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Modern pharmaceutical applications of Eudragit polymers in Hot Melt Extrusion and 3D printing technologies

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Abstract

Objective

The pharmaceutical production environment is increasingly adopting progressive methods like hot-melt extrusion (HME) and three-dimensional (3D) printing to expand personalized, effective, and scalable drug delivery systems. Both techniques rely heavily on the excipient Eudragit (EUD), which represents a broad family of methacrylate-based polymers. This review targets to supply a wide account of the application of EUD polymers in HME and 3D printing, with a centralization on their role in controlled drug release systems of sustained, immediate, and aimed types.

Materials and Methods

The review surveys the utilization of numerous grades of EUD, like EPO, RL, RS, L100, S100, and L100-55, in formulation design, process optimization, and drug release mechanisms. The discussion encompasses the evaluation of formulation strategies, processing situations, and post-processing stability. Innovations in recent years, containing smart and functionalized EUD-based systems with mucoadhesive, colon-specific, and theranostic properties, are also examined. Additionally, mechanical characteristics and drug-polymer compatibility are analyzed as critical determinants of successful formulation.

Results

EUD polymers have been demonstrated to support a broad spectrum of drug delivery platforms and dosage forms, proposing versatility and adaptability to pharmaceutical processing. Case studies and recent expansions show the capability of EUD to enable controlled release mechanisms, while also addressing particular therapeutic requirements. Smart functionalization of EUD systems has expanded their potential to include mucoadhesion, site-specific delivery, and diagnostic utilizations. However, challenges stay, containing issues of thermal degradation through processing, insufficient miscibility between drugs and polymers, and sensitivity to moisture. These limitations pose meaningful formulation challenges that must be managed carefully via process-specific and formulation-specific solutions.

Conclusions

This review underscores the central role of EUD polymers in next-generation pharmaceutical manufacturing, exclusively in the context of HME and additive manufacturing. While these polymers hold great promise for enabling progressive drug delivery systems, technical challenges persist, containing drug–polymer miscibility, risk of thermal degradation, and maintenance of post-processing integrity. Addressing these issues is crucial for unlocking the full potential of EUD polymers in future drug expansion. By integrating case studies, formulation strategies, and mechanistic perception, this review supplies a worth resource for researchers and formulators seeking to exploit the adaptability of EUD in modern pharmaceutical utilizations.

Keywords: 3D printing, Controlled drug release, Eudragit (EUD) polymers, Hot-melt extrusion (HME), Methacrylate copolymers

Abbreviations: 2,4-D=2,4-dichlorobenzaldehyde, BAP=benzyl amino purine, PC=paclitaxel.

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Introduction

The concept of controlled drug delivery is a dynamic and multifaceted area of simultaneous pharmaceuticals and medicine (Wang et al., 2020). Researchers are continually exploring novel attitudes to drug production, with a strong emphasis on technologies that progress physicochemical properties, bioavailability, and patient compliance (Dumpa et al., 2021). Controlled drug delivery systems are designed to raise therapeutic outcomes by minimizing under- and overdosing created by uncontrolled release, reducing the requirement for frequent administration, and delivering drugs to particular sites with greater precision. Among their advantages are the capability to hold stable drug levels, reduce side effects via optimized dosing, and progress patient adherence (Langer, 1980). An ideal drug delivery system should be passive,

free from leachable impurities, biocompatible, mechanically robust, comfortable for patients, capable of delivering higher drug loads, non-hazardous in the event of uncontrolled release, and easy to administer, withdraw, manufacture, and sterilize. It should also supply a high degree of specificity in targeting organs or tissues. Polymer-based drug delivery systems meet most of these requirements and have thus become a major centralization of biomaterials study in recent years (Ghosh, 2004). These polymers are exclusively advantageous because they are biodegradable, biocompatible, and easily cleared from the body, thereby reducing dosing frequency. They also hold drug concentrations within the therapeutic window and progress patient acceptance by masking unpleasant tastes and odors (Nikam et al., 2023). Furthermore, polymer-based systems can regulate release kinetics, raise the solubility of poorly water-soluble drugs, and enable site-specific delivery within the gastrointestinal tract (Patra et al., 2017). In recent decades, the pharmaceutical industry has witnessed major advancements in drug delivery, especially with the expansion of sophisticated manufacturing platforms like hot-melt extrusion (HME) and three-dimensional (3D) printing (Fina, 2020). These platforms have become prominent for producing solid dosage forms with accurate control over release kinetics, geometry, and site-specific targeting—features not easily achieved applying conventional tableting or coating techniques. The fused deposition modeling (FDM) method of 3D printing, which constructs dosage forms by layering melted material, is exclusively relevant, as it is closely linked to the HME process (Patil et al., 2024). HME, a solvent-free and continuous process, has gained widespread utilization due to its scalability, versatility, and suitability for preparing solid dispersions, exclusively for poorly water-soluble drugs. It permits thorough mixing of drugs and polymers at elevated temperatures and shear situations, consequence in homogeneous systems with increased bioavailability, taste masking, and stability. Thus, HME tasks both as a pharmaceutical manufacturing method and as a preparatory step for producing FDM-compatible filaments (Dos Santos et al., 2021). FDM-based 3D printing, applying these filaments, permits the on-request fabrication of personalized dosage forms with programmable geometries and tailored release profiles, aligning with the goals of precision medicine and flexible manufacturing. In the HME process, a blend of polymers and drugs is conveyed via a heated barrel applying a single- or twin-screw extruder and then extruded via a die into numerous shapes, which can be adjusted by the operator (Bandari et al., 2021). In some cases, additives like plasticizers are incorporated to progress material extrusion and processability (Tran et al., 2021). Processing temperatures typically exceed the polymer's glass transition temperature (T_g) and melting temperature (T_m), enabling molecular-level mixing of drugs and polymers. This supplies different benefits, containing the elimination of solvents, simplified production, and compatibility with automation, all highly valued in pharmaceutical manufacturing (Tambe et al., 2021). HME has been applied with diverse polymers to create

multiple dosage forms, like tablets (Cantin et al., 2021; Patki et al., 2020), pellets (Emam et al., 2021; Dumpa et al., 2018), implants (Stansbury & Idacavage, 2016), and transdermal systems (Koutsamanis et al., 2020). Its applying in mixture with 3D printing has further accelerated innovation in novel drug delivery systems. Among the most momentous polymers in these processes are Eudragit (EUD) polymers, a versatile class of polyacrylates with diverse solubility profiles that make them exclusively suitable for sustained-release formulations (Koutsamanis et al., 2020). Originally expanded in Darmstadt and Weiterstadt and marketed by Evonik Industries in the 1950s, EUD polymers stay essential in modern drug delivery. They are distinguished by their heat stability, tunable pH-dependent solubility, and functional adaptability. The EUD family includes methacrylate copolymers with different permeability, charge, and dissolution pH thresholds, permitting utilizations in time-controlled release (Eudragit RL/RS), gastro-resistance and gastrointestinal targeting (Eudragit L100/S100), and taste masking (Eudragit E PO). Their significance is underscored by their inclusion in the USP-NF, BP, PhEur, and the *Handbook of Pharmaceutical Excipients* (Patel et al., 2011). In spite of their versatility, the effective utilization of EUD polymers in HME and 3D printing poses challenges, containing narrow processing windows, drug–polymer miscibility issues, and the requirement for plasticizers to ensure sufficient melt flow, filament flexibility, and printability. While numerous investigations have examined EUD-based systems individually, wide evaluations of their behavior across multiple manufacturing and drug-release platforms stay scarce. This study addresses this gap by showing a systematic evaluation of the role of EUD in modern drug delivery, supplying a scientific and practical resource for formulation scientists, pharmaceutical engineers, and regulatory professionals.

