Ethyl Cellulose-Based Micro/Nano Particle Drug Delivery Systems: A Comprehensive Review on Recent Developments

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Abstract: This review evaluates the formulation performance, encapsulation efficiency, and drug-release behaviour of ethyl cellulose-based micro- and nanoparticles for drug delivery. A systematic search of the Scopus database identified 245 initial records, from which 20 studies were selected for final analysis based on strict inclusion criteria. The results indicate that ethyl cellulose-based systems achieve encapsulation efficiencies ranging from 11% to 100%. Critical variables, including polymer concentration and preparation methods such as solvent evaporation and nanoprecipitation, significantly influence particle size and release kinetics. Specifically, higher polymer concentrations typically result in larger particle sizes and more sustained drug release profiles. The review concludes that ethyl cellulose is a highly versatile polymer suitable for oral, topical, and gastro-retentive applications. Although its application is limited by low biodegradability, ethyl cellulose-based micro- and nanoparticles remain effective and promising platforms for enhancing therapeutic efficacy and achieving controlled drug delivery.

Keywords: Ethyl Cellulose, Microparticles, Nanoparticles, Encapsulation Efficiency, Drug Delivery, Sustained Release.

INTRODUCTION

Modern treatments cannot be achieved without effective drug delivery systems, as they are among the most important foundations of therapy and ensure that drugs reach the appropriate site of action at specific rates and durations. Reduced bioavailability, rapid drug degradation, and the need for frequent dosing contribute to fluctuations in plasma drug concentration, increased side effects, and decreased therapeutic efficacy and these limitations are widely associated with traditional drug administration methods [1]. Therefore, controlled and sustained drug delivery systems have been developed to maintain stable drug levels, minimise side effects, and improve therapeutic outcomes [2].

The need for efficient and advanced delivery of therapeutic agents to target tissues and cells has driven significant interest in micro- and nanoparticle-based drug delivery systems. These systems enable controlled drug release and can encapsulate and protect therapeutic agents from degradation, thereby ensuring drug stability and accurate delivery of the required dose [3]. Their small size and large surface area confer unique physical and chemical properties that enhance drug stability, modulate release behaviour, and enable targeted delivery to specific tissues or cells, ultimately improving therapeutic efficacy and reducing systemic toxicity [1].

Ethyl cellulose (EC) is a hydrophobic, non-ionic, nontoxic cellulose derivative with numerous properties that are suitable for making micro- and nano-drug delivery systems. Its hydrophobicity, biocompatibility, and ability to function as both a pharmaceutical adjuvant and a drug carrier qualify it for use in controlled-release formulations [4]. Although EC is safe and biocompatible, it breaks down very slowly in the body. This slow biodegradation can be a limitation for long-term implantable or fully degradable drug-delivery systems, where the material is expected to dissolve naturally after releasing the drug. EC forms a diffusion barrier that regulates drug release rates, making it particularly suitable for sustained-release matrices and encapsulation systems [1]. Pharmaceutical studies have demonstrated that the structural parameters of EC, such as polymer viscosity, molecular weight, and environmental conditions, enable EC□based systems to modulate drug release and delivery effectively [4].

Although the hydrophobic nature of EC enhances drug stability and controls release by acting as an inert barrier insoluble in water, gastric fluids, and intestinal fluids, it also presents limitations. Its poor biodegradability can restrict its widespread use in advanced drug delivery systems, and in some formulations, EC may exhibit limited drug-loading capacity due to its rigid hydrophobic matrix [1]. These

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challenges highlight the need for further optimisation and investigation of EC-based delivery platforms.

Despite the growing use of EC in drug delivery systems, the available studies are scattered and vary widely in terms of formulation methods, particle characteristics, and evaluated outcomes. In addition, there is a lack of a clear and focused summary comparing micro- and nanoparticle systems based on their performance. Therefore, a comprehensive review is needed to understand the role of EC better and to identify key factors that influence its effectiveness in drug-delivery applications.

METHODOLOGY

To ensure a well-defined selection of studies, a structured approach was used to establish the eligibility criteria for this review. The review focused on ethyl cellulose as a key polymer in the development of micro- and nanoparticle-based drug delivery systems. With respect to system types, studies involving particulate carriers such as nanoparticles and microparticles were included. While direct comparison was not the central aim, studies exploring variations in formulation methods or system design were considered, as they provide valuable insights into optimising performance. The outcomes of interest included critical formulation parameters, such as encapsulation efficiency and drug-release profiles, which reflect the effectiveness of the delivery system. Furthermore, variables influencing these outcomes, including preparation techniques and polymer characteristics, were also taken into account. Finally, this review incorporated experimental studies, including both *in vitro* and *in vivo* investigations, to provide a comprehensive understanding of the formulation and performance of ethyl cellulose-based drug delivery systems.

