WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 15, Issue 1, 592-627. Review Article ISSN 2277–7105

POLYMER ENGINEERING IN BILAYER AND MULTILAYER TABLETS: FROM FORMULATION DESIGN TO DRUG RELEASE – A REVIEW

Muskan Soni*, Dr. Kamlesh Dashora[1]

[1]Professor and H.O.D., [2] Professor

Institute of Pharmacy, Samrat Vikramaditya Vishwavidhalaya, Ujjain Madhya Pradesh.

Article Received on 05 Dec. 2025,
Article Revised on 25 Dec. 2025,
Article Published on 01 Jan. 2026

https://doi.org/10.5281/zenodo.18094248

***Corresponding Author**

Muskan Soni

Institute of Pharmacy, Samrat Vikramaditya Vishwavidhalaya, Ujjain Madhya Pradesh.

How to cite this Article: Muskan Soni*, Dr. Kamlesh Dashora[1]. (2026) POLYMER ENGINEERING IN BILAYER AND MULTILAYER TABLETS: FROM FORMULATION DESIGN TO DRUG RELEASE - A REVIEW. World Journal of Pharmaceutical Research, 15(1), 592–627.

ABSTRACT

Bilayer and multilayer tablets are advanced oral drug delivery systems that enable spatial and functional separation of active pharmaceutical ingredients (APIs) and excipients within a single dosage form, thereby overcoming the limitations of conventional single-layer tablets. These systems are particularly advantageous for chronic disease management and fixed-dose combination therapies, as they allow the integration of immediate, sustained, delayed, targeted, and sequential drug release profiles. Polymer engineering plays a central role in the design, performance, and manufacturability of bilayer and multilayer tablets, as polymers govern layer formation, interlayer adhesion, mechanical integrity, and drug release behavior. This review provides a comprehensive overview of polymer engineering strategies applied to bilayer and multilayer tablet systems, with a focus on formulation design and drug release control. Natural, semisynthetic, synthetic, and functional polymers used in immediate-release, sustained-release, delayed-release, gastroretentive, mucoadhesive, osmotic, and chronotherapeutic layers are critically discussed. Particular emphasis is placed on key polymer attributes such as viscosity grade, molecular weight, swelling behavior, permeability, and compressibility, and their influence on critical quality attributes including disintegration time, dissolution kinetics, interlayer adhesion, and mechanical strength. The application of Quality by Design (QbD) principles to polymer selection and optimization is highlighted, emphasizing critical material attributes, risk

assessment, and design space establishment to ensure robust and reproducible product performance. In addition, polymer–drug and polymer–polymer compatibility considerations, manufacturing challenges, and scale-up issues associated with multilayer tablet production are addressed. Recent advances in smart and stimuli-responsive polymers, nanostructured and hybrid polymer systems, and engineered polymer architectures are also reviewed, highlighting their potential to enable controlled, targeted, and patient-centric oral drug delivery. Overall, this review underscores polymer engineering as a system-defining approach for the development of robust, effective, and regulatory-compliant bilayer and multilayer tablet formulations.

KEYWORDS: Bilayer tablets; Multilayer tablets; Polymer engineering; Controlled drug release; Quality by Design (QbD); Drug–polymer compatibility; Targeted drug delivery.

INTRODUCTION

Overview of Bilayer and Multilayer Tablet Technology[1-4]

Bilayer and multilayer tablets are advanced oral drug delivery systems developed to overcome the limitations of conventional single-layer tablets. These systems enable the delivery of multiple drugs or the achievement of complex drug release profiles within a single dosage unit, which is particularly beneficial for the management of chronic diseases requiring long-term and combination therapy Bilayer tablets consist of two distinct layers, whereas multilayer tablets comprise three or more layers, each designed to perform a specific functional role.

A key advantage of these technologies is the spatial and functional separation of active pharmaceutical ingredients (APIs) and excipients, allowing independent modulation of drug release kinetics This feature is especially important in fixed-dose combination formulations involving drugs with differing physicochemical properties, pharmacokinetic behavior, or stability profiles. By segregating incompatible APIs into separate layers, bilayer and multilayer tablets minimize drug–drug interactions and enhance formulation stability.

These systems can incorporate immediate-release, sustained-release, delayed-release, or inert barrier layers to provide sequential or biphasic drug delivery. Such controlled release patterns improve therapeutic efficacy by ensuring rapid onset of action followed by prolonged drug release, thereby reducing dosing frequency and improving patient adherence.

Manufacturing requires specialized compression equipment and careful optimization of formulation and process variables, inclu5ding polymer selection and interlayer adhesion. Overall, bilayer and multilayer tablet technologies represent robust and flexible platforms for modern patient-centric oral drug delivery.

Rationale for Polymer Selection in Multilayer Dosage Forms[4,5,6]

The design of multilayer dosage forms, particularly multilayer tablets, represents a sophisticated approach in pharmaceutical technology aimed at achieving complex drug release profiles or separating incompatible active pharmaceutical ingredients (APIs) within a single unit. The polymer selection is the most critical determinant of the final product's performance, as polymers serve as the functional excipients that define the release kinetics of each distinct layer. The rationale for polymer choice is therefore driven by the desired therapeutic objective, the physicochemical properties of the API, and the need for mechanical integrity during manufacturing.

Table 1: Function-Driven Selection: Tailoring Layers For Release Kinetics.

Layer Type	Primary Function	Key Polymer Requirements	Representative Polymers	Impact on Drug Relase
Immediate Release (IR) Layer	Rapid disintegration and dissolution for initial dose	High water solubility, low viscosity, fast hydration	Low-viscosity HPMC, Polyvinylpyrrolidone (PVP), Croscarmellose Sodium	Immediate drug availability; rapid onset of action
Sustained Release (SR) / Matrix Layer (Hydrophilic)	Prolonged drug release via swelling/gel formation	High viscosity, strong gel formation, controlled erosion	HPMC K4M/K15M/K100M, Carbopol, Sodium Carboxymethylcellulose (NaCMC)	Diffusion- and erosion-controlled release; duration increases with viscosity
Sustained Release (SR) / Matrix Layer (Hydrophobic)	pH-independent, diffusion-controlled release	Low permeability, non-erodible matrix	Ethylcellulose, Polymethacrylates (Eudragit RS/RL)	Sustained release governed by diffusion through polymer channels
Barrier / Modulating Layer	Prevent drug–drug interaction; introduce lag time	nertness, low permeability or controlled swelling	Ethylcellulose (impermeable), High-viscosity HPMC (swellable)	Delayed hydration; controlled interaction between layers
Enteric / pH-Sensitive Layer	Protection in gastric pH; intestinal targeting	pH-dependent solubility; ionizable groups	Eudragit L/S, Cellulose Acetate Phthalate (CAP), HPMC Phthalate (HPMCP)	Site-specific release in intestine (≥ pH 5.5)

Physicochemical and Manufacturing Criteria

Table 2: Physiochemical and Manufacturing Rationale.