Eudragit Polymers

Until the 1950s, all oral drugs—regardless of their sophistication—shared a major limitation: they lacked the capability to control the timing or site of release of their active components. To address this, Eudragit (EUD) was expanded by Röhm & Haas GmbH in Darmstadt. The name *Eudragit* derives from the Greek word *Εύ* (“good”) and the German word *dragieren* (“sugar coating”), signifying an “exceptional functional coating” solution to this challenge. The introduction of the first EUD-coated pharmaceuticals marked a turning point in pharmaceutical history. EUD products are specialty polymers with diverse solubility characteristics, which Röhm researchers distinguished as a key feature for drug delivery. Their first pharmacological coatings, expanded in 1953, were alkaline-soluble and resistant to gastric acids, thereby enabling the release of active compounds in the intestine rather than the stomach. Variants of this original EUD type

are still broadly applied for coating oral solid dosage forms like tablets, capsules, and granules (Yurtsal & Hasdemir, 2022). In the late 1950s, further improvements introduced EUD coatings that dissolve in gastric acid. Subsequent generations of EUD were expanded to regulate drug release over extended durations, known as retard preparations, which withstand gastric acid and hold therapeutic activity throughout the gastrointestinal tract, thereby progressing the effectiveness of particular medications. Today, EUD study and production are integrated into the Chemicals Business Area of Evonik Industries AG, with manufacturing facilities in Darmstadt, Weiterstadt, and Worms. EUD is synthesized via polymerization of acrylic and methacrylic acids or their esters, like butyl ester or dimethylaminoethyl ester. It is officially distinguished in different pharmacopeias, containing the USP-NF, BP, Ph. Eur., and the *Handbook of Pharmaceutical Excipients* (Patel et al., 2011). Over time, EUD acrylic polymers have been introduced in a chronological sequence of grades, each tailored to particular pharmaceutical requirements (Patel et al., 2011). Structurally, EUD polymers are synthetic acrylic copolymers, prepared from esters of acrylic and methacrylic acid applying free radical polymerization (Wen & Park, 2010; Nollenberger & Albers, 2013). Their physicochemical properties are identified by their functional groups (Figure 1), while their solubility within the gastrointestinal tract is governed by monomer conformation and polymerization situations (Wen & Park, 2010). Due to their resistance to digestive enzymes and bodily fluids, EUD polymers are classified as non-biodegradable. Originally marketed as organic solvent solutions, the product line has since expanded to include alternative physical forms like aqueous dispersions (D), granules (100), powders (PO), and organic solutions. The introduction of aqueous dispersions has meaningfully reduced environmental impact (Malá et al., 2014; Thakral et al., 2013). EUD polymers exhibit excellent film-forming potencies, containing high flexibility, low water vapor permeability, strong pigment-binding capacity, and broad formulation versatility (Nollenberger & Albers, 2013; Ceballos et al., 2005). They are broadly applied in pharmaceutical manufacturing to design solid dosage forms with tailored release profiles for modified-release utilizations. Additionally, they protect active pharmaceutical components from environmental stressors like humidity and light, and serve traditional film-coating purposes (Wen & Park, 2010; Nollenberger & Albers, 2013). EUD polymers also prevent interactions between the drug core and coating layers, further progressing stability and patient compliance (Nollenberger & Albers, 2013). A comparative summary of the different EUD grades, their functional groups, and solubility characteristics is shown in Table 1.

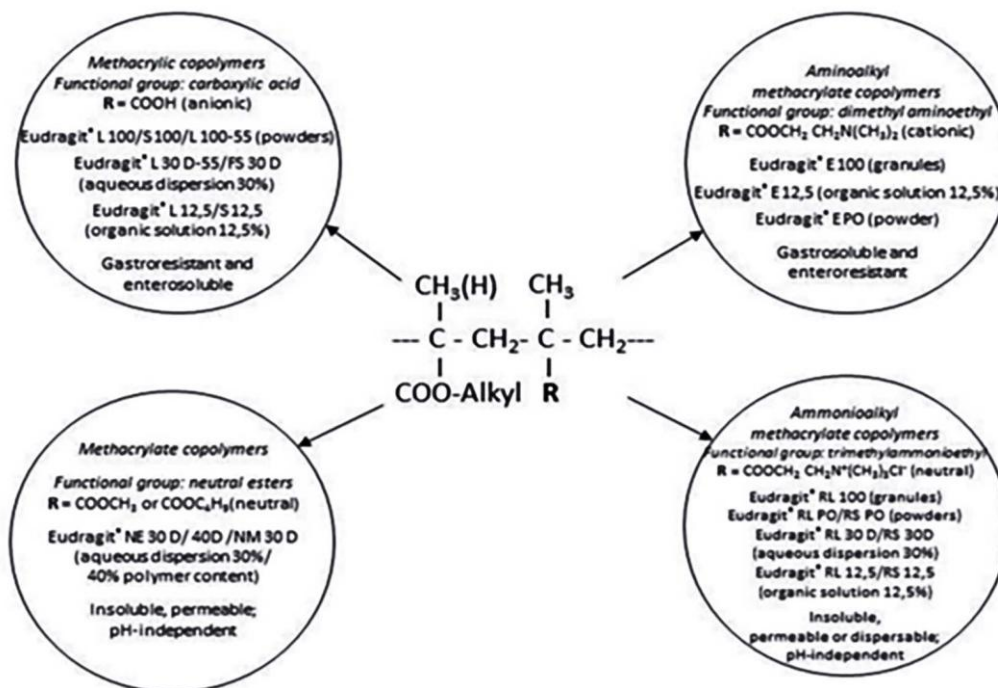


Figure 1. Structures of representative Eudragit copolymers, illustrating their functional groups (R) and related physicochemical properties (adapted from Naiserová et al., 2019).

Table 1. Comparative summary of major Eudragit grades applied in pharmaceutical utilizations

Eudragit Grade	Functional Group	pH Solubility Range	Solubility Behavior	Primary Utilizations
Eudragit E PO	Dimethylaminoethyl methacrylate	Soluble below pH 5.0	Cationic, dissolves in gastric pH	Taste masking; immediate gastric release
Eudragit L100	Methacrylic acid–methyl methacrylate (1:1)	Soluble above pH 6.0	Anionic; enteric soluble	Enteric coating; small intestine targeting
Eudragit S100	Methacrylic acid–methyl methacrylate (1:2)	Soluble above pH 7.0	Anionic; delayed release	Colon targeting; enteric coating
Eudragit L100-55	Methacrylic acid–ethyl acrylate (1:1)	Soluble above pH 5.5	Anionic; gastric-resistant	Enteric tablets; pediatric-friendly formulations
Eudragit RS PO	Ethyl acrylate, methyl methacrylate + 5% quaternary ammonium compound (QAC)	pH-independent; insoluble	Swellable; low permeability	Sustained release (low permeability)
Eudragit RL PO	Ethyl acrylate, methyl methacrylate + 10% quaternary ammonium compound (QAC)	pH-independent; insoluble	Swellable; higher permeability	Sustained release (higher permeability)

Characterization and types of Eudragit polymers: Methacrylate copolymers can be broadly categorized into pH-dependent soluble types and pH-independent insoluble types. The anionic copolymers Eudragit L, S, and FS, which display pH-dependent solubility, are predominantly employed in gastro-resistant dosage forms. In contrast, the pH-independent copolymers, like Eudragit NE, NM, RL, and RS, are broadly applied in sustained-release formulations (Vasileiou et al., 2017; Vysloužil et al., 2013). With the exception of the acid-soluble Eudragit E, all EUD polymers are applied in modified-release drug delivery (Gallardo et al., 2008).

Classification of Eudragit polymers: EUD polymers can be classified based on their intended utilization or the type of formulation generated (Patel et al., 2011; Bulja et al., 2017). The important classes include: Time-controlled drug release via sustained-release formulations, Gastro-resistance and gastrointestinal (GI) targeting via enteric formulations, and Moisture protection and taste/odor masking via protective formulations.

Eudragit for time-controlled drug release: EUD polymers are commonly employed to expand formulations with customized release profiles, enabling controlled release of active pharmaceutical components over predetermined time frames. By regulating drug delivery throughout the gastrointestinal tract (GIT), these polymers progress therapeutic effectiveness and raise patient compliance. Tailored release profiles can be achieved by combining different Eudragit grades, exclusively Eudragit RL and Eudragit RS, which differ in permeability. Neutral ester dispersions like Eudragit NE and Eudragit NM supply sustained-release properties without the requirement for additional plasticizers. Collectively, these polymers enable cost-effective processing and therapeutically optimized dosage forms by proposing: Sustained and time-controlled release of drugs, Reduced dosing frequency, Increased patient adherence, and Progressed manufacturing efficiency. A comparative summary of the distinguishing characteristics of selected Eudragit grades (RL, RS, NE, and NM) is shown in Table 2 (Evonik Industries, 2023).

Eudragit for gastro-resistance and gastrointestinal (GI) targeting: Eudragit polymers are broadly employed in enteric formulations to protect active pharmaceutical ingredients (APIs) from degradation in the gastric environment and to raise therapeutic effectiveness. The most commonly applied grades for this purpose are Eudragit L and Eudragit S, which serve as coating polymers enabling drug targeting to particular regions of the gastrointestinal tract. These anionic methacrylate copolymers exhibit pH-dependent solubility: they stay intact in gastric fluid and dissolve at increasing pH levels, thereby supplying controlled and site-specific drug release (Chandak & Prasad Verma, 2010). A further advantage of these polymers is their capability to be

combined in different proportions, permitting modulation of the dissolution threshold and enabling accurate targeting within the intestine or colon.