Search Strategy

A comprehensive literature search was conducted in Scopus to identify studies on ethyl cellulose-based micro- and nanoparticles for drug delivery. The search strategy was developed by combining key terms related to the polymer and the type of delivery system. Specifically, the term “ethyl cellulose” was used alongside system-related keywords, such as “nanoparticles” OR “microparticles,” to ensure retrieval of studies focusing on particulate formulations. In addition, application-related terms including “drug delivery”, “controlled release”, and “sustained release” were incorporated to narrow the search to pharmaceutical studies. These keywords were combined using Boolean operators (AND, OR) to refine and optimise the search results. Moreover, filters were applied to include only English-language articles published within a selected time range to ensure relevance and quality. To further enhance the search process, the reference lists of the included articles were also reviewed to identify any additional relevant studies that may not have been captured in the initial database search.

Inclusion and Exclusion Criteria

Studies were considered eligible for inclusion in this systematic review if they met the following criteria: (1) articles published between 2015 and 2025 in peer-reviewed journals, (2) studies investigating ethyl cellulose as a primary or significant component in the formulation, (3) studies focusing on micro- or nanoparticle-based drug delivery systems, (4) studies reporting relevant formulation outcomes such as particle size, encapsulation efficiency, drug loading, or drug release behavior, and (5) full-text articles available for access. In addition, both *in vitro* and *in vivo* studies were included to ensure a comprehensive evaluation of the formulation's performance. Conversely, studies were excluded if they (1) did not involve ethyl cellulose as part of the formulation, (2) focused on drug delivery systems other than micro- or nanoparticles, (3) were not related to pharmaceutical drug delivery applications, (4) were published in languages other than English, or (5) consisted of review articles, conference abstracts, or studies lacking sufficient experimental data.

Study Selection

The study selection process was conducted in several stages to ensure the inclusion of relevant, high-quality studies. Initially, a total of 245 records were identified through a Scopus database search. Following the removal of 26 duplicate records, 219 unique articles remained for screening.

During the first screening stage, the titles and abstracts of all 219 articles were reviewed based on the predefined inclusion and exclusion criteria. At this stage, 153 articles were excluded for reasons such as restricted access or irrelevance to ethyl cellulose-based micro- and nanoparticles for drug delivery. An additional 20 articles were excluded because they were not directly related to the topic of interest. The

remaining 46 articles were assessed in full text for eligibility. During this stage, 26 studies were excluded for reasons including the absence of ethyl cellulose in the formulation, the lack of micro- or nanoparticle-based systems, or insufficient experimental data on formulation characteristics such as particle size, encapsulation efficiency, or drug-release behaviour.

Finally, 20 studies met all the inclusion criteria and were included in the final analysis. The study selection process is summarised in Figure **1**, which illustrates the step-by-step identification, screening, eligibility assessment, and final inclusion of studies.

Heterogeneity and Risk of Bias

In addition, there was noticeable heterogeneity among the included studies in terms of drug type, polymer ratios, preparation methods, particle sizes, and *in vitro* drug release testing conditions. Because of these differences, direct comparison between studies was limited, and a statistical meta-analysis could not be performed. Several studies also lacked complete reporting of formulation parameters or release-kinetic data, which introduces a potential risk of bias. These factors should be considered when interpreting the overall findings of this review.

RESULTS & DISCUSSION

This systematic review included 20 studies on ethyl cellulose-based micro- and nanoparticles for drug delivery. The selected studies used ethyl cellulose either alone or in combination with other polymers, demonstrating its broad use across various formulations. A variety of drugs, both water-soluble and poorly soluble, were incorporated into these systems. In terms of particle type, both microparticles and nanoparticles were reported, with preparation methods varying by study design. In addition, key formulation outcomes, such as encapsulation efficiency and drug-release profiles, were evaluated in most studies. Many of the included studies showed sustained or controlled drug release, indicating the effectiveness of ethyl cellulose in drug delivery. Although the methods and formulations varied between studies, the overall findings highlight the important role of ethyl cellulose in improving drug delivery systems. A summary of the main characteristics and findings of the included studies is presented in Table **1**.