Selection Criterion	Rationale in Multilayer Dosage Forms	Key Polymer Property
Drug Compatibility	The polymer must not chemically interact with the API or other excipients, which is especially critical when separating incompatible APIs.	Chemical structure, inertness, non-ionic nature (e.g., HPMC).
Molecular Weight & Viscosity	Directly controls the rate of drug release from hydrophilic matrices by influencing the gel layer's thickness and density.	Viscosity grade (e.g., HPMC K4M vs. K100M), chain length.
Solubility & Hydration Rate	Determines the mechanism of release (diffusion vs. erosion) and the time required to establish the controlled-release barrier.	Hydrophilicity/Hydrophobicity, glass transition temperature
Compressibility & Flow	Essential for high-speed tableting. Poor flow or compressibility can lead to weight variation, capping, and, most critically, delamination (layer separation) .	Particle size, shape, and mechanical properties (plasticity/elasticity).
Regulatory Status & Safety	All polymers must be approved for pharmaceutical use and be non-toxic and biocompatible.	Pharmacopeial compliance (USP/EP), Biocompatibility.

Emerging and Novel Polymeric Systems[10-14]

Table 3: Emerging and Novel Polymeric Systems.

Polymer Technology	Key Characteristics	Rationale in Multilayer Tablets	Typical Stimuli / Process	Representative Polymers / Systems
Stimuli-Responsive (Smart) Polymers	Reversible or irreversible changes in swelling, solubility, or conformation in response to stimuli	Enable on-demand, site-specific, pulsatile, or lag-time drug release in bilayer and multilayer systems	pH, temperature, enzymes, light	pH-sensitive polymethacrylates (Eudragit L/S), temperature-responsive polymers (e.g., PNIPAM-based systems), enzyme-responsive polymers
Polyelectrolyte Multilayer (PEM) Films	Nanometer-scale layers with precise control over thickness and composition	Allow engineering of ultra-thin barrier or release-modulating layers with highly controlled diffusion	Layer-by-Layer (LbL) deposition using oppositely charged polymers	Poly(allylamine hydrochloride) (PAH), Poly(styrene sulfonate) (PSS), chitosan–alginate systems
Polymers for Additive Manufacturing (3D Printing)	Tailored thermal, mechanical, and rheological properties suitable for printing	Enable fabrication of complex multilayer geometries (core–shell, concentric rings) and personalized dosage forms	Fused Deposition Modeling (FDM), semi-solid extrusion	Modified HPMC, Polyvinyl Alcohol (PVA), Polymethacrylates (Eudragit®)

Advantages of Polymer-Based Layered Systems Over Conventional Tablets[12,17]

The evolution of oral solid dosage forms has seen a significant shift from conventional, immediate-release tablets to sophisticated polymer-based layered systems, such as multilayer tablets, matrix systems, and layered capsules. This transition is driven by the inherent limitations of conventional tablets, which often suffer from poor bioavailability and undesirable fluctuations in plasma drug concentration, leading to sub-optimal therapeutic outcomes. Polymer-based layered systems overcome these challenges by offering superior control over drug release kinetics, enhanced therapeutic efficacy, and greater formulation flexibility.

Enhanced Drug Release Kinetics

- Enable controlled and near zero-order drug release.
- Maintain plasma drug levels within the therapeutic window.
- Reduce peak-related toxicity and sub-therapeutic effects.
- Support advanced designs such as osmotic and pulsatile release systems.

Improved Therapeutic Efficacy and Safety

- Minimize dose dumping and fluctuations in drug concentration.
- Reduce dosing frequency and improve patient compliance.
- Provide optimized pharmacokinetic profiles with better safety margins.

Formulation Flexibility and Compatibility

- Allow separation of incompatible APIs into different layers.
- Enable independent control of release from each layer.
- Support use of diverse polymers to fine-tune dissolution and drug release

Table 4: The Key Differences Between Conventional Tablets and Polymer-Based Layered Systems.

Feature	Conventional Tablets	Polymer-Based Layered Systems
Drug Release Kinetics	Typically first-order (rapid peak and decline)	Zero-order, sustained, or pulsatile release
Plasma Drug Level	Fluctuating (peaks and troughs)	Stable, maintained within therapeutic window
Dosing Frequency	High (multiple times a day)	Low (once or twice a day)
Drug Compatibility	Limited; incompatible drugs require separate formulations	High; incompatible drugs can be isolated in separate layers
Drug	Limited; incompatible drugs	High; incompatible drugs can be

Compatibility	require separate formulations	isolated in separate layers
Therapeutic Efficacy	Sub-optimal due to plasma fluctuations	Optimized due to controlled release
Mechanism Example	Simple disintegration and dissolution	Matrix diffusion, osmotic pressure, layer-by-layer erosion

Fundamentals, Design Concepts, and Classification of Bilayer and Multilayer Tablets[15-18]

A layered tablet is a compressed dosage form consisting of two or more distinct layers of granulation, each containing one or more active pharmaceutical ingredients (APIs) or excipients. The primary rationale for developing these systems is to achieve specific therapeutic goals that are unattainable with a monolithic tablet structure

Fundamental principles of layered tablets

- Separate incompatible APIs to improve stability.
- Enable immediate and sustained drug release in one tablet.
- Allow sequential, time-controlled drug release.
- Support patent extension and product differentiation.
- Reduce dosing frequency and improve patient compliance.

Design Concepts for Bilayer and Multilayer Tablets

The design of layered tablets is a complex process that focuses on the formulation of each layer to achieve the desired drug release profile and ensure the physical integrity of the final product. The core design concepts revolve around controlling the release rate of the API(s).

Drug Release Profile Designs

Table 5: Design Concept Based on Drug Release.

Design Concept	Description	Therapeutic Application
Immediate Release/Sustained Release (IR/SR)	One layer acts as a loading dose for rapid onset of action, and the second layer provides a maintenance dose over time.	Acute symptoms requiring quick relief followed by prolonged action.
Sequential Release	Two different APIs are released one after the other, often separated by a barrier layer or a slow-releasing layer.	Combination therapy where one drug's action must precede the other.
Zero-Order Release	The tablet is designed to release the drug at a constant rate, independent of the amount of drug remaining in the dosage form.	Maintaining a steady-state plasma concentration for drugs with a narrow therapeutic window.
Programmed/Pulsatile	The drug is released after a	Chronotherapy, such as

Release	predetermined lag time or in bursts, often to mimic the body's natural circadian rhythm.	treating nocturnal asthma or morning hypertension.

Formulation and Manufacturing Considerations[1,9,12]

A critical aspect of the design is ensuring robust layer-to-layer adhesion to prevent delamination (layer separation) during manufacturing, handling, and storage. This requires careful selection of excipients, optimization of compression forces, and control over the particle size and moisture content of the granulations. Furthermore, the design must account for potential cross-contamination between layers during the tableting process, which is managed through specialized tablet presses and process controls.