Table 2. Distinguishing characteristics of selected Eudragit grades (RL, RS, NE, and NM)

Trade Name	T _g (°C)	Form / Permeability	Physical Properties
Eudragit RL 100	63 ± 5	Granules / High permeability	Colorless, clear to cloudy granules; faint amine-like odor
Eudragit RL PO	63 ± 5	Powder / High permeability	White powder; faint amine-like odor
Eudragit RL 30 D	55	30% aqueous dispersion / High permeability	Milky-white, low-viscosity liquid; faint odor
Eudragit RL 12.5	—	12.5% organic solution / High permeability	Light yellow, low-viscosity liquid; clear to slightly cloudy with solvent odor
Eudragit RS 100	65	Granules / Low permeability	Colorless, clear to cloudy granules; faint amine-like odor
Eudragit RS PO	65	Powder / Low permeability	White powder; faint amine-like odor
Eudragit RS 30 D	55	30% aqueous dispersion / Low permeability	Milky-white, low-viscosity liquid; faint odor
Eudragit RS 12.5	—	12.5% organic solution / Low permeability	Light yellow, low-viscosity liquid; clear to slightly cloudy with solvent odor
Eudragit NE 30 D	-8	30% aqueous dispersion / Low permeability	Milky-white, low-viscosity liquid; faint odor
Eudragit NE 40 D	-8	40% aqueous dispersion / Low permeability	Milky-white, low-viscosity liquid; faint odor
Eudragit NM 30 D	11	30% aqueous dispersion / Low permeability	Milky-white, low-viscosity liquid; faint odor

The benefits of Eudragit for enteric coatings include: pH-dependent drug release tailored to GI physiology, Progressed stability of acid-sensitive active components, Increased therapeutic effectiveness via site-specific release, Excellent storage stability, and Colon-aimed delivery (especially with Eudragit S grades). Structurally, Eudragit L and S are copolymers derived from methacrylic acid and ethyl acrylate, with a weight-average molar mass of almost 125,000 g/mol (Evonik Industries, 2023). These materials are available as white, free-flowing powders or dispersions, proposing versatile processing and formulation flexibility. Eudragit L grades (e.g., L 100, L 12.5, L 30D-55, and L 100-55) dissolve at lower intestinal pH values (~5.5–6.0), making them suitable for drug release in the duodenum and jejunum. In contrast, Eudragit S grades (e.g., S 100, S 12.5) dissolve only at higher pH (~7.0), thereby enabling colon targeting. The distinguishing characteristics of selected Eudragit L and S grades are summarized in Table 3.

Table 3. Distinguishing characteristics of Eudragit L and Eudragit S grades

Trade Name	Tg (°C)	Form	Target GI Region	Dissolution Behavior	Physical Properties
Eudragit L 100	>130	Powder	Jejunum	Dissolves above pH 6.0	White powder; faint odor
Eudragit L 12.5	>130	12.5% organic solution	Jejunum	Dissolves above pH 6.0	Colorless to slightly cloudy liquid; odor of isopropyl alcohol
Eudragit L 30D-55	96	30% aqueous dispersion	Duodenum	Dissolves above pH 5.5	Milky-white, low-viscosity liquid; faint odor
Eudragit L 100-55	96	Powder	Duodenum	Dissolves above pH 5.5	White powder; faint odor
Eudragit S 100	>130	Powder	Colon	Dissolves above pH 7.0	White powder; faint odor
Eudragit S 12.5	>130	12.5% organic solution	Colon	Dissolves above pH 7.0	Colorless to slightly cloudy liquid; odor of isopropyl alcohol

Eudragit for moisture protection and taste masking: Eudragit polymers also perform a critical role in protective coatings, exclusively for increasing the stability of moisture- and light-sensitive drug substances and progressing patient acceptability. Among these, Eudragit E grades are broadly employed due to their cationic nature, derived from dimethylaminoethyl methacrylate as the functional group (Bulja et al., 2017; Chandak & Prasad Verma, 2010). Eudragit E polymers supply multiple advantages: Moisture protection for sensitive APIs, Taste and odor masking to progress patient adherence, pH-dependent solubility, dissolving rapidly in gastric fluid (below pH 5), Increased dosage form aesthetics, like smooth and glossy coatings, Cost-effective processing, since effective efficiency is achieved with thin, minimal coating layers, and progressed swallowability and gastrointestinal transit. These characteristics make Eudragit E exclusively suitable for oral dosage forms, especially chewable tablets, granules, and pediatric formulations. The primary grades include Eudragit E 100, Eudragit E 12.5, and Eudragit E PO, which differ mainly in form and physical characteristics. Their distinguishing properties are summarized in Table 4 (Evonik Industries, 2023).

Eudragit polymers in drug delivery systems-ophthalmic drug delivery: One of the major challenges in ophthalmic drug delivery is achieving and holding a therapeutically effective drug concentration at the target site. This is restricted by different physiological and anatomical barriers, containing rapid tear turnover, restricted corneal permeability, and the protective blink reflex, all of which meaningfully reduce drug residence time and absorption (Ch'Ng et al., 1985). Consequently, conventional eye drops typically demonstrate poor bioavailability, with less than 10% of the administered dose reaching intraocular tissues (Farkouh et al., 2016).

Table 4. Distinguishing characteristics of Eudragit E grades

Trade name	Form	Physical properties
Eudragit E 100	Granules	Colorless to yellowish granules with a characteristic amine-like odor
Eudragit E 12.5	12.5% organic solution	Light yellow, low-viscosity liquid; clear to slightly cloudy; characteristic solvent odor
Eudragit E PO	Powder	White powder with a characteristic amine-like odor

Eudragit (EUD) polymers exhibit favorable characteristics for ophthalmic formulations, like biocompatibility, non-toxicity, cationic charge, and the capability to supply sustained and controlled release, making them exclusively suitable for overcoming ocular delivery challenges (Harris & Robinson, 1992; Khopade & Jain, 1995). Ana Rita et al. (2007) expanded ocular drug delivery systems for acetazolamide applying Eudragit RS 100 and RL 100 via compressed anti-solvent technology. The consequencing microparticles exhibited a slower release rate compared to conventional drug formulations, with diffusion being the primary release mechanism and polymer swelling further participating to drug transport (Duarte et al., 2007). Similarly, Verma et al. (2013) formulated acetazolamide-loaded Eudragit RL 100 nanoparticles via a nanoprecipitation method. This system meaningfully progressed ocular bioavailability and extended the release duration of the drug. In another study, Zhang et al. (2014) investigated genistein-loaded nanostructured lipid carriers (GEN-NLC) coated with cationic Eudragit RS 100 applying melt-emulsification and surface adsorption techniques. The Eudragit-coated GEN-NLC demonstrated extended precorneal residence, increased corneal penetration, and progressed pharmacological effectiveness compared to uncoated carriers. These results highlight the potential of Eudragit-based surface modifications for increasing drug retention, absorption, and therapeutic outcomes in ophthalmic drug delivery (Mortazavi et al., 2005; Zhang et al., 2014).

Buccal and sublingual drug delivery: The buccal and sublingual mucosae propose advantageous routes for systemic drug delivery due to their rich vascularization, avoidance of hepatic first-pass metabolism, and potential for either rapid or sustained drug release, depending on the formulation plan (Narang & Sharma, 2011). The permeability of the buccal mucosa is estimated to be 4–4000 times higher than that of the skin. Sublingual administration permits for rapid absorption and progressed bioavailability of small-molecule drugs; however, it is less suitable for sustained-release formulations. In contrast, the buccal mucosa demonstrates lower permeability but is more appropriate for sustained-release systems. As a result, buccal delivery has emerged as a hopeful route for the administration of peptide-based drugs with low molecular weight, high potency, and long biological half-life (Harris & Robinson, 1992; Mohammadabadi

& Mozafari, 2018). The relative permeability of oral mucosae typically decreases in the subsequent order: sublingual > buccal > palatal (Ch'Ng et al., 1985). At physiological pH, mucus exhibits a negative charge due to sialic acid and sulfate residues, which participates to mucoadhesion. In this environment, mucus forms a cohesive gel that adheres to epithelial surfaces (Ali et al., 1998). Consequently, bioadhesive polymers are broadly applied in buccal drug delivery systems. Such polymers have long been applied in dentistry and surgery for adhesion to both hard and soft tissues. An optimal buccal film should possess flexibility, elasticity, softness, and mechanical strength to withstand oral activities. Additionally, it must exhibit strong mucoadhesive properties to stay in place for the intended duration, while limiting swelling to avoid discomfort. Thus, the mechanical, bioadhesive, and swelling characteristics of buccal films are key determinants of their efficiency (Nair & Chien, 1996). Both buccal and sublingual routes are broadly utilized for systemic therapy due to their transmucosal permeability (Hoogstraate et al., 1996). The sublingual mucosa, being thinner, more permeable, and more vascularized than the buccal mucosa, supplies a rapid onset of action, making it suitable for drugs requiring quick therapeutic effects (Giri et al., 2010). Conversely, the buccal mucosa, although less permeable, proposes a broad, stable surface suitable for the utilization of retentive systems, thereby enabling extended and controlled drug release (Madhav et al., 2009; Shakya et al., 2011). Diarra et al. (2003) expanded an intra-buccal controlled-release system for fluoride delivery by formulating tablets with a granular matrix composed of hydroxyapatite, Eudragit®, and ethyl cellulose. This matrix design achieved sufficiently high local concentrations for therapeutic effectiveness while minimizing systemic side effects.