Preparation Methods

Across the included studies, ethyl cellulose (EC) micro- and nanoparticles were prepared using a range of techniques, most commonly solvent evaporation, nanoprecipitation, spray drying, and emulsion–diffusion methods. These preparation techniques played a central role in determining particle size, encapsulation efficiency, and drug-release behaviour. Solvent evaporation, whether in O/W, W/O/W, or non-aqueous emulsions, was the most frequently used method and consistently produced particles with high encapsulation efficiency and sustained-release profiles [5]. This method enables EC to form a dense hydrophobic matrix, thereby slowing drug diffusion and enhancing stability. Studies using high-pressure emulsification,

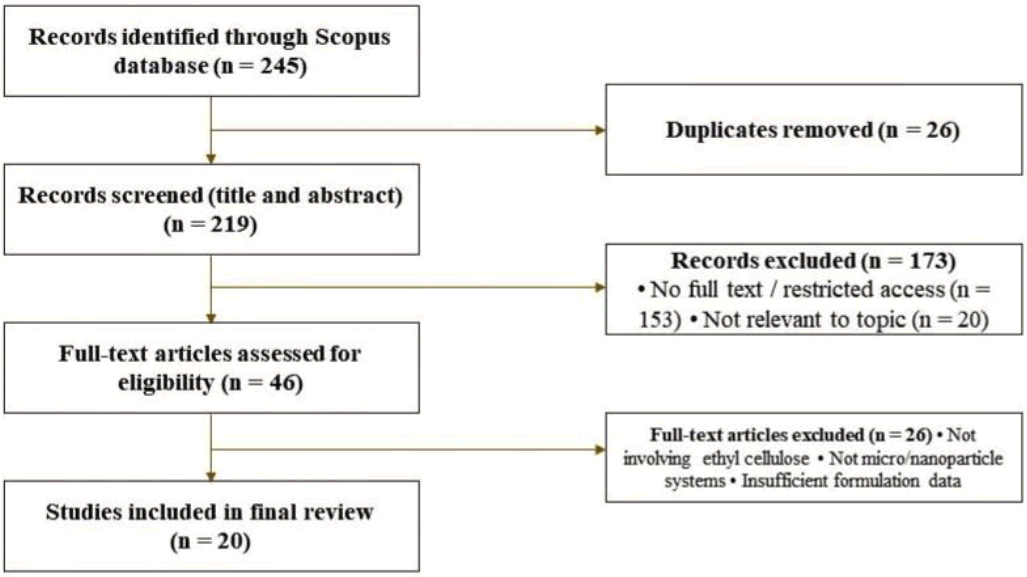

Figure 1: The flow chart of searching and selecting studies.

Table 1: Characteristics of Ethyl Cellulose Microparticles (MPs) Obtained from Included Studies

	Polymer	Drug	Particle Type	Method	Encapsulation Study Efficiency (EE)	Release Profile	Key Findings
Muhaimin & Bodmeier (2025) [17]	EC (also compared with PLGA, PCL)	Propranolol HCl (Pro), Carbamazepine (CBZ)	MPs	Solvent evaporation (O/W and W/O/W emulsions; MP blends), Effect of dispersion time interval (DTI)	Pro: ~72–76%; CBZ: ~90–95%	Sustained release up to 28 days; slower release with higher DTI; CBZ released faster than Pro	EC showed the highest encapsulation efficiency and better controlled release compared to PLGA and PCL. Increasing DTI slowed the release due to pore blocking.
Nawaz M. *et al.* (2025) [20]	EC + Eudragit E100 + stearyl alcohol	Furosemide	MPs (floating, gastro-retentive)	Solvent diffusion–evaporation (O/W emulsion)	~64–82% (highest ~82%)	Sustained release (~90% in 12 h; up to 24 h); initial burst then controlled release	EC provided matrix structure and sustained release. Higher EC → larger particles and slower drug release. The combination with Eudragit improved porosity and the release rate. System improved bioavailability, stability, and gastric retention (>12 h).
Gonçalves *et al.* (2022) [7]	EC + PEG	Retinoic acid, curcumin, resveratrol	MPs	Spray-drying of solution-based systems	>90% (for EC + PEG microparticles)	All drugs showed fast release with profiles stabilising within ~60–80 min	High EE (>90%) for all drugs. Co‑encapsulation did not affect EE or particle formation. Fast release completed within ~60–80 min
Sukmawati *et al.*, (2021) [9]	EC	Betanin (beetroot extract)	MPs	Emulsification method	11.49% (EC 5%); 18.03% (EC 10%); 26.57% (EC 20%)	Followed the Higuchi model; the largest release rate at EC 20%, with a diffusion mechanism	Microparticles effectively protected betanin stability; higher EC concentration increased particle size, entrapment efficiency, and sustained release; antioxidant activity was highest at 20% EC.
Aboueisha *et al.*, (2019) [18]	EC	Fenoprofen Calcium (FC)	MPs	Oil-in-water (O/W) Emulsion Solvent Evaporation (ESE)	H1: 59.69% H2: 61.06% H3: 82.57% (increased with increasing polymer content)	H3 provided sustained release over 12h	H3 (1:2 drug:polymer) showed the best sustained release, prolonged efficacy, no drug-polymer interactions (FTIR/DSC), and better flow and therapeutic effects than those of marketed capsules.
Raza H. *et al.*, (2020) [5]	EC + PEG	Metformin HCl	MPs	Emulsion solvent evaporation	32.98%–82.13% depending on formulation (EP-1 to EP-12)	Sustained release (~73–91% in 12 h); initial burst then controlled release	EC controlled drug release by forming a matrix. Increasing EC → larger particles, higher EE, and slower release. PEG increased porosity → faster release. The system showed good sustained release and improved drug dispersion.
Durgapal *et al.*, (2016) [8]	EC alone (FM1–FM4) and EC + HPMC combinations (FM9–FM12)	Ciprofloxacin	Floating MPs	Non‑aqueous solvent evaporation	EC-only: 92.48–97.92%; EC/HPMC: 91.99–98.76%	Sustained release in 0.1N HCl; floating >15–22 h; swelling 14–25%; release kinetics influenced by polymer ratio	EC increased particle size, yield, floating duration, and sustained release; EC/HPMC (FM9) showed the best performance with the highest floating time (22 h), 90% floating capacity, and ~99% entrapment.
Badewale *et al.* (2025) [23]	EC + Eudragit RS 100	Curcumin, Silymarin, Piperine	Gastro-retentive floating microspheres	Solvent evaporation (floating microspheres)	>98% (optimised batch F3)	Sustained release up to 12 h (≈66–73% drug release);	High entrapment and buoyancy; prolonged gastric retention; improved bioavailability of poorly soluble drugs; promising for hepatoprotection
Kharb and Tanwar (2021) [16]	EC+ PVP	Pregabalin	Microspheres (floating, gastroretentive)	W/O/O multiple emulsion solvent evaporation	96.43 ± 3.14% (optimised)	T60% ≈ 332 min; sustained release over 12 h	High encapsulation efficiency, excellent floating ability (~90%), particle size ~203 µm; suitable for reducing dosing frequency.