-1. Bilayer Tablets

These are the simplest form of layered tablets, consisting of two distinct layers. They are the most common type and are primarily used to separate two incompatible APIs or to combine two different release profiles (e.g., IR/SR).

2. Multilayer Tablets

This category includes tablets with three or more layers, such as trilayer tablets (three layers) or quadrilayer tablets (four layers). The increased number of layers allows for more complex drug release patterns, such as the sequential release of three different components or the use of a non-drug-containing barrier layer to further separate two active layers.

3. Tablet-in-Tablet (Core-Shell)

This is a specialized form of multilayer tablet where an inner core tablet is completely enclosed by an outer layer This design is particularly useful for:

- Protecting a highly sensitive core drug from the environment or from the components of the outer layer.
- Providing a delayed-release profile, where the outer layer acts as a coating that must dissolve before the core is released.

4. Coated Core Tablets

While often considered a separate category, coated core tablets function as a layered system. A core tablet is coated with a functional layer, such as an enteric coating (to prevent dissolution in the stomach) or a film coating for taste masking or moisture protection. In the

context of drug release, a functional coating acts as a barrier layer, making it conceptually similar to a layered system.

ROLE OF POLYMER[20-25]

Polymers play a pivotal role in the design and performance of bilayer and multilayer tablet systems, functioning not only as excipients but also as critical structural and functional determinants. In multilayered oral dosage forms, polymers are responsible for maintaining distinct layer identity**,** ensuring mechanical integrity through adequate interlayer adhesion, and modulating drug release kinetics. The successful development of bilayer and multilayer tablets therefore relies heavily on the rational selection and optimization of polymeric materials.

Polymers in Layer Separation[23,25]

Layer separation is a fundamental requirement in bilayer and multilayer tablet systems, particularly when drugs with different release profiles, physicochemical properties, **or** potential incompatibilities are incorporated within a single dosage form. Polymers contribute significantly to maintaining the physical and functional independence of individual layers.

High-molecular-weight and high-viscosity polymers form coherent matrices that act as physical and diffusional barriers, thereby preventing intermixing of drug layers during compression and subsequent storage. The deformation behavior of polymers under compressional stress also influences interfacial integrity, as polymers exhibiting controlled plastic deformation facilitate layer formation while preserving sharp interlayer boundaries. Additionally, polymer particle size distribution and surface morphology play important roles in minimizing powder migration at the layer interface.

Inadequate polymer selection may result **in** layer blending or interfacial diffusion**,** ultimately compromising the intended biphasic or sequential drug release pattern.

Polymers in Interlayer Adhesion

Interlayer adhesion is a critical quality attribute of bilayer and multilayer tablets, as insufficient bonding between layers may lead to delamination, capping, or mechanical failure during manufacturing, handling, or transportation. Polymers enhance interlayer adhesion through a combination of mechanical interlocking and physicochemical interactions**.**

During compression, polymers with suitable plasticity undergo deformation, increasing the contact area between adjacent layers. This promotes interpenetration of polymer **chains** across the interface and facilitates the formation of hydrogen bonding and secondary intermolecular forces. Hydrophilic polymers, in particular, exhibit strong binding characteristics due to their affinity for moisture and their ability to form cohesive matrices.

However, excessive polymeric binding may result in over-adhesion, leading to loss of layer distinction and alteration of release characteristics. Therefore, a careful balance between adhesive strength and layer independence must be achieved.

Polymers in Functional Drug Release

The most significant contribution of polymers in bilayer and multilayer tablets lies in their ability to control drug release behavior. Polymers regulate drug release through multiple mechanisms, including swelling-controlled diffusion, matrix erosion, pH-dependent solubility, and osmotic pressure-driven transport.

Hydrophilic swellable polymers form gel layers upon hydration, which act as diffusion barriers and modulate the rate of drug release. Erodible polymers contribute to time-dependent release through gradual matrix dissolution, whereas pH-responsive polymers enable delayed or site-specific drug delivery. In osmotic multilayer systems, semi-permeable polymeric membranes govern water influx and maintain controlled, near zero-order drug release profiles.

Through appropriate polymer selection and layer configuration, bilayer and multilayer tablets can be engineered to achieve immediate, sustained, delayed, gastroretentive, mucoadhesive, or osmotic drug delivery within a single dosage form.

Integrated Polymer Functionality in Multilayer Systems

In bilayer and multilayer tablet systems, polymers simultaneously fulfill structural, mechanical, and functional roles**.** They ensure layer separation, promote interlayer adhesion, maintain tablet integrity, and modulate drug release kinetics. Consequently, polymers serve as system-defining components**,** directly influencing formulation robustness, manufacturing reproducibility, and therapeutic performance.

Polymer Classification Used in Bilayer and Multilayer Tablets[1,2 ,5 16]

Polymers are the backbone of bilayer and multilayer tablet technology, governing layer separation, interfacial adhesion, mechanical strength, and site-specific or time-controlled drug release. Based on origin and functional role, polymers employed in these advanced oral dosage forms are broadly classified into natural, semisynthetic, synthetic, and functional polymers**.** Appropriate selection and combination of polymers enable the design of tablets with immediate, delayed, sustained, floating, mucoadhesive, or osmotic release characteristics.

Natural Polymers

Natural polymers are obtained from plant, animal, or microbial sources. They are widely valued for their biocompatibility, biodegradability, low toxicity, and regulatory acceptance**.**

- Hydrophilic nature with swelling and gel-forming ability
- Suitable for immediate, sustained, and mucoadhesive layers
- Economical and environmentally sustainable

Commonly Used Natural Polymers

- Starch and modified starches – binder and disintegrant in IR layers
- Guar gum, Xanthan gum – matrix formers for sustained release
- Sodium alginate – gel-forming, floating, and controlled release systems
- **C**hitosan – mucoadhesive and permeation-enhancing polymer
- Pectin, Carrageenan – colon-targeted and controlled release

Application in Bilayer/Multilayer Tablets

Natural polymers are frequently used in sustained-release layers or mucoadhesive layers**,** while also contributing to interlayer adhesion due to their swelling behavior.

. Semisynthetic Polymers

Semisynthetic polymers are chemically modified natural polymers, offering better reproducibility, mechanical strength, and controlled hydration than their natural counterparts.

- Predictable swelling and erosion kinetics
- Excellent compressibility and film-forming ability
- Widely accepted in pharmacopeial formulations

Commonly Used Semisynthetic Polymers

- Hydroxypropyl methylcellulose (HPMC) – most widely used matrix former
- Hydroxypropyl cellulose (HPC) – binder and release modifier
- Carboxymethyl cellulose sodium (CMC-Na) – hydrophilic matrix polymer
- Ethyl cellulose (EC) – water-insoluble, diffusion-controlled release

Application in Bilayer/Multilayer Tablets

Semisynthetic polymers are central to controlled and sustained-release layers, ensuring layer integrity, uniform drug release**, and** mechanical stability during compression.