Oral drug delivery: Oral administration stays the most preferred route of drug delivery due to its convenience and high patient compliance. However, it is often restricted by variable plasma concentrations, frequent dosing requirements, and gastrointestinal side effects, exclusively with poorly tolerated or rapidly metabolized drugs. The incorporation of Eudragit (EUD) polymers into oral dosage forms proposes effective solutions to these challenges by enabling controlled and sustained drug release. Methacrylate-based EUD polymers, especially the RS and RL grades, are broadly applied in oral drug delivery systems due to their adjustable permeability and capability to form durable, pH-independent films. For example, Badir et al. expanded vancomycin-loaded nanoparticles applying Eudragit RS via a double-emulsion solvent evaporation method. The formulation demonstrated a biphasic release profile, consisting of an initial burst followed by extended release over 24 hours, making it suitable for sustained oral delivery of peptide antibiotics (Heidarpour et al., 2011; Delf Loveymi et al., 2012). Similarly, Cetin et al. (2010) formulated diclofenac sodium nanoparticles with Eudragit L100 and poly(lactic-co-glycolic acid) (PLGA), achieving controlled release and reducing the gastrointestinal adverse effects commonly related

to NSAID therapy. Eudragit has also been applied to raise the solubility of poorly water-soluble compounds. Tang et al. (2011) prepared Eudragit E100 nanoparticles via nanoprecipitation to progress the oral bioavailability of flavonoids like genistein. Their system achieved a two-fold improve in drug release compared to conventional capsules. In another study, Momoh et al. (2014) generated diclofenac sodium microspheres with Eudragit RS100 and RL100 applying solvent evaporation, achieving sustained release while reducing mucosal irritation related to extended NSAID therapy. Collectively, these investigations demonstrate the versatility of Eudragit polymers in improving drug release kinetics, progressing bioavailability, and reducing gastrointestinal side effects, making them worth excipients in oral formulations.

Colon drug delivery: The colon represents a unique target for drug delivery, exclusively for the treatment of local diseases (e.g., inflammatory bowel disease) or for systemic delivery of drugs that degrade in the upper gastrointestinal tract. Eudragit polymers, exclusively the pH-sensitive grades that dissolve above pH 7, are broadly employed in colonic drug delivery. Quinteros et al. (2010) expanded a mesalamine delivery system by coating tablet cores with dual protective layers. The inner layer, composed of chitosan, shielded the drug from premature release in the small intestine, while the outer layer of Eudragit L100 prevented degradation of the chitosan-coated core until reaching the colon, where enzymatic activity-initiated drug release. Similarly, Lee et al. (2012) investigated thiolated Eudragit microspheres for oral vaccine delivery against *enterotoxigenic Escherichia coli*. Their outcomes demonstrated the capability of the system to stimulate both systemic and mucosal immunity, emphasizing its potential for oral vaccine utilizations. Eudragit has also been investigated in parasitic infection management. Dea-Ayuela et al. (2006) prepared Eudragit L100 microcapsules via spray drying for oral vaccination against *Trichinella spiralis*. These microcapsules supplied effective antigen protection and delivery, supporting their potential in oral immunization strategies. Voltan et al. (2007) later designed core-shell nanoparticles consisting of a poly (methyl methacrylate) (PMMA) core coated with Eudragit L100/55 via emulsion polymerization. These anionic nanoparticles proposed a versatile platform for protein adsorption, presenting a hopeful approach for protein-based oral vaccines. Together, these results underscore the role of Eudragit-based formulations in aimed colonic delivery, vaccine expansion, and parasite management, demonstrating their importance in both therapeutic and prophylactic utilizations.

Transdermal drug delivery: Eudragit polymers have also been investigated in transdermal systems to raise drug permeation and skin adherence. Małolepsza-Jarmołowska et al. (2003) evaluated the mechanical properties of cast Eudragit E100 films modified with cohesiveness promoters (succinic or citric acid) and triacetin as a plasticizer. The consequencing films were

elastic, self-adhesive, transparent, and pale yellow in color, exhibiting strong adherence to the skin without wrinkling. Drug release from the system followed erosion-controlled kinetics of the hydrophilic Eudragit E100 polymer, consequence in complete drug release within 20 minutes. These results highlight the potential of Eudragit-based films as fast-acting transdermal delivery systems.

Vaginal drug delivery: Vaginal drug delivery proposes advantages for localized therapy, but challenges like acidic pH, enzymatic activity, and mucosal instability often hinder effective drug transport. Eudragit polymers have shown promise in overcoming these barriers. Mulligan (1993) demonstrated that Eudragit RS100 suppositories including sildenafil supplied adequate release profiles. Similarly, Kadian and Harikumar (2009) formulated intravaginal tablets combining lactic acid and Eudragit E100 (1:1 ratio), which dissolved into a gel at physiological vaginal pH (3.8–4.4). These gels proposed an acid reserve capable of neutralizing excess alkalinity, thereby progressing treatment of acute infections. More progressive attitudes have employed nanotechnology. Yoo et al. (2011) prepared biocompatible pH-sensitive nanoparticles applying Eudragit S100 via a modified quasi-emulsion solvent diffusion method. Encapsulating fluorescent probes (sodium fluorescein or Nile red), these nanoparticles protected labile compounds from acidic degradation and achieved therapeutically relevant concentrations within the vaginal mucosa. The authors concluded that Eudragit-based pH-sensitive nanoparticles are hopeful carriers for vaginal delivery of microbicides, peptides, and protein therapeutics.

Gene delivery: Gene therapy represents a rapidly advancing field with potential utilizations in both inherited and acquired disorders. Eudragit-based nanoparticles have been investigated as non-viral carriers for nucleic acids due to their biocompatibility and capability to protect genetic cargo. Wang et al. (2003) synthesized nanoparticles from PLGA blended with Eudragit E100, successfully delivering plasmid DNA encoding mouse interleukin-10 and preventing autoimmune diabetes in vivo. Other investigations have announced the applying of Eudragit L100/55 nanoparticles as anionic carriers for protein surface adsorption, proposing a versatile platform for DNA and protein-based delivery while holding structural integrity essential for immunogenicity (Voltan et al., 2007). In addition, nanoparticles prepared with Eudragit RL100 and RS100 have been employed for the effective administration of antisense oligodeoxynucleotides, further affirming the role of Eudragit polymers in gene silencing and therapy.

Vaccine delivery: Eudragit polymers are broadly utilized in oral and mucosal vaccine delivery owing to their pH sensitivity and protective properties. Lee et al. (2012) investigated thiolated Eudragit microspheres for oral immunization against *enterotoxigenic Escherichia coli*. The system successfully induced both systemic and mucosal immunity, proposing its potential as a vaccine carrier. Similarly, Dea-Ayuela et al. (2006) expanded Eudragit L100 microcapsules via

spray drying for oral vaccination against the nematode *Trichinella spiralis*. These microcapsules demonstrated protective effects and supported antigen delivery in harsh gastrointestinal situations. Expanding on this, Voltan et al. (2007) designed core-shell poly(methyl methacrylate) (PMMA) nanoparticles with an outer shell of Eudragit L100/55. The anionic nanoparticles supplied a versatile platform for protein adsorption, establishing them as hopeful tools for oral and mucosal vaccine delivery.

Hot-melt extrusion (HME)

The hot-melt extrusion (HME) process relies on an extruder comprising a motor-driven screw housed within a modular barrel, heating elements distributed across different barrel zones, and a shaping die at the outlet. The screw geometry can be configured to convey, compress, and homogenize raw materials effectively. Heat is generated both externally, via barrel heaters, and internally, via shear forces, consequencing in the melting of polymer carriers and active pharmaceutical ingredients (APIs). The rotating screw not only facilitates forward movement of the materials but also ensures uniform mixing. Key process parameters, like barrel temperature, screw speed (RPM), feed rate, die pressure, and vacuum level for devolatilization—are carefully monitored and controlled. These parameters are reproducible, scalable, and adjustable, permitting for accurate modulation of the terminal product's properties. Figure 2 shows a typical modular hot-melt extruder, emphasizing its separate functional zones. HME has gained meaningful attention in pharmaceutical manufacturing due to its capability to raise drug solubility and bioavailability, as well as to enable the expansion of innovative drug delivery systems. Additional advantages include continuous processing, elimination of solvents, and broad compatibility with diverse excipients and APIs (Patil et al., 2016).

Types of screw extruders: In pharmaceutical hot-melt extrusion (HME), screw extruders are classified based on their configuration and mechanical action, with each design tailored to particular processing requirements and regulatory standards for dosage form manufacturing. The most common types include single-screw extruders (SSEs), twin-screw extruders (TSEs), and multi-screw extruders (MSEs). Each type proposes separate advantages in terms of mixing efficiency, shear control, and processing versatility. **Single-screw extruders (SSEs):** Single-screw extruders are the earliest and most broadly established type of extruder, valued for their mechanical simplicity, low maintenance, and cost efficiency. Since their introduction in the late 19th century, SSEs have undergone relatively restricted technological expansion (Johnson et al., 2025). An SSE consists of a continuously rotating screw within a barrel, capable of producing high-quality molten material and generating stable pressure for consistent throughput. Within an

SSE, operations like feeding, conveying, melting, devolatilization, pumping, shaping, and light mixing can be achieved.