such as the formulation of amphotericin B nanoparticles, have demonstrated that applying shear forces can reduce particle size and improve drug dispersion, ultimately enhancing bioavailability.

Nanoprecipitation, used to prepare rifampicin and etoricoxib nanoparticles, typically yields smaller particles with narrower size distributions due to rapid polymer precipitation during solvent exchange [6]. However, this method can result in lower encapsulation efficiency for hydrophilic drugs because of rapid diffusion into the aqueous phase. Spray drying, as observed in the retinoic acid microparticle study, produced uniform particles with very high encapsulation efficiency (>90%). However, the release was faster due to the porous structure formed during drying [7]. Overall, the preparation method strongly influenced the compactness of the EC matrix, the degree of drug entrapment, and the resulting release kinetics.

Types and Sizes of EC Particles

EC has been used to develop different particulate systems, mainly microparticles and nanoparticles, each offering distinct advantages depending on the therapeutic goal. Microparticles were widely reported in formulations designed for oral sustained release, floating systems, and gastro-retentive delivery. Their larger size allows them to hold more polymer, creating a thicker diffusion barrier and slowing drug release. Several studies demonstrated that increasing EC concentration in microparticles leads to larger particle size, higher encapsulation efficiency, and slower drug diffusion [5]. Floating microparticles, such as those developed for furosemide and ciprofloxacin, relied on EC's low density and hydrophobicity to remain buoyant in gastric fluid for extended periods, supporting prolonged gastric residence and sustained drug release [8]. EC microparticles were also effective in protecting sensitive compounds such as betanin and fenoprofen, with the polymer matrix shielding the drugs from degradation and providing controlled release over several hours [9]. Overall, microparticles were most suitable for applications requiring extended release, gastric retention, or stabilisation of labile drugs.

In contrast, nanoparticles were used to improve solubility, enhance absorption, or achieve more efficient penetration into cells or tissues. Their small size increases surface area and enables closer interaction with biological membranes, which is particularly beneficial for poorly soluble drugs such as valsartan, amphotericin B, and bosentan. EC nanoparticles significantly enhanced solubility and bioavailability in these cases, demonstrating the advantage of nanoscale carriers for drugs with limited aqueous solubility [10]. Nanoparticles also exhibited strong sustained-release behaviour, as observed with dexamethasone, mesalamine, and rifampicin, in which EC formed a tight polymeric network that slowed drug diffusion and maintained prolonged therapeutic levels [11]. In some studies, hybrid systems such as EC–chitosan nanoparticles were developed to combine the hydrophobic barrier of EC with the mucoadhesive properties of chitosan, thereby improving intestinal adhesion and controlled release [12]. Nanosponges, another nanoscale structure made from EC, provided highly porous networks that enhanced the solubility and skin penetration of drugs such as posaconazole [13] and simvastatin [14]. These nano sponges have a sponge-like network with internal pores and cavities where the drug is trapped.