Synthetic Polymers

Synthetic polymers are man-made materials designed for high structural integrity, chemical stability, and precise control over drug release mechanisms.

- Excellent batch-to-batch consistency
- High mechanical strength and low friability
- Suitable for diffusion- and erosion-controlled systems

Commonly Used Synthetic Polymers

- Polyvinylpyrrolidone (PVP) – binder and solubilizer
- Polyethylene oxide (PEO) – swellable matrix former
- Polymethacrylates (Eudragit® series**)** – pH-dependent and sustained release
- Polyvinyl alcohol (PVA) – film-forming and adhesive polymer

Application in Bilayer/Multilayer Tablets

Synthetic polymers are extensively used in **delayed-release, enteric-coated, and osmotic multilayer systems**, particularly where **precision and robustness** are required.

Functional Polymers

Functional polymers are classified based on the specific role they play in tablet performance**,** irrespective of their origin. These polymers are crucial in defining the therapeutic objective of bilayer and multilayer systems.

Release-Controlling Polymers

- HPMC, EC, PEO, Eudragit® RS/RL
- Regulate drug diffusion, swelling, and erosion

Mucoadhesive Polymers

- Chitosan, Carbopol®, Sodium alginate
- Prolong gastric or intestinal residence time

Floating and Gastroretentive Polymers

- HPMC, Xanthan gum, Sodium alginate
- Reduce tablet density and enhance buoyancy

Barrier and Separating Polymers

- EC, Eudragit® NE
- Prevent drug migration between layers and maintain layer distinction

Osmotic and Semipermeable Polymers

- Cellulose acetate, PVA
- Enable controlled water influx and zero-order release

Application in Bilayer/Multilayer Tablets

Functional polymers determine layer separation, adhesion strength, release kinetics, and site specificity**,** making them indispensable in fixed-dose combinations a**nd** chronotherapeutic systems**.**

POLYMERS USED FOR IMMEDIATE-RELEASE (IR) LAYER

Natural Polymers

Natural polymers are widely used **in** immediate-release (IR) tablet formulations due to their biocompatibility, biodegradability, low toxicity, and regulatory acceptance. In IR layers of bilayer and multilayer tablets, these polymers primarily function as disintegrants, binders, **and dissolution enhancers**, facilitating rapid tablet breakup and fast drug release without forming a retarding matrix.

Table 6: Natural Polymers Used For Immediate-Release (Ir) Layer.

Category	Polymer	Role	Mechanism	Application / Note
Starch & Starch-Based Polymers	Native starch (maize, potato, rice)	Disintegrant	Swelling on water uptake	Promotes rapid tablet disintegration
	Pregelatinized starch	Binder–disintegrant	Rapid hydration and swelling	Improves tablet strength with fast disintegration

Cellulose-Based Natural Polymers	Microcrystalline cellulose (MCC)	Binder, disintegration aid	Wicking and capillary action	Enhances porosity and rapid drug release
	Powdered cellulose	Disintegrant	Water penetration and fiber swelling	Supports fast tablet breakup
Natural Gums & Mucilages (Low Conc.)	Guar gum	Disintegrant (low levels)	Rapid hydration and swelling	Higher levels may retard drug release
	Xanthan gum	Disintegration aid	Water uptake and matrix loosening	Used sparingly in IR layers
	Tragacanth	Binder–disintegrant	Swelling and erosion	Suitable for rapid disintegration
Alginates & Marine Polymers	Sodium alginate (low viscosity)	Disintegrant, wetting agent	Rapid hydration, gel-free swelling	Enhances drug dispersion in IR layers
Plant-Derived Fibers & Mucilages	Isapghula husk (Plantago ovata)	Natural disintegrant	Swelling-induced rupture	Effective natural alternative
	Fenugreek seed mucilage	Disintegrant	Rapid hydration and expansion	Supports fast tablet disintegration

Functional Role of Natural Polymers in IR Layer

Table 7: Function of Natural Polymer.

Function	Contribution of Natural Polymers
Rapid disintegration	Swelling and wicking mechanisms
Fast drug release	Increased tablet porosity
Tablet integrity	Binder–disintegrant balance
Biocompatibility	Safe and non-toxic materials
Regulatory acceptance	Widely pharmacopeial

Synthetic polymer for rapid drug release

Synthetic polymers are widely employed in immediate-release (IR) formulations to achieve rapid drug release and fast onset of action, particularly in bilayer and multilayer tablet systems. Their consistent molecular weight, high purity, and excellent reproducibility make them preferable to natural materials when precise control over disintegration and dissolution is required. In IR layers, these polymers are selected to dissolve quickly in gastrointestinal fluids, enhance wettability, and avoid gel formation that could delay drug release. Commonly used synthetic polymers include polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polyvinyl alcohol (PVA), and surface-active polymers such as poloxamers, all of which contribute to rapid hydration and improved drug dispersion.

Polyvinylpyrrolidone (PVP) functions primarily as a water-soluble binder and solubility enhancer, promoting rapid wetting of drug particles and uniform dispersion after tablet disintegration. Polyethylene glycol (PEG) and polyvinyl alcohol (PVA) further accelerate drug release by increasing hydrophilicity of the matrix and reducing interfacial tension between drug and dissolution medium. Poloxamers, owing to their amphiphilic nature, enhance dissolution of poorly soluble drugs through micellar solubilization. Additionally, synthetic superdisintegrant polymers such as crospovidone indirectly support rapid drug release by enabling fast tablet breakup through capillary action and deformation recovery. Collectively, these synthetic polymers ensure efficient disintegration, rapid dissolution, and reliable performance of immediate-release layers in bilayer and multilayer tablet formulations.

Polymer combinations for optimized disintegration

Polymer combinations are strategically employed in immediate-release (IR) layers to achieve optimized and reproducible tablet disintegration. Instead of relying on a single excipient, formulators often combine a superdisintegrant with a rapidly dissolving polymer or a low-viscosity binder to exploit synergistic mechanisms such as swelling, wicking, and capillary action. For example, the combination of crospovidone with polyvinylpyrrolidone (PVP) enhances both tablet breakup and drug wettability, while croscarmellose sodium combined with low-viscosity HPMC or hydroxypropyl cellulose (HPC-SL) improves water penetration without forming a gel barrier. Such combinations ensure rapid ingress of dissolution medium into the tablet matrix, leading to uniform and fast disintegration even at higher compression forces.