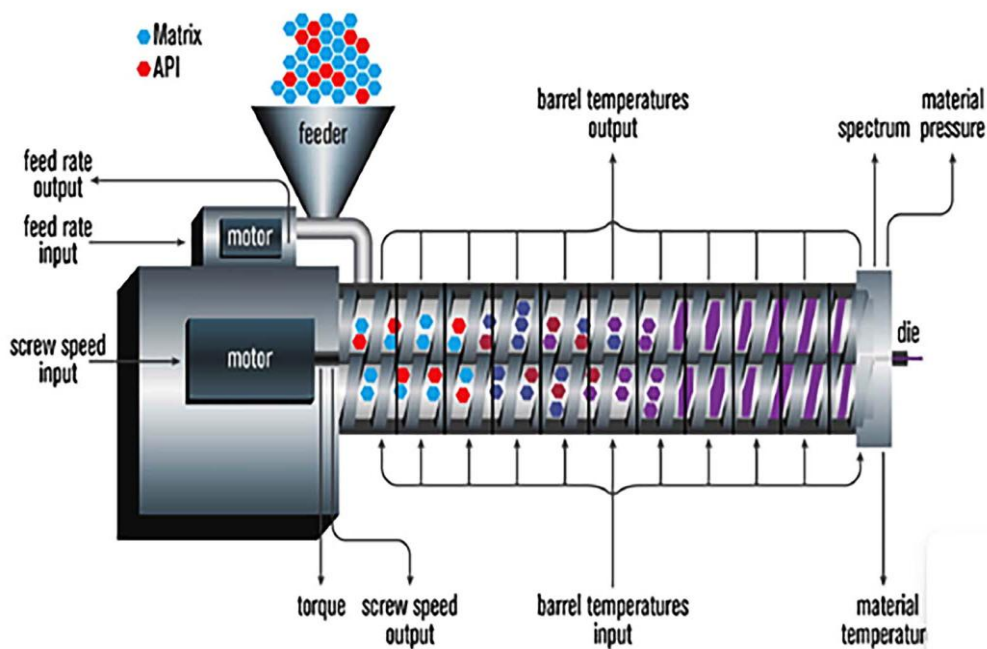


Figure 2. A schematic diagram of a typical hot-melt extruder

Raw materials are introduced via a feed hopper and subsequently transported along the barrel via the rotating flighted screw. The output rate is directly impressed by the screw's revolutions per minute (Crowley et al., 2007). Due to their essential features—low cost, simplicity, and reliable efficiency, SSEs stay broadly applied in HME for the production of extruded products, although they are gradually being supplanted by more versatile technologies (Ghebre-Sellassie et al., 2003).

Twin-screw extruders (TSEs): Twin-screw extruders, first expanded in the 1930s, were designed to overcome the limitations of single-screw systems by integrating multiple mechanical tasks into a continuous operation (Crowley et al., 2007). A TSE features two parallel, rotating agitator assemblies mounted on shafts. This configuration permits for different screw designs and operating situations across the extruder's zones—from material feeding via the hopper, to melting, mixing, and ultimately conveying the product to the metered pumping zone (Crowley et al., 2007; Collins et al., 2021). TSEs can be classified as either co-rotating (screws rotating in the same direction) or counter-rotating (screws rotating in opposite directions). In pharmaceutical HME, TSEs are preferred due to their self-cleaning capability, increased mixing efficiency, reduced residence time, and overall process flexibility [68]. These features make TSEs

exclusively effective for manufacturing amorphous solid dispersions, controlled-release matrices, and formulations involving thermolabile APIs (Crowley et al., 2007; Breitenbach, 2002).

Multi-Screw extruders (MSEs): Multi-screw extruders (MSEs), an emerging class of progressive extrusion technology, utilize more than two screws and are applied in the processing of complex pharmaceutical formulations. Depending on the design, screws may be arranged in a linear configuration (three or five screws) or in a circular pattern (six or eight screws) (Kohlgrüber, 2007). MSEs supply superior distributive mixing compared to SSEs and need lower shear energy, which reduces the risk of thermal degradation in heat-sensitive materials. Positive displacement flow in intermeshing screw regions ensures uniform melt quality, making MSEs highly suitable for formulations involving viscous polymers, high drug loadings, or continuous twin systems (Loukus et al., 2004).

HME in pharmaceutical utilizations and study: Hot-melt extrusion (HME) technology has proven to be transformative in pharmaceutical manufacturing, owing to its capability to integrate multiple processing steps, like blending, melting, homogenizing, shaping, and devolatilization—into a single continuous operation. Beyond its technical merits, HME aligns well with regulatory frameworks, exclusively via its compatibility with Quality by Design (QbD) principles and Process Analytical Technology (PAT) tools, in line with U.S. FDA guidance on modern pharmaceutical manufacturing (Feng & Zhang, 2018; Martin, 2013). Originally expanded and broadly applied in the food and plastics industries, HME has increasingly been adapted for pharmaceutical utilizations, where it participates to progressed solubility, controlled release kinetics, and the expansion of personalized dosage forms. One of its most meaningful utilizations is the preparation of solid dispersions, especially for poorly water-soluble active pharmaceutical ingredients (APIs), like ritonavir, troglitazone, and suvorexant (Repka et al., 2018; Zhang et al., 2017). A solid dispersion is defined as a molecular-level distribution of an API within a hydrophilic carrier matrix, either crystalline or amorphous, that raises dissolution and bioavailability (Martin, 2013; Patil et al., 2016; Zarrabi et al., 2020). The shear forces and thermal energy generated through HME promote molecular dispersion, thereby converting APIs into amorphous solid dispersions with markedly progressed solubility and oral bioavailability, exclusively for Biopharmaceutics Classification System (BCS) Class II and IV drugs. Furthermore, HME permits the design of sustained, controlled, and aimed-release drug delivery systems by tailoring formulation conformation, screw configuration, and processing situations (Repka et al., 2008). For example, sustained-release lipid matrices, like those incorporating diclofenac sodium, have been expanded via HME and subsequently compressed into tablets (Vithani et al., 2013). A notable example of site-specific drug delivery via HME is the work of

Bruce et al., who prepared colon-aimed tablets of 5-aminosalicylic acid applying Eudragit S100 and a methacrylic acid–methyl methacrylate copolymer (1:2). Incorporation of the plasticizer triethyl citrate (TEC) reduced the glass transition temperature (T_g), thereby progressing processing situations, while also affecting drug release kinetics via leaching effects. Additionally, the inclusion of citric acid as a pH modifier regulated drug release by lowering the microenvironmental pH, thereby delaying polymer ionization and dissolution onset. Beyond increasing solubility and enabling modified release, HME also proposes advantages in taste masking, a critical factor in pediatric and geriatric formulations where palatability directly impresses patient adherence. This is often achieved by incorporating taste-masking agents like Eudragit E-PO, which suppress bitterness by preventing drug release in saliva and permitting dissolution only at the lower pH (<5) of the stomach (Keating et al., 2018). In summary, HME represents a versatile, multipurpose platform in pharmaceutical product expansion, with utilizations spanning solubility enhancement, controlled and aimed delivery, taste masking, and dose reduction. Its inherent adaptability to continuous manufacturing further strengthens its role in modern drug expansion pipelines. As a scalable, regulatory-compliant, and future-ready technology, HME continues to gain prominence as a cornerstone of progressive pharmaceutical manufacturing.

Eudragit in hot-melt extrusion (HME)-based formulations

Hot-melt extrusion (HME) has evolved into a transformative technology in modern pharmaceutical manufacturing, enabling the processing of thermoplastic polymers and active pharmaceutical ingredients (APIs) into dosage forms with uniform size and controlled-release properties. Among the most broadly applied excipients in HME are Eudragit (EUD) polymers, which are highly valued for their tunable pH-dependent solubility, excellent melt processability, and capability to stabilize amorphous drug dispersions (Repka et al., 2007). Eudragit polymers are incorporated in HME due to their thermoplastic behavior, compatibility with plasticizers, and capacity to form stable solid dispersions and amorphous drug forms (Repka et al., 2007). Their functionality spans matrix formation, taste masking, and aimed delivery, depending on their chemical structure and pH solubility profile (Ghebre-Sellassie et al., 2003). Common grades include: Eudragit RL and RS (water-insoluble, pH-independent): applied in sustained-release systems, Eudragit L100 and S100 (pH-dependent enteric): applied in delayed-release and colon-aimed systems, and Eudragit EPO: primarily applied in taste masking and immediate-release formulations (Baumann et al., 2021). These polymers are typically processed at 100–160 °C, with plasticizers like triethyl citrate (TEC) and polyethylene glycol (PEG) aiding extrusion by lowering the processing temperature. A broad body of study shows the versatility of Eudragit in HME:

Sustained release; Dos Santos et al. (2021) demonstrated matrix-type formulations with Eudragit RL and RS, chosen for their low permeability and pH-independent solubility. Applying a twin-screw extruder, drug release was extended over 9–12 hours, affirming their suitability for HME (Jaloud & Alqahtani, 2021). Immediate vs. delayed release: Gupta et al. (2015) systematically reviewed Eudragit-based copolymers like EPO and L100-55. EPO effectively masked bitterness of APIs, while L100-55 served as an enteric matrix for delayed release. Extrusion at 110–130 °C, followed by SEM and DSC analysis, affirmed amorphization and smooth extrudate morphology (Gioumouxouzis et al., 2018; Nikam et al., 2023). Colon-aimed systems: Singh et al. (2015) and Andrés Real et al. (2022) emphasized the role of Eudragit L100-55 and S100 in colon-specific and enteric drug delivery. Yurtsal & Hasdemir (2022) demonstrated stable HME filaments applying Eudragit S100 with TEC, showing no release at gastric pH and >90% release at colonic pH. Amorphization and solubility enhancement: Jablan & Jug (2015) showed that Eudragit L100 and RS100 completely converted crystalline drugs to amorphous forms via HME, with meaningful improvements in solubility and bioavailability. Smart and pulsatile delivery: Tan et al. (2018) reviewed Eudragit's role in pH-triggered release (e.g., L100 at pH >6, S100 at pH >7) and discussed plasticizer effects on filament flexibility and drug distribution. More recently, Gaurkhede et al. (2024) designed a capsule structure applying Eudragit L100 as an outer shell, engineered with a “lock-and-key” pulsatile release mechanism. This design enabled rapid intestinal disintegration while protecting the drug in the stomach. Hydrophilic drug systems: Shojaie et al. (2023) announced the applying of Eudragit RL PO as a matrix former in sustained-release extrudates of hydrophilic drugs, with TEC enabling lower-temperature processing. Extended release was held for over 8 hours (Khodaverdi et al., 2012). Collectively, these investigations underscore the multifunctional role of Eudragit polymers in HME, spanning immediate release (EPO), sustained release (RL/RS), and aimed delivery (L100/S100). Blending of RL/RS grades permits accurate control over matrix permeability, while pH-sensitive polymers (e.g., L100-55, S100) permit site-specific release in the intestine or colon (Crowley et al., 2007). Thus, Eudragit stays one of the most versatile and broadly applied polymer families in HME, supporting the expansion of customized, stable, and patient-centric dosage forms. A comparative overview of pharmaceutical case studies involving Eudragit in HME is shown in Table 5.

Challenges and Considerations in Applying Eudragit with HME: In spite of their versatility and widespread utilization in pharmaceutical HME, Eudragit polymers show different formulation and processing challenges that must be carefully addressed through product expansion. One critical limitation is the narrow thermal processing window of particular grades. For example, Eudragit EPO, with a glass transition temperature (T_g) of ~42–45 °C, is prone to

thermal degradation or discoloration if extruded outside its optimal range (Nikam et al., 2023). This meaningfully restricts processing latitude and necessitates accurate temperature control to hold polymer integrity and drug stability. Another challenge is drug–polymer miscibility, exclusively in high-dose formulations with poorly soluble or thermally sensitive APIs. Partial miscibility may lead to phase separation, drug crystallization, and unpredictable release kinetics.

Table 5. Pharmaceutical-grade Eudragit polymers applied in HME-based filaments

Polymer	Manufacturer	Drug	Plasticizer	Outcome	Reference
Eudragit E PO	–	Felodipine	PEG 4000	Taste masking	Alhijaj et al., 2016
	–	5-ASA, Captopril, Prednisolone, Theophylline	Triethyl citrate	Immediate release	Sadia et al., 2016
	Evonik Industries	Warfarin	Triethyl citrate	progressed stability	Arafat et al., 2018
Eudragit E	–	Theophylline	Triethyl citrate	Taste masking	Pietrzak et al., 2015
Eudragit RL PO	–	Theophylline	Stearic acid, PEG 4000	Sustained release	Korte & Quodbach, 2018
Eudragit R	–	Quinine	Triethyl citrate	Taste masking	Kempin et al., 2017
Eudragit L100-55	–	5-Fluorouracil	Triethyl citrate	Colon-aimed delivery	Gioumouxouzis et al., 2018
Eudragit S100	–	5-Fluorouracil	Triethyl citrate	pH-triggered release	Gioumouxouzis et al., 2018
Eudragit S100	–	Dexamethasone	Triethyl citrate	Colon-aimed release	Zaid Alkilani et al., 2024
Eudragit L100	–	Acetaminophen	Triethyl citrate	Sustained release	J. Zhang et al., 2017

This issue is often exacerbated by the hydrophobic nature of some Eudragit grades (e.g., RS and RL), requiring specialized strategies like premixing with solubilizers or the applying of high-shear extrusion zones to progress drug dispersion (Crowley et al., 2007). The role of plasticizers is also crucial. Agents like triethyl citrate (TEC), polyethylene glycol (PEG), and stearic acid are commonly incorporated to reduce Tg, facilitating extrusion at moderate temperatures. However, plasticizer levels must be carefully optimized. Insufficient or excessive concentrations can lead to mechanical weakness, excessive filament flexibility, or altered drug-release kinetics (Ghebre-Sellassie et al., 2003). Furthermore, inappropriate levels can improve extrusion torque, leading to variability in throughput and improved strain on manufacturing equipment. In 3D printing utilizations, plasticizer content directly affects filament printability, feeding behavior, brittleness,

and dimensional fidelity through cooling (Fan et al., 2021). Moisture sensitivity and storage stability show additional concerns. For instance, Eudragit L100-55 is prone to moisture uptake, which may alter its dissolution characteristics and compromise pH-triggered release. Hence, proper packaging and storage situations are essential to hold the long-term efficiency of Eudragit-based extrudates (Nikam et al., 2023). Eventually, scale-up and batch-to-batch reproducibility are meaningful considerations. Variability in processing parameters like temperature or screw speed can create fluctuations in torque, melt viscosity, or drug dispersion, potentially leading to non-compliance with regulatory standards. To mitigate this, the applying of Process Analytical Technologies (PAT) and continuous monitoring is recommended to ensure consistent quality (Censi et al., 2018). When applied to 3D printing via fused deposition modeling (FDM), these challenges become even more critical. Factors like polymer viscosity, thermal degradation, or residual plasticizer levels directly impact printability, dimensional accuracy, and interlayer adhesion of printed dosage forms. For example, an imbalance in plasticizer concentration can result in brittle or overly soft filaments, leading to printing failures, nozzle clogging, or uneven drug distribution (Verstraete et al., 2018).

In summary, these challenges highlight the necessity of rational formulation design, thorough material characterization, and process optimization when employing Eudragit polymers in HME-based systems.

Three-dimensional printing of pharmaceuticals

In recent years, the scientific community has shown growing interest in additive manufacturing (AM), or three-dimensional (3D) printing, across diverse fields, containing pharmaceuticals. 3D printing is an emerging technology that fabricates constructs via layer-by-layer deposition, enabling accurate spatial control over materials (Bhushan & Caspers, 2017; Gioumouxouzis et al., 2019; Pereira et al., 2020; Ursan et al., 2013). The process begins with the digital design of the construct applying computer-aided design (CAD) software. The model is then sliced into multiple layers, each represented by a numerical code that dictates the deposition pattern. When this code is uploaded to the printer, the nozzle executes the printing path along the x, y, and z axes with high precision (Ursan et al., 2013). Parameters like nozzle diameter, deposition speed, and material properties supply further control, enabling fine-tuning of the construct's internal micro- and macro-architecture. This layer-by-layer precision affords different advantages over conventional manufacturing. Chief among them is the capability to fabricate personalized or on-request dosage forms, which are difficult to achieve with traditional attitudes (Liu et al., 2019; Nadernezhad et al., 2016). Patient-specific medicines—tailored in dose, release

rate, or dosage form—represent a cornerstone of future medicine, with potential benefits like reduced dosing frequency, lower treatment costs, and progressed therapeutic outcomes (BG et al., 2023). In conventional pharmaceutical manufacturing, adjusting dose strength or improving release kinetics typically needs extensive formulation and process redevelopment. In contrast, 3D printing permits these modifications to be achieved by simply altering software design parameters or ink conformation (Alomari et al., 2015). For example, by customizing tablet geometry, porosity, or infill density, drug release kinetics can be finely tuned (Goyanes et al., 2015). Another major advantage is the capability to combine multiple APIs into a single dosage form, thereby reducing pill burden and increasing compliance—especially in elderly patients on polypharmacy regimens (Genina et al., 2017). Complex, multifunctional dosage forms can be fabricated by co-depositing multiple drugs and excipients, applying functional coatings (Zhang et al., 2017), or incorporating micro- and nanoparticles for controlled release (Beck et al., 2017). Importantly, 3D printing also proposes high reproducibility compared with traditional manufacturing routes (Pardeike et al., 2011). Perhaps the most transformative aspect of 3D printing is its capability to place the patient at the center of drug manufacturing, shifting from a “one-size-fits-all” model to patient-centric medicines (Kjar & Huang, 2019). Among numerous utilizations, the oral solid dosage form (OSD) has demonstrated the greatest potential. A landmark moment occurred in 2015, when the U.S. Food and Drug Administration (FDA) approved the first 3D-printed drug product, SPRITAM® (levetiracetam)—an orally disintegrating tablet manufactured applying ZipDose® technology (Aprecia Pharmaceuticals, Langhorne, PA, USA) (Wen-Kai et al., 2018). Multiple 3D printing techniques have been investigated in pharmaceutical manufacturing, containing: Powder bed binding, Photopolymerization, Inkjet printing, and Extrusion-based printing (Wang et al., 2023). Each has unique benefits and limitations. For example, high printing temperatures needed in certain extrusion-based methods may create API degradation, while the conversion of pharmaceutical excipients into printable inks stays a meaningful barrier for many formulations (Fuenmayor et al., 2019; Trenfield et al., 2018). Among these, fused deposition modeling (FDM) is currently the most broadly applied in pharmaceuticals due to its simplicity, availability, and cost-effectiveness (Chai et al., 2017). In FDM, the dosage form is digitally designed applying CAD software and converted into a standard tessellation language (STL) file, which directs the printer. The printer is supplied with a drug-loaded thermoplastic filament, typically prepared via hot-melt extrusion (HME), which is heated, extruded, and deposited layer-by-layer to form the terminal three-dimensional structure (Goyanes et al., 2016; Ursan et al., 2013).