Overall, the distinction between microparticles and nanoparticles in EC-based systems reflects their different functional roles. Microparticles are better suited for long-acting oral formulations and gastro-retentive systems, while nanoparticles are more effective for enhancing solubility, improving permeability, and achieving controlled release at the nanoscale. The versatility of EC allows it to be adapted to both particle types, supporting a wide range of therapeutic applications across the included studies.

Drug Delivery Applications

EC-based particulate systems were applied across oral, topical, and gastro-retentive drug delivery routes. Oral delivery was the most common application, particularly for drugs with poor solubility or short half-life. EC nanoparticles significantly improved the oral bioavailability of amphotericin B, valsartan, and mesalamine by enhancing solubility, protecting the drug from degradation, and providing sustained release [15]. Gastro-retentive microparticles, such as those containing furosemide or pregabalin, benefited from EC's buoyancy and slow hydration, enabling prolonged gastric residence and reduced dosing frequency [16].

Topical applications were also supported by EC nano sponges, which improved dermal penetration and drug retention, as demonstrated in simvastatin [14] and posaconazole [13] formulations. These systems provided controlled release and enhanced skin deposition, making them suitable for wound healing and antifungal therapy. Overall, EC's hydrophobicity, film‐forming ability, and stability make it adaptable to multiple delivery routes, with each system leveraging different physicochemical advantages of the polymer.

Encapsulation Efficiency and Drug Loading

Encapsulation efficiency (EE) and drug loading showed wide variation across the included studies, but several clear patterns were consistent. Overall, EE was strongly influenced by four main factors: the amount of ethyl cellulose (EC) used, the drug-to-polymer ratio, the preparation method, and the presence of additional polymers or pore-forming agents. In simple terms, formulations containing more EC or using drugs with low water solubility generally trapped more drug within the particles, leading to higher EE values.

Across many studies, increasing the EC concentration improved EE because the thicker polymer matrix was better at retaining the drug and

preventing its escape during preparation. For example, EC microparticles containing propranolol and carbamazepine achieved EE values of approximately 72–76% and 90–95%, respectively, and performed better than PLGA and PCL in retaining the drugs within the particles [17]. A similar trend was seen in fenoprofen calcium microparticles, where increasing the drug-to-polymer ratio to 1:2 raised EE from about 60% to more than 80%, and the optimised formulation also produced more stable and sustained drug release [18].

Several studies have confirmed that higher EC levels typically lead to larger particles and slower drug release because the denser polymer network makes it harder for the drug to diffuse out [5]. In metformin microparticles, EE ranged from about 33% to 82%, with higher EC content giving better encapsulation and more prolonged release. When PEG was added, it increased porosity, which made the drug escape faster and reduced the sustained release effect [5]. On the other hand, formulations with low EC content or highly water-soluble drugs sometimes showed lower EE. This was observed with rifampicin nanoparticles, which had an EE of approximately 21%, reflecting the difficulty of retaining a highly soluble drug during nanoprecipitation [6].

Some particle types, such as nanosponge and nanocapsule, naturally achieve very high EE values (often 90–99%) because their porous or core–shell structures are designed to trap large amounts of drug. This was reported for simvastatin nano sponges and acetazolamide nano capsules, both of which showed excellent drug retention and controlled release [14].

Overall, the evidence shows that optimising EC concentration and formulation design is essential. Higher EC levels generally improve encapsulation but also slow down release, so each formulation must balance these factors to achieve the desired therapeutic effect.

Drug Release Behaviour

Across the included studies, ethyl cellulose (EC) consistently demonstrated sustained, controlled drug release. However, the exact release pattern depended on factors such as polymer concentration, particle size, drug solubility, and preparation method. A common observation was an initial burst release followed by a slower, prolonged phase. This pattern occurred because drug molecules near the particle surface dissolve quickly, whereas the remaining drug must diffuse through the dense EC matrix, thereby slowing the release rate. This behaviour was reported in several formulations, including furosemide microparticles, metformin microparticles, and mesalamine nanoparticles, all of which showed a rapid early phase followed by controlled release over many hours [5].