Optimized polymer combinations also improve mechanical strength while maintaining rapid drug release, which is particularly critical in bilayer and multilayer tablets where interlayer integrity must be preserved. Blends such as sodium starch glycolate with microcrystalline cellulose (MCC) or pregelatinized starch with PEG balance binding efficiency and disintegration speed by creating a porous structure that facilitates fluid uptake. These synergistic systems reduce variability in disintegration time, enhance robustness during manufacturing, and support consistent in-vivo performance. Consequently, rational selection of polymer combinations is a key formulation strategy to achieve fast, reliable, and optimized disintegration in immediate-release layers without compromising tablet integrity or adjacent sustained-release layers.

Polymers Used in Sustained and Controlled Release Layers[11,26,28]

Polymers used in sustained- and controlled-release layers are the key determinants of drug release kinetics, layer integrity, and overall therapeutic performance of bilayer and multilayer tablets. These polymers are specifically selected to retard drug release through mechanisms such as diffusion, swelling, erosion, or osmotic control, thereby maintaining drug plasma concentration within the therapeutic window for prolonged periods. Both hydrophilic and hydrophobic polymers are commonly employed, either alone or in combination, to tailor release profiles according to the physicochemical properties of the drug and the desired release duration.

Hydrophilic matrix-forming polymers

Hydrophilic matrix-forming polymers are the most extensively used polymers in sustained and controlled release layers of bilayer and multilayer tablets due to their simplicity, safety, and reliable performance. These polymers hydrate rapidly upon contact with gastrointestinal fluids and form a viscous gel layer around the tablet surface. This gel layer acts as a diffusional barrier, controlling the ingress of dissolution medium and the egress of drug molecules. Drug release from hydrophilic matrices is governed by a combination of diffusion through the swollen gel layer and gradual polymer erosion, allowing predictable and reproducible release kinetics over an extended period.

Common hydrophilic matrix-forming polymers include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polyethylene oxide (PEO), sodium alginate, xanthan gum, and guar gum. Among these, HPMC of different viscosity grades is most widely employed, as viscosity directly influences gel strength and drug release rate—higher viscosity grades produce thicker gel layers and slower release, whereas lower viscosity grades allow faster erosion and diffusion. Natural hydrophilic polymers such as xanthan gum and sodium alginate further contribute to matrix integrity through swelling and chain entanglement. In bilayer and multilayer tablets, hydrophilic matrix-forming polymers ensure layer cohesion, resistance to dose dumping, and sustained therapeutic drug levels, making them indispensable for controlled oral drug delivery systems.

Hydrophobic polymers for sustained release

Hydrophobic and insoluble polymers are widely used in sustained- and controlled-release layers to achieve diffusion-controlled, pH-independent drug release. Unlike hydrophilic polymers, these materials do not swell or dissolve in gastrointestinal fluids; instead, they

form an inert matrix that limits water penetration and drug diffusion. Drug release from hydrophobic matrices primarily occurs through diffusion via pores and channels created within the polymer network, often generated by leaching of soluble excipients. This mechanism provides a more uniform and prolonged release profile and minimizes the risk of rapid drug loss or dose dumping.

Common hydrophobic and insoluble polymers include ethyl cellulose, cellulose acetate, polyvinyl acetate, and polymethacrylates. Ethyl cellulose is the most frequently employed due to its excellent compressibility, chemical stability, and compatibility with a wide range of drugs. Polymethacrylate polymers are particularly useful for fine-tuning permeability and achieving reproducible release kinetics. In bilayer and multilayer tablets, hydrophobic polymers are often combined with hydrophilic matrix-formers to balance diffusion and erosion mechanisms, ensuring robust layer integrity, controlled drug release, and reliable in-vivo performance over extended dosing intervals.

Swellable and gel-forming polymers[7,9,19,26,]

Swellable and gel-forming polymers play a central role in sustained and controlled drug-release layers by regulating hydration, swelling, and matrix integrity. Upon contact with gastrointestinal fluids, these polymers absorb water and undergo volumetric expansion, forming a coherent viscous gel layer on the tablet surface. This gel barrier controls drug release by slowing solvent penetration and creating a diffusion path for drug molecules. As hydration progresses, the outer gel layer may gradually erode while the inner core continues to swell, resulting in a controlled and predictable release profile governed by diffusion–erosion mechanisms.

Common swellable and gel-forming polymers include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polyethylene oxide (PEO), sodium alginate, xanthan gum, and guar gum. The viscosity grade and molecular weight of these polymers strongly influence gel strength and drug-release rate—higher viscosity grades form thicker, more robust gels that prolong release, whereas lower viscosity grades allow faster erosion and release. In bilayer and multilayer tablets, swellable gel-forming polymers ensure layer cohesion, resistance to dose dumping, and sustained therapeutic drug levels, making them indispensable for designing reliable controlled-release oral dosage forms.

Erosion-controlled and diffusion-controlled polymer system

Erosion-controlled polymer systems regulate drug release primarily through the gradual dissolution or erosion of the polymer matrix itself. In these systems, polymers hydrate and weaken over time, causing the outer layers of the tablet to erode and release the embedded drug in a controlled manner. Drug release is therefore closely linked to the rate of polymer erosion, which depends on polymer viscosity, solubility, and environmental conditions such as pH and agitation. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC, low to medium viscosity grades), hydroxypropyl cellulose (HPC), polyethylene oxide (PEO), and natural gums like xanthan gum and sodium alginate are commonly used in erosion-controlled matrices. These systems are particularly useful when uniform release is desired without reliance on pore formation, and they are widely applied in sustained-release layers of bilayer and multilayer tablets.

Diffusion-controlled polymer systems, in contrast, control drug release through the movement of drug molecules across an intact polymer barrier. The polymer matrix remains largely insoluble and non-erodible, and drug release occurs as gastrointestinal fluids penetrate the matrix, dissolve the drug, and allow it to diffuse outward through microscopic pores or channels. Hydrophobic and insoluble polymers such as ethyl cellulose, cellulose acetate, polyvinyl acetate, and polymethacrylates are typically employed in diffusion-controlled systems. These polymers provide pH-independent and reproducible release kinetics. In bilayer and multilayer tablets, diffusion-controlled layers are often combined with erosion-controlled or immediate-release layers to achieve balanced, predictable, and prolonged drug delivery, enhancing therapeutic efficacy and patient compliance.

Fig. 1: Different types of tablets.

POLYMERS USED IN DELAYED AND TARGETED RELEASE LAYERS[5,20,32]

Polymers used in delayed and targeted release layers are critical for achieving spatial and temporal control of drug delivery in bilayer and multilayer tablet systems. These polymers are designed to withhold drug release during transit through the stomach and/or upper intestine and to trigger release only after exposure to specific physiological conditions such as changes in pH, enzymatic activity, or residence time. Delayed and targeted release strategies are particularly beneficial for drugs that are acid-sensitive, gastric-irritant, unstable in the upper gastrointestinal tract, or intended to act locally in the intestine or colon. In multilayer tablets, such polymers often function as barrier or protective layers, ensuring precise release at the desired site without compromising tablet integrity.