Types of 3D printing technologies

3D printing, also known as additive manufacturing (AM), is rapidly gaining recognition as a cutting-edge technology for fabricating complex structures across multiple fields, containing pharmaceuticals. These techniques build three-dimensional objects by selectively depositing or solidifying material in a layer-by-layer manner. Figure 3 shows a schematic overview of the most broadly applied 3D printing technologies with potential in pharmaceuticals, containing material extrusion, material jetting, binder jetting, selective laser sintering (SLS), and stereolithography (SLA) (Gittard et al., 2011; Huang et al., 2015; Vorndran et al., 2010).

Material extrusion: Extrusion-based printing is among the most prevalent and cost-effective AM techniques. Two major methods are employed: semisolid extrusion and fused deposition modeling (FDM). In both cases, the material is continuously extruded via a nozzle while the nozzle and/or build platform moves in the x, y, and z axes to create the predesigned geometry (Vithani et al., 2018). Semisolid extrusion permits the applying of diverse materials, containing printing inks, drugs, proteins, and viable cells (bioprinting). Extrusion can be achieved by mechanical or pneumatic forces, often assisted by heat (Ahn et al., 2015). The rheological characteristics of the inks are crucial: very viscous inks may create irregular extrusion, while low-viscosity inks may compromise resolution and mechanical stability. Ideally, inks exhibit shear-thinning behavior, reducing viscosity through extrusion and recovering viscosity immediately after deposition, thereby preserving shape fidelity (Vithani et al., 2018). Solidification occurs via chemical or physical processes, containing photo-crosslinking by UV exposure or co-deposition of crosslinking agents (Ahn et al., 2015). Fused deposition modeling (FDM) is broadly applied in pharmaceutical study due to its simplicity and cost-effectiveness. It typically employs drug-loaded thermoplastic filaments, often prepared by hot-melt extrusion (HME), which are melted and extruded layer-by-layer (Vithani et al., 2018). The resolution of FDM is constrained by nozzle size, usually $\sim 400 \mu\text{m}$. Semisolid extrusion generally proposes lower resolution due to ink spreading. However, hybrid electrospinning-based extrusion systems can achieve filament diameters as fine as $10 \mu\text{m}$, representing the highest resolution extrusion-based approach currently available (Vithani et al., 2018).

Material jetting: Material jetting, also referred to as inkjet 3D printing, is analogous to conventional 2D inkjet printing. In this method, low-viscosity fluids are dispensed as droplets of controlled volume onto a substrate, with the print head moving in the x, y, and z axes to build 3D structures. Two primary types exist based on droplet ejection force: thermal inkjet and acoustic inkjet (Bhushan & Caspers, 2017). Post-printing crosslinking is essential, and may occur via ionic, thermal, photo, or pH-dependent processes (Hospodiuk et al., 2017). A meaningful advantage is

the capability to simultaneously print multiple materials, even those with separate physicochemical properties, making the technology attractive for drug formulations and bioprinting of viable cells (Bhattacharjee et al., 2016; Hospodiuk et al., 2017). However, technical challenges stay. Droplets often spread prior to complete crosslinking, reducing resolution. The sharpest features are usually achieved when printed parallel to the jetting direction (Bhushan & Caspers, 2017). Print fidelity and resolution are strongly impressed by droplet size, fluid rheology, and print speed, requiring careful optimization.

Binder jetting: Unlike material jetting, binder jetting utilizes a liquid binder to selectively fuse regions of a powder bed. Each layer is created by spreading powder over the build surface, followed by selective deposition of binder in the desired geometry. The powder bed is then lowered, fresh powder spread, and the process repeated until the terminal object is complete (Bhushan & Caspers, 2017). Advantages include: No requirement for sacrificial supports, since the surrounding powder bed stabilizes the part through fabrication, Compatibility with a broad range of materials, containing polymers, metals, and ceramics, often at room temperature, making it suitable for heat-sensitive APIs (Ngo et al., 2018), and the capability to create highly porous structures, beneficial for utilizations like controlled-release drug delivery. However, parts generated by binder jetting usually need post-processing (e.g., chemical treatment or sintering) to raise mechanical properties. Resolution depends on powder size, with features as fine as 50 μm achievable (Bhushan & Caspers, 2017).

Selective laser sintering (SLS): Selective laser sintering (SLS) shares similarities with binder jetting; however, instead of applying a liquid binder, a laser beam is employed to selectively fuse powder particles. This mechanism imposes restrictions on the types of materials that can be processed. While thermoplastic polymers are most often applied in SLS for biomedical utilizations, metals and ceramics stay broadly applied in other fields (Mazzoli, 2013). The particle size of the feedstock performs a crucial role in identifying the terminal print's mechanical properties, particle spreading efficiency, and feature resolution. Careful optimization of powder particle size is therefore essential (Dadbakhsh et al., 2016). Material characteristics also directly impress the achievable resolution. Compared with other 3D printing methods, SLS is distinguished as a high-resolution technique, capable of producing features as fine as 30 μm (Regenfuss et al., 2007), although some reports describe resolutions closer to 100 μm (Goyanes et al., 2016). Similar to binder jetting, SLS-fabricated objects are typically porous and often need post-processing to raise mechanical strength and surface smoothness. In spite of these limitations, SLS proposes notable advantages: it generally needs no support structures, is relatively rapid, and is attended cost-effective.