Most EC-based systems released the drug primarily via diffusion-controlled mechanisms, as expected given the hydrophobic and non-swelling nature of EC. Many studies have reported that the release profile followed the Higuchi model, indicating that drug molecules diffuse gradually from the polymer matrix into the surrounding medium. This was observed in betanin microparticles, fenoprofen calcium microparticles, metformin microparticles, amphotericin B nanoparticles, and repaglinide nanoparticles, all of which showed diffusion-driven release profiles [18]. In some cases, the release followed first-order kinetics, meaning the release rate decreased over time as the drug concentration inside the particles became lower. This was seen in acetazolamide nanocapsules and etoricoxib nanoparticles [19].

A few studies demonstrated more complex release mechanisms. For example, dexamethasone-loaded EC nanoparticles exhibited non-Fickian release, indicating that drug diffusion was influenced not only by concentration gradients but also by polymer relaxation, in which the EC matrix slowly reorganises, allowing drug molecules to escape [20, 21]. Similarly, mesalamine nanoparticles followed the Korsmeyer–Peppas model, indicating a combination of diffusion and polymer structural changes [11]. These findings suggest that EC can support multiple release mechanisms depending on formulation design.

Polymer concentration played a major role in determining release behaviour. Increasing the amount of EC generally produces a slower, more prolonged release because a thicker polymer matrix creates a stronger barrier to drug diffusion. This trend was consistently reported in furosemide microparticles, betanin microparticles, metformin microparticles, and propranolol/carbamazepine microparticles, where higher EC levels resulted in reduced release rates[20] and longer release durations [5, 9, 17]. In contrast, adding hydrophilic polymers such as PEG or HPMC increased porosity and water penetration, leading to faster release, as seen in metformin microparticles and ciprofloxacin floating microparticles [8].

Overall, the drug-release behaviour of EC-based systems demonstrates that EC is highly effective at producing predictable, sustained, and controlled release profiles. Its hydrophobic nature slows water penetration, its rigid matrix restricts drug movement, and its compatibility with other polymers allows fine-tuning of release rates. These characteristics make EC a versatile polymer for designing long-acting drug delivery systems across a wide range of therapeutic applications. Characteristics of Ethyl Cellulose Microparticles and nanoparticles Obtained from Included Studies are summarised in Tables **1** and **2**, respectively.

Summary of Release Kinetics across Studies

Across the included studies, various mathematical models were used to describe drug release from ethyl cellulose systems, reflecting the underlying release mechanisms (Table **3**). The Higuchi model was the most frequently reported, indicating diffusion-controlled release from the polymer matrix, as seen in formulations such as betanin [9], fenoprofen [18], metformin [5], and amphotericin B [10]. In contrast, some formulations followed the Korsmeyer–Peppas model, which describes a combination of diffusion and polymer relaxation, particularly in systems such as dexamethasone [21] and mesalamine [11] nanoparticles. These differences highlight how polymer composition, particle structure, and preparation method influence the release mechanism.

Other studies reported first-order or zero-order kinetics, showing additional variability in release behaviour. First-order kinetics, where the release rate decreases over time, were observed in acetazolamide nanocapsules [22] and etoricoxib nanoparticles [19]. Zero-order kinetics, which indicate a constant release rate independent of drug concentration, were less common but appeared in optimised floating microspheres [23]. Overall, the variation in kinetic models demonstrates that ethyl cellulose systems do not follow a single release pattern; instead, the mechanism depends on factors such as drug solubility, polymer ratio, and particle morphology.

Factors Affecting System Performance

Several formulation variables were found to influence the performance of EC-based particulate systems. Particle size played a major role in release behaviour and bioavailability: smaller nanoparticles enhanced solubility and absorption, while larger microparticles prolonged gastric retention and sustained release. Polymer ratio was another critical factor; increasing EC content improved encapsulation efficiency and slowed release, while incorporating hydrophilic polymers such as PEG or HPMC increased porosity and accelerated drug diffusion [8].

Drug properties, particularly solubility and lipophilicity, strongly affected entrapment and release. Lipophilic drugs such as curcumin, bosentan, and simvastatin showed excellent compatibility with EC, achieving high EE and stable sustained release [24]. Hydrophilic drugs require modified techniques or co‐polymers to prevent rapid diffusion during preparation. Surface modifications, such as chitosan coating, enhanced mucoadhesion and intestinal retention, demonstrating the potential for targeted delivery [12]. Collectively, these factors highlight the importance of optimising formulation parameters to achieve desired therapeutic outcomes.

***In vitro* vs. *In vivo* Outcomes**

To provide a clearer understanding of the clinical relevance of EC-based particulate systems, it is important to distinguish between the *in vitro* and *in vivo* findings reported in the included studies. Most of the studies in this review evaluated their formulations solely using *in vitro* experiments, such as drug-release testing, encapsulation efficiency measurements, and stability assessments. These *in vitro* results consistently showed that EC-based systems can achieve high encapsulation efficiency, protect drugs from degradation, and provide sustained or controlled release profiles [17, 5].

