their use reduces environmental pollution and occupational risks, while also lowering regulatory issues related to residual solvent limits. In addition, green solvents tend to have good evaporation rates and provide good polymer solubility. This helps maintain the efficiency of formulations and supports drug delivery systems that follow global sustainability and green chemistry principles[31-33].

b) Scalable manufacturing: For successful industrial translation, the scalability of the ESE method is essential. Continuous ESE processes and high-shear homogenization techniques enable reproducible and controlled production of micro- and nanospheres at a large scale. These systems create uniform droplet formation, narrow particle size distribution, and consistent encapsulation efficiency. Maintaining process parameters like shear rate, temperature, and solvent removal during continuous operation improves batch-to-batch reproducibility. This makes large-scale manufacturing of nanoscale drug carriers practical for commercial pharmaceutical applications[17,20,32].

c) Targeted and stimuli-responsive delivery: Targeted and stimuli-responsive drug delivery uses ethyl cellulose (EC) nanospheres. Surface modification is crucial for better therapeutic results. By attaching EC nanospheres to specific ligands like antibodies, peptides, or folate groups, we can target diseased tissues or cells directly. Also, using pH-sensitive polymers or biodegradable coatings allows the system to respond to triggers. This means drug release can occur due to changes in pH, enzymes, or temperature. This method improves drug availability at the target site, lowers side effects, and boosts overall treatment effectiveness[19,22].

d) Integration with biologics: The incorporation of biologics, such as proteins, peptides, and nucleic acids, into polymeric nanocarriers poses unique formulation challenges because of their sensitivity. Encapsulating these biomolecules requires mild and biocompatible solvents, as well as optimized emulsification conditions to avoid denaturation or loss of biological activity. Gentle mixing, controlled temperature, and limited

exposure to organic phases are crucial for preserving molecular integrity. Successfully incorporating biologics into EC-based systems can greatly improve their stability, protect them from enzymatic breakdown, and enhance their therapeutic effectiveness[21].

e) Regulatory and clinical translation: Regulatory acceptance is a key factor in the clinical use of polymeric drug delivery systems. It is important to use ICH Q3C-compliant solvents and approved surfactants to ensure patient safety and reduce toxicological risks. In addition, scalable and controlled manufacturing processes are necessary to meet regulatory standards for consistency, quality, and safety. Using standardized excipients and validated production methods makes it easier to gain regulatory approval and speeds up the move from laboratory research to clinical and commercial use[12,31].

f) Advanced characterization techniques: Advance characterization techniques are essential for developing and controlling the quality of micro- and nanospheres. In-line particle size monitoring allows for real-time checks on formulation consistency. Zeta potential measurements offer insights into surface charge and colloidal stability. Analyzing surface morphology with methods like scanning or transmission electron microscopy helps us understand particle structure and drug distribution. These analytical tools work together to support a quality-by-design approach. This allows for systematic optimization of formulation parameters and ensures reliable, reproducible, and high-quality drug delivery systems[20,28].

Overall, green solvent-based ESE methods will remain central to next-generation micro/nanosphere drug delivery systems.

Table 1: Chronological summary of studies on emulsion solvent evaporation–based microspheres and nanospheres