In bilayer and multilayer tablet design, delayed and targeted release polymers are often combined with immediate- or sustained-release layers to create multifunctional dosage forms. Such combinations allow an initial protection or lag phase followed by controlled drug release at the desired site, improving therapeutic efficacy and reducing dosing frequency. Overall, polymers used in delayed and targeted release layers enable sophisticated control over drug release kinetics, minimize adverse gastric effects, and support patient-centric drug delivery by aligning drug release with physiological and pathological requirements.

pH-dependent and entric coated polymers

pH-dependent polymers are widely used in delayed and targeted release layers to achieve site-specific drug delivery within the gastrointestinal tract. These polymers remain insoluble in the acidic gastric environment and dissolve at higher intestinal pH, thereby protecting acid-labile drugs, reducing gastric irritation, and ensuring controlled release at the desired site. In bilayer and multilayer tablets, they commonly function as outer or barrier layers to delay drug release until intestinal transit.

Enteric coating polymers play a crucial role in multilayer tablet systems by providing gastric resistance and ensuring drug release only after the dosage form reaches the intestine. In multilayer tablets, enteric polymers are commonly applied as an outer coating layer or as an intermediate barrier layer surrounding the drug-containing core. Their primary function is to remain intact in the acidic environment of the stomach (pH 1–3) and to dissolve or become permeable at higher intestinal pH values. This approach is particularly important for protecting acid-labile drugs, minimizing gastric irritation, and achieving delayed or site-specific drug release.

Cellulose-based polymers such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, and hydroxypropyl methylcellulose acetate succinate are extensively used for enteric protection. Their dissolution behavior can be tailored by modifying substitution levels and coating thickness, allowing precise control of lag time and release onset.

Methacrylic acid copolymers offer additional flexibility due to their well-defined pH-dependent solubility and excellent film-forming properties, enabling targeted release in specific intestinal regions with sharp release transitions. Overall, pH-dependent polymers are essential components of advanced bilayer and multilayer tablets, providing predictable, site-specific drug release with improved stability, safety, and patient compliance.

Colon-targeted polymer systems

Colon-targeted polymer systems are designed to deliver drugs selectively to the colon by protecting the dosage form during transit through the stomach and small intestine. These systems are especially useful for treating colonic diseases or for drugs that benefit from absorption in the colon due to lower enzymatic activity and longer residence time. In multilayer tablets, colon targeting is typically achieved using barrier, coating, or matrix layers that respond to colonic-specific physiological triggers.

The most widely used approach involves microflora-activated polymers, which resist digestion in the upper gastrointestinal tract but are degraded by colonic bacteria. Natural polysaccharides such as pectin, guar gum, xanthan gum, chitosan, dextran, and inulin remain intact until reaching the colon, where enzymatic degradation triggers drug release. In multilayer systems, these polymers are often protected by outer layers to prevent premature swelling or erosion.

To improve targeting reliability, microflora-sensitive polymers are frequently combined with pH-dependent or time-dependent systems. pH-sensitive outer layers prevent early release, while inner polysaccharide matrices enable enzymatic activation in the colon. Such hybrid multilayer designs reduce variability due to gastrointestinal pH and transit time.

Chronotherapeutic polymer approaches

Chronotherapeutic polymer approaches are designed to align drug release with circadian rhythms, disease progression, or time-dependent symptom severity. Many disorders, including diabetes, hypertension, asthma, arthritis, and cardiovascular diseases, show pronounced diurnal variation in symptoms. By incorporating polymers that create a programmable lag phase followed by rapid or controlled drug release, these systems ensure that peak drug levels coincide with periods of greatest disease activity. Bilayer and multilayer tablets are particularly well suited for chronotherapy, as they allow spatial separation of drug layers and precise control of release timing using polymeric barriers.

Time-dependent polymeric barrier systems are the most commonly used chronotherapeutic strategy. In these systems, hydrophilic polymers such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, or polyethylene oxide swell, erode, or dissolve gradually to generate a defined lag time before drug release. The lag phase can be accurately adjusted by modifying polymer viscosity and layer thickness, and drug release thereafter may be immediate or sustained. This approach is largely independent of gastrointestinal pH and provides reproducible release timing.

Pulsatile or rupture-based polymer systems offer an alternative strategy, where swelling of an inner polymer layer builds internal pressure until an outer coating ruptures, resulting in a rapid burst of drug release after a preset delay. In multilayer tablets, chronotherapeutic polymers are often combined with immediate- or sustained-release layers to create

multifunctional dosage forms, enabling precise temporal control, improved therapeutic efficacy, reduced side effects, and enhanced patient compliance.

Adhesive and Barrier Polymers in Multilayer Tablets[27,30]

Adhesive polymers ensure strong interlayer bonding and mechanical integrity in bilayer and multilayer tablets. They prevent defects such as delamination and capping by enhancing interfacial contact during compression. Polymers like HPMC, HPC, PVP, and polyethylene oxide deform plastically and promote hydrogen bonding and mechanical interlocking, ensuring stable tablet structure without affecting drug release.

Barrier polymers are used to separate incompatible drugs and protect formulations from chemical or moisture-induced interactions. Hydrophobic, low-permeability polymers such as ethyl cellulose, polymethacrylates, cellulose acetate, and polyvinyl acetate act as physical and diffusional shields. Together, adhesive and barrier polymers are critical for maintaining layer integrity, stability, and consistent therapeutic performance in multilayer tablet systems.

Table 8: Polymerscbased On Diffent Tablet System.

Tablet System	Polymer Category	Commonly Used Polymers	Primary Function	Key Application/Benefit
Floating Bilayer Tablets	Hydrophilic swellable & gel-forming polymers	HPMC, HPC, PEO, Sodium alginate, Xanthan gum, Guar gum	Swelling, gel formation, buoyancy	Prolonged gastric residence time and controlled drug release
	Supportive hydrophobic polymers	Ethyl cellulose, Polymethacrylates	Matrix stabilization, erosion control	Maintains tablet integrity during floating
Bioadhesive / Mucoadhesive Systems	Mucoadhesive polymers	Chitosan, Carbopol, Polycarbophil, Sodium alginate	Adhesion to mucosal surface	Prolonged residence time and enhanced bioavailability
	Hydrophilic matrix polymers	HPMC, Xanthan gum	Swelling and adhesion support	Sustained and localized drug delivery
Osmotic Multilayer Tablets	Semipermeable polymers	Cellulose acetate, Polyvinyl alcohol (PVA)	Regulated water influx	pH-independent, reproducible drug release
	Swellable “push-layer” polymers	Polyethylene oxide (PEO), HPMC	Osmotic pressure generation	Zero-order or near zero-order release
Stimuli-Responsive Systems	pH-dependent polymers	Methacrylic acid copolymers, CAP, HPMCP, HPMCAS	Dissolution at specific Ph	Delayed and site-specific intestinal release
	Enzymatically degradable polymers	Pectin, Guar gum, Dextran, Chitosan	Microbial degradation	Colon-targeted drug delivery

	Time-dependent polymers	HPMC, HPC, PEO	Swelling/erosion-controlled lag time	Chronotherapeutic and pulsatile release

Table 9: Polymers Based on Mechnism of Drug Release.