However, only a small number of studies included *in vivo* investigations, which limits the ability to assess clinical translatability fully. For example, mesalamine EC nanoparticles demonstrated improved antioxidant activity and therapeutic efficacy in an animal model of ulcerative colitis [11]. Similarly, simvastatin nano sponges enhanced wound healing *in vivo* [14], and amphotericin B nanoparticles showed improved oral bioavailability and reduced toxicity in animal studies [10]. These findings suggest potential therapeutic benefits, but the overall number of *in vivo* studies remains limited.

Therefore, while *in vitro* data strongly support the potential of EC-based systems, the lack of extensive *in vivo* evidence means that their clinical performance cannot yet be fully confirmed. More animal studies and early-phase clinical trials are needed to validate the promising laboratory results.

Table 2: Characteristics of Ethyl Cellulose Nanoparticles from Included Studies

Study	Polymer	Drug	Particle Type	Method	Encapsulation Efficiency (EE)	Release Profile	Key Findings
Hajba-Horváth *et al*., (2020) [15]	EC	Valsartan	NPs	Single emulsion–solvent evaporation (oil-in-water)	Not numerically reported (EE measured, but values not provided)	EC: increased solubility in intestinal medium; PMMA: prolonged release;	EC nanoparticles enhanced valsartan solubility; PMMA nanoparticles produced slower, sustained release; both systems formed amorphous drug
Luca *et al*., (2020) [24]	EC	Bosentan	NPs	Solvent evaporation (emulsification technique)	1:2 formulation: (lower) 1:3 formulation: 95.5% EE, 97.5% drug content	1:3 formulation released 25% in 6 h (controlled release)	The optimal drug-to-polymer ratio of 1:3 resulted in improved drug loading and more controlled release, suitable for long-term therapy in pulmonary hypertension.
Calderó *et al*., (2016) [21]	EC	Dexamethasone (DXM)	Polymeric NPs	Low-energy emulsification (PIC/self-emulsification) → nano-emulsion → solvent evaporation	EC retained 92–96% of the drug inside the nanoparticles.	Prolonged release; slower than free DXM;	EC nanoparticles (124–153 nm) showed very high DXM encapsulation efficiency (92–96%). Drug release was slower than free DXM.
Sailaja & Begum (2018) [19]	EC; Carbopol 934 (gel base)	Etoricoxib	Polymeric NPs	Nanoprecipitation (drug+EC in acetone into 0.6% PVA under stirring, solvent removal)	F3 (1:2): ~79.3% entrapment efficiency (highest among formulations)	F3 NPs: 87.1% cumulative release over 12 h (sustained);	F3 (1:2 drug: polymer) was optimal: highest EE (79.3%), high drug content (97%), stable zeta potential (–43.8 mV), and best sustained release.
Mohammed and Al-Gawhari (2022) [13]	EC, PVA (stabiliser)	Posaconazole (PCZ)	Nanosponges (EC NS) -a sponge-like network with internal pores where the drug is trapped.	Emulsion–solvent diffusion	Not reported	NS showed sustained *in vitro* release over 7 h;	EC nanosponges markedly enhanced PCZ solubility and sustained release; NS-loaded carbopol gel significantly improved dissolution and topical delivery versus pure PCZ gel, suggesting better dermal antifungal performance.
Aboelazayem *et al*., (2025) [14]	EC	Simvastatin	Nanosponges (~786 nm)	Emulsion solvent evaporation	97.86–98.65% (all NS formulas)	Sustained release; slower than SV suspension; influenced by solvent choice, drug amount, and PVA concentration.	EC nanosponges were porous, high-surface-area carriers with excellent EE (~98%), strong sustained release, and significantly enhanced skin retention and wound healing *in vivo*.
Gautam *et al*., (2024) [11]	EC	Mesalamine (MES, 5-ASA)	Polymeric NPs	O/W emulsion–solvent evaporation	87.9 ± 1.6% entrapment efficiency (optimised formulation)	Burst ~52% release in simulated gastric medium (2 h), then sustained to ~93% over 48 h in intestinal/colonic media;	Optimised EC NPs achieved high EE and controlled colonic delivery; *in vivo*, MES-NPs increased GSH and SOD and reduced LPO in ulcerative colitis, indicating enhanced antioxidant and therapeutic effect.
Namazi (2023) [12]	Ethyl cellulose (core) + Chitosan (coat)	Repaglinide (RPG)	Polymeric nanoparticles (EC/CS NPs)	Emulsification solvent-evaporation (O/W)	66% (optimised batch)	30% release in acidic medium; 90% in PBS over 24 h;	The EC/CS ratio strongly affected size, EE, and release; the CS coating improved mucoadhesion; EC increased drug loading; the nanoparticles showed sustained release and strong intestinal adhesion.