Sl. No.	Author (et al.)	Year	Polymer	Solvent system	Surfactant	Particle type	Major contribution	Ref. No.
1	Florence et al.	1982	Polymeric systems	Organic solvents	Tween series	Microspheres	Explained surfactant role in emulsion stabilization	[14]
2	Bodmeier& McGinity	1987	Ethyl cellulose	DCM	PVA	Microspheres	First systematic solvent evaporation microencapsulation	[4]
3	Jain	2000	Biodegradable polymers	DCM	PVA	Microspheres	Scale-up considerations for solvent evaporation	[5]
4	Yang et al.	2001	Ethyl cellulose	DCM	Tween 80	Microspheres	Effect of polymer concentration on release kinetics	[6]
5	Siepmann &Göpferich	2001	Polymeric matrices	Organic solvents	Non-ionic	Microspheres	Mechanistic understanding of polymer solidification	[24]
6	Brigger et al.	2002	Polymeric carriers	DCM	PVA	Nanospheres	Drug targeting advantages of nanospheres	[19]
7	Lamprecht et al.	2004	Ethyl cellulose	DCM	Tween 80	Nanospheres	Demonstrated nanoscale EC particles	[18]
8	Müller & Keck et al.	2004	Polymeric nanoparticles	Ethyl acetate	Non-ionic	Nanospheres	Stability of nanoparticulate systems	[22]
9	Torchilin et al.	2005	Functional polymers	Mixed solvents	PEG-based	Nanospheres	Multifunctional nanocarriers concept	[30]
10	Freitas et al.	2005	PLGA	DCM	PVA	Microspheres	Solvent removal and particle hardening	[11]
11	Reis et al.	2006	Polymeric	DCM	PVA	Nanospheres	Effect of	[17]

			systems				homogenization on size reduction	
12	Mohanraj & Chen	2006	Polymeric carriers	Ethyl acetate	Tween 20	Nanospheres	Therapeutic advantages of nanospheres	[20]
13	Choudhury et al.	2008	Ethyl cellulose	DCM:Ethanol	Tween 80	Microspheres	Improved encapsulation efficiency	[8]
14	Costa & Lobo	2001	Polymer matrices	Volatile solvents	—	Microspheres	Drug release modeling	[28]
15	Dash et al.	2010	Polymeric systems	Organic solvents	Tween 80	Microspheres	Controlled release behavior	[16]
16	Singh et al.	2010	Ethyl cellulose	DCM	Tween 80	Microspheres	Review of formulation variables	[26]
17	Rao &Geckeler	2011	Polymeric nanoparticles	Ethyl acetate	Non-ionic	Nanospheres	Green solvent feasibility	[13]
18	Nair & Koul	2011	Polymeric carriers	Organic solvents	PVA	Microspheres	Industrial relevance and challenges	[21]
19	Kulkarni et al.	2021	Ethyl cellulose	DCM	Tween 80	Floating microspheres	Enhanced gastric retention	[2]
20	Patel et al.	2020	Ethyl cellulose	Ethyl acetate	Tween 20	Nanospheres	Green solvent-based EC nanospheres	[31]
21	Kumar et al.	2022	Ethyl cellulose	Mixed solvents	Tween 80	Nanospheres	Effect of homogenization speed	[32]
22	Sharma et al.	2024	Polymeric systems	Green solvents	Non-ionic	Nanospheres	Eco-friendly scalable formulation	[33]

DCM-Dichloromethane, PVA- Poly Vinyl Alcohol

6. Conclusion

The emulsion–solvent evaporation technique remains a simple, versatile, and widely accepted method for the preparation of polymeric microspheres and nanospheres. Ethyl cellulose is a suitable polymer for sustained drug delivery due to its biocompatibility and film-forming properties. Replacing chlorinated solvents such as dichloromethane with safer alternatives like ethyl acetate supports greener formulation practices without compromising product quality. Control of formulation variables and the use of high-shear homogenization enable effective size reduction from microspheres to nanospheres. Overall, this method offers a scalable and environmentally conscious approach for developing advanced particulate drug delivery systems.

Acknowledgement: We acknowledge the support of The Pharmaceutical College, Barpali, for providing access to library and research facilities for this review. We also grateful to colleagues and peers who provided valuable suggestions and constructive feedback during the preparation of this manuscript.

Author's Contribution: All authors contributed equally to the conception and design of the review. Literature search, data collection, analysis, and manuscript drafting were performed by the authors. All authors critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work

Funding Source: This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The authors declare that there is no conflict of interest regarding the publication of this review article.

Ethical Approval: This article is a review based on previously published studies; therefore, ethical approval was not required.

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