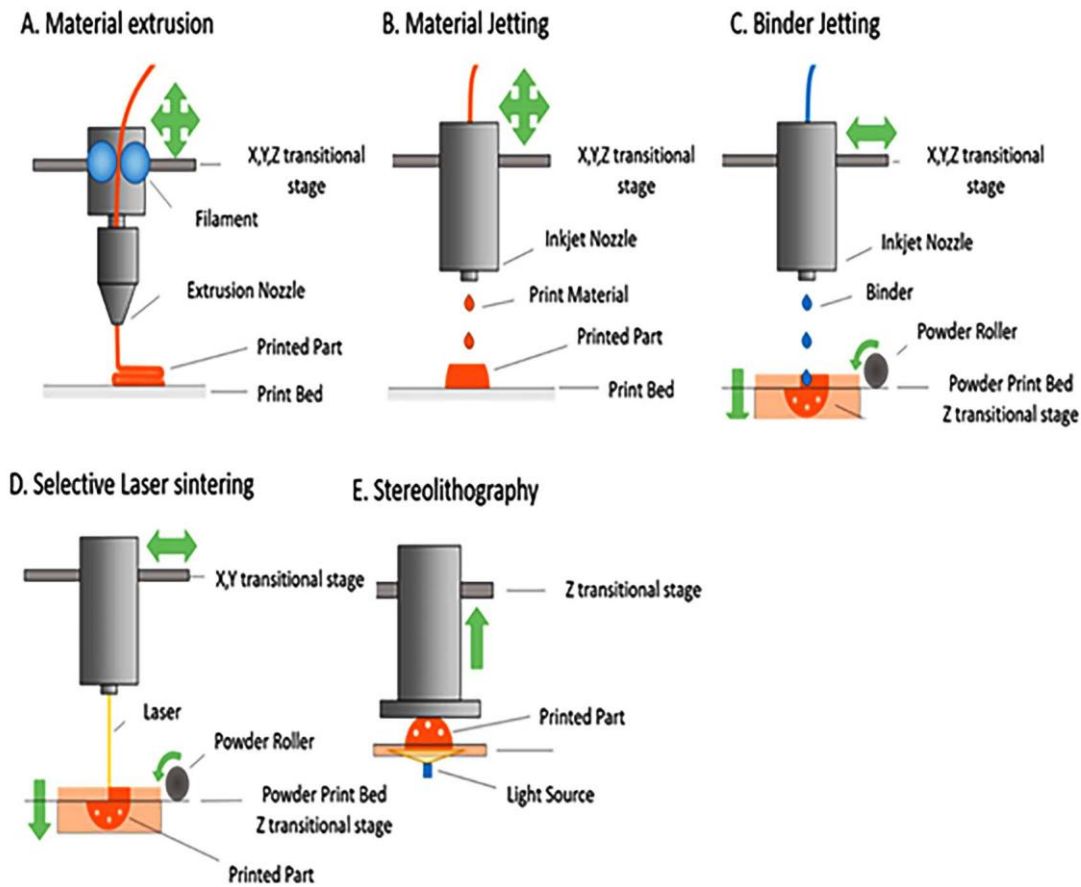


Figure 3. Typical mechanisms of additive manufacturing (AM). Layer-by-layer material deposition is the defining principle of AM techniques. (A) Material extrusion: thermoplastic materials are typically extruded via a heated nozzle, although semisolid materials may also be deposited applying mechanical or pneumatic systems. **(B) Material jetting:** droplets of the entire printing material are dispensed applying inkjet-based print heads. **(C) Binder jetting:** a liquid binder is selectively deposited via an inkjet nozzle onto a powder bed, with the surrounding powder providing support and eliminating the requirement for sacrificial structures. **(D) Selective laser sintering (SLS):** a laser beam selectively fuses regions of the powder bed to build the 3D structure. **(E) Stereolithography (SLA):** liquid resin in a vat is polymerized layer by layer by a directed light source to form the terminal part. Adapted from Fuenmayor et al. (2019) and Trenfield et al. (2018).

Stereolithography (SLA): Stereolithography (SLA) is the earliest and most established form of additive manufacturing (Huang et al., 2020). Its principle is derived from

photolithography and is based on the interaction of light with photopolymerizable resins. In SLA, a vat of liquid resin is selectively exposed to a light source, which cures the resin layer by layer based on the predefined design. Two primary configurations are employed. In the bottom-up approach, the light source is positioned beneath a transparent resin tank base, curing each layer while the build platform moves upward. This setup needs relatively smaller volumes of resin (Vithani et al., 2018). Conversely, in the top-down approach, the light source is projected from above, and the build platform moves downward into the vat, necessitating larger resin volumes to keep the part fully submerged (Manapat et al., 2017). Variants of SLA include digital light processing (DLP) and continuous liquid interface production (CLIP), both of which raise resolution and speed (Vithani et al., 2018). SLA is regarded as a high-resolution technique, but challenges stay: light scattering can create non-specific polymerization, affecting print quality (Hwang et al., 2018). Additionally, post-curing, post-processing, and sacrificial support structures are often needed. The choice of materials is restricted, with photocurable polymers being the most broadly applied (Vithani et al., 2018). A highly specialized and more expensive variant, two-photon polymerization (TPP), employs two laser beams to polymerize resin, enabling the fabrication of nanostructures with unprecedented resolution, down to 120 nm (Kawata et al., 2001; Maruo et al., 1997).

Conclusions: The applying of Eudragit (EUD) polymers in progressive formulation platforms like hot-melt extrusion (HME) and three-dimensional (3D) printing has meaningfully transformed the landscape of drug delivery design and expansion. These polymers are worth excipients due to their tunable solubility, flexibility in utilization, and capability to withstand high processing temperatures, enabling the design of aimed, sustained, and personalized drug release profiles. Their utilizations develop from conventional applies, like taste masking and enteric coating, to cutting-edge attitudes, containing colon-specific delivery systems and mucoadhesive technologies. Across a broad spectrum of dosage forms, different grades of EUD polymers have consistently demonstrated versatility and adaptability. This review has highlighted key advances in the utilization of EUD polymers within HME and additive manufacturing, supported by extensive examples, formulation strategies, and mechanistic discernments. In spite of this promise, different technical challenges stay. These include the miscibility of drugs and polymers, the risk of thermal degradation, and the maintenance of stability through and after processing. Such challenges must be addressed in a formulation-specific manner. Future work should therefore centralize on rational selection of polymer–drug–plasticizer systems, expansion of predictive models for drug release behavior, and optimization of processing situations to ensure both scalability and regulatory compliance. In conclusion, the integration of EUD polymers with HME and 3D printing represents a powerful approach to advancing personalized medicine. These

technologies have the potential to generate dosage forms that are not only effective and stable but also tailored to the particular therapeutic and individual requirements of patients.

Author contributions

FRSA: Concept of the investigation, Methodology, Project supervision, Resources, Validation, Writing – original draft, Writing – review & editing.

Data availability statement

This is a review paper, but information is available on request from the corresponding author.

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Ethical considerations

Not applicable

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Conflict of interest

The authors declare no conflict of interest.

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کاربردهای دارویی نوین پلیمرهای یودرژیت (Eudragit) در فناوری‌های Hot Melt Extrusion و چاپ سه‌بعدی

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چکیده

هدف: محیط تولید دارو به طور فزاینده‌ای روش‌های پیشرفته‌ای همچون اکستروژن ذوبی داغ (HME) و چاپ سه‌بعدی (3D) را برای گسترش سامانه‌های دارورسانی شخصی‌سازی شده، کارآمد و مقیاس پذیر به کار می‌گیرد. هر دو فناوری به شدت بر ماده جانبی یودرژیت (EUD) متکی اند که خانواده گسترده‌ای از پلیمرهای متاکریلاتی را دربر می‌گیرد. این مقاله مروری با هدف ارائه گزارشی جامع از کاربرد پلیمرهای EUD در HME و چاپ سه‌بعدی، با تمرکز بر نقش آن‌ها در سامانه‌های کنترل شده دارورسانی از نوع پایدار، فوری و هدفمند انجام شد.

مواد و روش‌ها: در این مقاله مروری، استفاده از گریدهای مختلف EUD نظیر EPO، RL، RS، L100، S100 و L100-55 در طراحی فرمولاسیون، بهینه‌سازی فرآیند و سازوکارهای رهایش دارو بررسی شد. بحث شامل ارزیابی راهبردهای فرمولاسیون، شرایط فرآیندی و پایداری پس از فرآیند است. نوآوری‌های اخیر، شامل سامانه‌های هوشمند و عملکردی مبتنی بر EUD با ویژگی‌های mucoadhesive، هدف‌گیری اختصاصی کولون و خصوصیات درمان-تشخیصی (theranostic)، نیز مورد توجه قرار گرفتند. همچنین ویژگی‌های مکانیکی و سازگاری دارو-پلیمر به‌عنوان عوامل تعیین‌کننده حیاتی موفقیت در فرمولاسیون تحلیل شدند.

نتایج: پلیمرهای EUD نشان داده‌اند که از طیف وسیعی از پلتفرم‌ها و اشکال دارورسانی پشتیبانی می‌کنند و قابلیت انعطاف‌پذیری و انطباق‌پذیری بالایی در فرآیندهای داروسازی دارند. مطالعات موردی و پیشرفت‌های اخیر بیانگر توانایی EUD در فراهم‌سازی مکانیزم‌های رهایش کنترل شده هستند، در حالی که به نیازهای درمانی خاص نیز پاسخ می‌دهند. عملکرد هوشمند پلیمرهای EUD ظرفیت آن‌ها را برای ایجاد ویژگی‌هایی همچون mucoadhesive، رهایش اختصاصی در محل و کاربردهای تشخیصی گسترش

داده است. با این حال، چالش‌هایی همچون تخریب حرارتی طی فرآیند، ناسازگاری یا امتزاج ناکافی بین دارو و پلیمر و حساسیت به رطوبت همچنان باقی است. این محدودیت‌ها چالش‌های مهمی در فرمولاسیون ایجاد می‌کنند که باید از طریق راه‌حل‌های اختصاصی فرایند و فرمولاسیون مدیریت شوند.

نتیجه‌گیری: این مطالعه مروری بر نقش محوری پلیمرهای EUD در تولیدات دارویی نسل آینده، به‌ویژه در زمینه HME و ساخت افزایشی (چاپ سه‌بعدی)، تأکید می‌کند. اگرچه این پلیمرها نویدبخش توسعه سامانه‌های نوین دارورسانی هستند، اما چالش‌های فنی همچون ناسازگاری دارو-پلیمر، خطر تخریب حرارتی و حفظ یکپارچگی پس از فرآیند همچنان پابرجاست. رفع این مسائل برای بهره‌برداری کامل از پتانسیل پلیمرهای EUD در توسعه داروهای آینده ضروری است. با ادغام مطالعات موردی، راهبردهای فرمولاسیون و درک مکانیزمی، این مرور منبع ارزشمندی برای پژوهشگران و فرمولاتورها به‌شمار می‌رود تا بتوانند از قابلیت انطباق‌پذیری EUD در کاربردهای دارویی نوین بهره‌مند شوند.

کلمات کلیدی: اکستروژن ذوبی داغ (HME)، پلیمرهای یودرژیت (EUD)، چاپ سه‌بعدی، رهایش کنترل‌شده دارو، کوپلیمرهای متاکریلات

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