Mechanism of Drug Release	Polymer Type	Commonly Used Polymers	Release Control Principle	Typical Application	Typical Application
Immediate / Rapid Release	Fast-hydrating & soluble polymers	PVP, PEG, PVA, Low-viscosity HPMC, HPC-SL	Rapid dissolution and tablet disintegration	Immediate-release layer for fast onset of action	Immediate-release layer for fast onset of action
Swelling-Controlled Release	Hydrophilic swellable polymers	HPMC (medium–high viscosity), HPC, PEO, Xanthan gum, Guar gum	Polymer swelling forms gel barrier controlling diffusion	Sustained-release layers	Sustained-release layers
Erosion-Controlled Release	Hydrophilic erodible polymers	Low–medium viscosity HPMC, HPC, Sodium alginate	Gradual matrix erosion releases drug	Uniform sustained release	Uniform sustained release
Diffusion-Controlled Release	Hydrophobic / insoluble polymers	Ethyl cellulose, Cellulose acetate, Polymethacrylates	Drug diffuses through insoluble matrix or pores	Long-term controlled release	Long-term controlled release
Swelling + Diffusion (Hybrid)	Hydrophilic–hydrophobic blends	HPMC + Ethyl cellulose, PEO + EC	Combined swelling and diffusion	More predictable release kinetics	More predictable release kinetics
Osmotically Controlled Release	Semipermeable & swellable polymers	Cellulose acetate, PVA, PEO	Osmotic pressure drives drug release	Zero-order, pH-independent release	Zero-order, pH-independent release
pH-Dependent Release	Enteric / pH-sensitive polymers	Methacrylic acid copolymers, CAP, HPMCP, HPMCAS	Polymer dissolves at specific GI pH	Delayed & intestinal targeting	Delayed & intestinal targeting
Enzyme-Triggered Release	Biodegradable polysaccharides	Pectin, Guar gum, Dextran, Chitosan	Microbial enzymatic degradation	Colon-targeted delivery	Colon-targeted delivery
Time-Dependent (Lag-Time) Release	Swellable / erodible barrier polymers	HPMC, HPC, PEO	Programmable swelling or erosion delay	Chronotherapeutic systems	Chronotherapeutic systems
Floating / Gastroretentive Release	Low-density gel-forming polymers	HPMC, Sodium alginate, Xanthan gum	Swelling + buoyancy	Upper GI retention	Upper GI retention
Mucoadhesive Release	Bioadhesive polymers	Chitosan, Carbopol, Polycarbophil, Alginate	Adhesion to mucosa	Prolonged local drug action	Prolonged local drug action

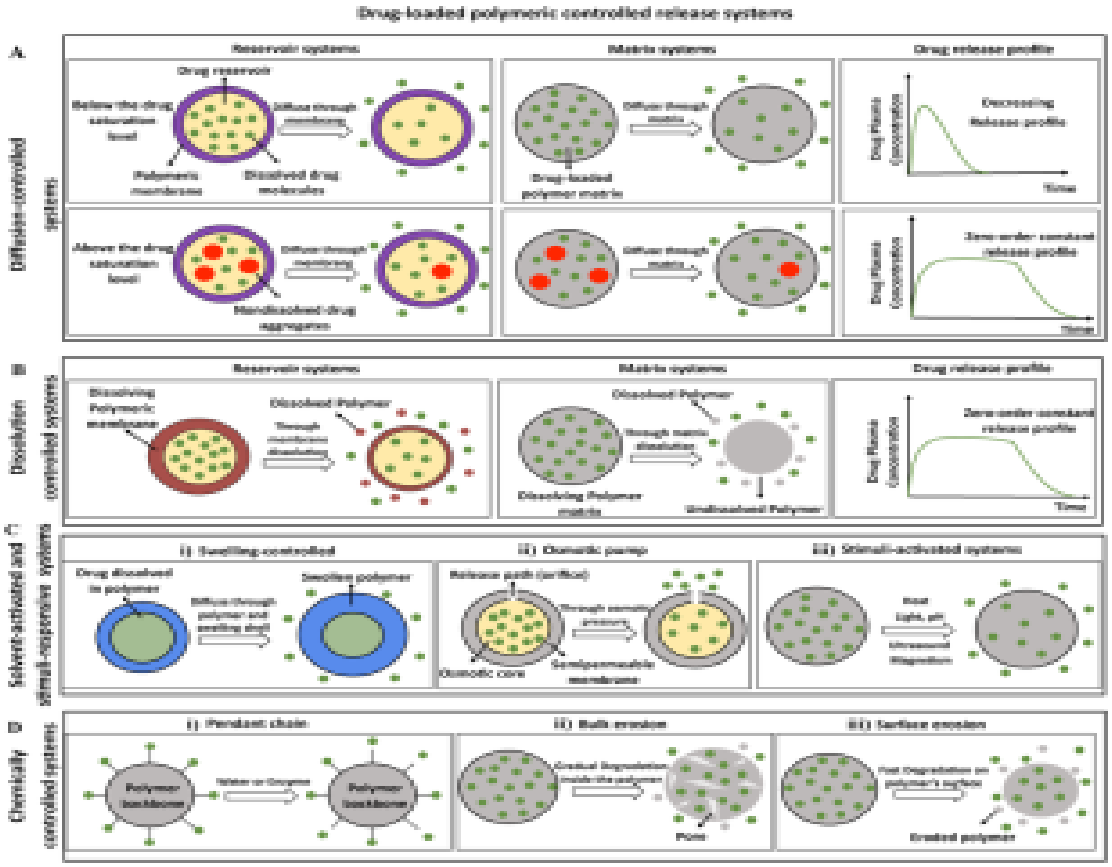

Fig. 2: Showing different types of drug release through polymer.

Role of Polymers in Quality by Design (QbD) Approach[17,14,36,45]

Polymers play a pivotal role in the Quality by Design (QbD) approach to bilayer and multilayer tablet development, as they are considered critical material attributes (CMAs) that directly influence product quality and performance. Polymer properties such as viscosity grade, molecular weight, particle size, swelling behavior, and permeability significantly affect critical quality attributes (CQAs), including disintegration time, dissolution profile, mechanical strength, and interlayer adhesion. Within a QbD framework, systematic selection and optimization of polymers through risk assessment and design of experiments enable robust control of drug release mechanisms, minimize batch-to-batch variability, and ensure consistent therapeutic performance throughout the product lifecycle.