(Table 2). Continued.

Study	Polymer	Drug	Particle Type	Method	Encapsulation Efficiency (EE)	Release Profile	Key Findings
Kaur *et al*., (2020) [10]	EC	Amphotericin B (AmB)	Polymeric NPs	High-pressure emulsification solvent evaporation (HPESE)	60 ± 2%	Sustained release up to 72 h;	EC nanoparticles maintained AmB in monomeric (less toxic) form, improved oral bioavailability (~15-fold vs native AmB), reduced hemolysis (8-fold less than Fungizone®), showed strong gastric stability, and enhanced antifungal activity.
ined release*:* *20*.65% i6) [6]	EC	Rifampicin (RIF)	Polymeric NPs	Nano precipitation	20.98%	Sustained release: 20.65% in 24 h vs 90% in 15 min for free drug	Stable for 180 days; cytocompatible; molecular dynamics confirmed strong EC–RIF interactions; suitable for TB therapy.

Table 3: Summary of Release Kinetics

Kinetic Model	Release Mechanism	Representative Drug/Formulation	Reference
Higuchi Model	Diffusion-controlled release from the ethyl cellulose matrix	Betanin nanoparticles	Sukmawati *et al*., 2021 [9]
		Fenoprofen microspheres	Aboueisha *et al*., 2019 [18]
		Metformin-loaded system	Raza *et al*., 2020 [5]
		Amphotericin B formulation	Kaur *et al*., 2020 [10]
Korsmeyer–Peppas Model	Combined diffusion and polymer relaxation (anomalous transport) and or swelling	Dexamethasone nanoparticles	Calderó *et al*., 2016 [21]
		Mesalamine nanoparticles	Gautam *et al*., 2025 [11]
First-Order Kinetics	Release rate depends on the remaining drug concentration in the carrier; it decreases over time	Acetazolamide nanocapsules	Quinteros *et al*., 2016 [22]
		Etoricoxib nanoparticles	Sailaja & Begum, 2018 [19]
Zero-Order Kinetics (Uncommon)	Constant release rate independent of drug concentration	Floating microspheres	Badewale *et al*., 2025 [23]

LIMITATIONS

Although this review provides a clear overview of ethyl cellulose-based micro- and nanoparticle systems, several limitations should be acknowledged. First, the included studies used different preparation methods, drug types, and testing conditions, which makes direct comparison difficult. Many studies also lacked complete data on important parameters such as encapsulation efficiency, release kinetics, or long-term stability, limiting the ability to draw strong conclusions. In addition, most findings were based on *in vitro* experiments, with only a few studies providing *in vivo* evidence, leaving the real clinical performance of these systems uncertain. Finally, the review included only English-language articles published within a specific time range, so that some relevant studies may have been missed. These limitations highlight the need for more standardised and comprehensive research on ethyl cellulose‐based delivery systems.

CONCLUSION

This review demonstrates that EC is a highly versatile and effective polymer for the development of micro- and nanoparticle drug delivery systems. Across 20 studies, EC consistently provided high encapsulation efficiency, strong physical stability, and sustained or controlled drug release. Its hydrophobic nature enables excellent compatibility with poorly soluble drugs, while its ability to form dense matrices supports long-acting formulations. The reviewed literature shows that preparation method, polymer

concentration, particle size, and drug properties are key determinants of system performance. EC microparticles are particularly suitable for gastro-retentive and prolonged release applications, whereas EC nanoparticles enhance solubility, absorption, and targeted delivery. Hybrid systems, such as nanocapsules and nanosponges, further expand the applicability of EC for topical and transdermal routes. Overall, although EC-based particulate systems show promising sustained-release behaviour and improved drug stability *in vitro*, the limited number of *in vivo* studies means that their therapeutic benefits cannot yet be fully confirmed. More animal studies and clinical investigations are needed to validate their potential and support their translation into clinical practice. Continued research into polymer modifications, combination systems, and advanced preparation techniques will further strengthen EC's role in modern drug delivery.

SELF-DECLARATION

During the preparation of this systematic review, a few digital tools were used to support the writing and language-editing process. Grammarly was used to improve grammar and sentence structure; Jenni AI was used to enhance the clarity, organisation of ideas, and references in line with journal format; and Google Translate was occasionally used to verify wording and ensure accurate English expression. These tools were used solely to enhance readability and language quality. All content was carefully reviewed, validated, and revised by the authors. The authors accept full responsibility for the accuracy, originality, and overall quality of the final manuscript.

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