Critical material attributes (CMAs) of polymers

Critical material attributes (CMAs) of polymers are fundamental determinants of the performance and quality of bilayer and multilayer tablet formulations. Key polymer CMAs include viscosity grade, molecular weight, particle size and distribution, degree of substitution, hydration rate, swelling capacity, permeability, and compressibility. These

attributes directly influence critical quality attributes (CQAs) such as disintegration time, drug release kinetics, mechanical strength, interlayer adhesion, and stability. Variations in polymer CMAs can alter gel formation, diffusion pathways, erosion behavior, and bonding at layer interfaces, potentially leading to batch-to-batch variability. Therefore, comprehensive characterization and control of polymer CMAs are essential within a Quality by Design (QbD) framework to ensure robust, reproducible, and predictable product performance.

Impact of polymer grade and viscosity

Polymer grade and viscosity have a profound impact on the performance of bilayer and multilayer tablet formulations, particularly on drug release behavior and mechanical integrity. Higher-viscosity polymer grades typically form stronger and thicker gel layers upon hydration, which slow drug diffusion and erosion, resulting in prolonged and more controlled release profiles. In contrast, lower-viscosity grades hydrate rapidly and erode faster, leading to quicker drug release and shorter lag times. Polymer grade also influences compressibility, interlayer adhesion, and resistance to delamination, as differences in particle size and molecular weight affect deformation during compression. Consequently, careful selection and optimization of polymer grade and viscosity are critical to achieving consistent drug release and robust tablet performance within a Quality by Design framework.

 As polymer viscosity increases, a stronger gel layer is formed, resulting in slower drug diffusion and reduced drug release.

 This trend explains why high-viscosity HPMC/PEO grades are used for sustained release, while low-viscosity grades favor faster release.

Polymer variability and design space

Polymer variability and design space are critical considerations in the Quality by Design (QbD)–based development of bilayer and multilayer tablets. Polymer variability may arise from differences in grade, viscosity, molecular weight, substitution pattern, particle size, or supplier-to-supplier differences, all of which can significantly influence drug release behavior, disintegration, mechanical strength, and interlayer adhesion. Within a QbD framework, this variability is systematically studied to define a design space, which represents the multidimensional range of polymer attributes and concentrations that consistently yield acceptable product quality. By understanding how changes in polymer properties affect critical quality attributes, formulators can establish robust operating ranges

that accommodate normal variability while ensuring predictable performance, regulatory flexibility, and consistent product quality throughout the product lifecycle.

Risk assessment and optimization of polymer levels

Risk assessment and optimization of polymer levels are essential steps in a Quality by Design (QbD)–driven formulation strategy for bilayer and multilayer tablets. Risk assessment tools such as Ishikawa diagrams and failure mode and effects analysis are used to identify polymer-related risks affecting critical quality attributes, including disintegration, dissolution, interlayer adhesion, and mechanical strength. High-risk factors—such as polymer type, viscosity grade, and concentration—are then systematically evaluated using design of experiments to establish optimal polymer levels. This approach enables identification of robust formulation ranges that balance drug release control with tablet integrity, minimizes batch-to-batch variability, and ensures consistent product performance throughout manufacturing and the product lifecycle.

POLYMER–DRUG AND POLYMER–POLYMER COMPATIBILITY[44,39,30]

Polymer–drug and polymer–polymer compatibility is essential for the stability and performance of bilayer and multilayer tablets. Polymer–drug compatibility ensures that no chemical or physical interactions occur that could affect drug stability or release. Polymer–polymer compatibility is equally important to maintain interlayer adhesion and prevent delamination or moisture migration. Compatibility is commonly assessed using techniques such as FTIR, DSC, and stability studies, ensuring robust formulation integrity and consistent drug delivery.

Drug–Polymer Interaction Studies

Drug–polymer interaction studies are performed to identify any chemical or physical interactions that may affect drug stability, release behavior, or bioavailability. These studies help detect hydrogen bonding, complex formation, or changes in crystallinity that could alter dissolution profiles or lead to instability during storage. Early evaluation of drug–polymer interactions is essential to ensure safe, stable, and predictable performance of bilayer and multilayer tablet formulations.

Analytical Methods Used for Drug–Polymer Interaction Studies

Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR is used to detect chemical interactions by monitoring shifts, disappearance, or formation of characteristic functional group peaks in drug–polymer mixtures compared to individual components.

Differential Scanning Calorimetry (DSC)

DSC evaluates thermal behavior and identifies changes in melting point, glass transition temperature, or enthalpy, which may indicate physical or chemical interactions between the drug and polymer.

X-Ray Diffraction (XRD)

XRD is employed to assess changes in crystalline structure or polymorphic transitions of the drug when combined with polymers, indicating possible solid-state interactions.

Stability Studies

Accelerated and long-term stability studies are conducted on drug–polymer blends to monitor changes in physical appearance, drug content, and dissolution behavior over time, confirming compatibility under storage conditions.

Polymer miscibility in layered formulations

Polymer miscibility in layered formulations is a critical factor influencing interlayer adhesion, mechanical integrity, and consistent drug release in bilayer and multilayer tablets. Miscible or partially miscible polymers enable intimate contact and interpenetration at the layer interface, promoting strong bonding and reducing the risk of delamination or layer separation during compression and storage. In contrast, poor miscibility between adjacent polymers can lead to weak interfacial cohesion, moisture migration, and variability in drug release profiles. Therefore, polymers with compatible physicochemical properties—such as similar polarity, glass transition temperature, compressibility, and moisture affinity—are carefully selected to ensure stable layered structures and reliable performance of multilayer tablet systems.

MANUFACTURING CHALLENGES RELATED TO POLYMER IN MULTĪLAYER[20,16,7,8,2,5]

- Differences in polymer compressibility between layers can cause weak interfacial bonding.

- Particle size and particle size distribution mismatch may lead to poor layer contact and non-uniform compaction.
- Variations in polymer deformation behavior (plastic vs elastic) increase the risk of delamination.
- High elastic recovery of certain polymers can cause post-compression layer separation.
- Lubrication sensitivity of polymers may reduce interlayer adhesion when excess lubricant is present.
- High-speed tableting conditions amplify polymer-related defects such as capping and lamination.
- Inconsistent moisture sensitivity across polymer layers can affect compression behavior and stability

Flow and compressibility issue

Flow and compressibility issues are common challenges in multilayer tablet manufacturing due to the inherent properties of polymeric excipients. Poor flowability of polymers, often caused by fine particle size, irregular morphology, or high cohesiveness, can result in non-uniform die filling and layer weight variation. Differences in flow behavior between layers may further disrupt proper layer formation during compression. In addition, inadequate polymer compressibility or high elastic recovery can lead to weak tablet hardness, poor interlayer adhesion, and defects such as capping or delamination. Variations in polymer grade and moisture content can further influence compaction behavior, making careful control of polymer properties essential for robust multilayer tablet production.

 As compressibility index increases (poorer flow and compaction behavior), tablet hardness decreases.

 This trend explains why polymers with poor flow or high elastic recovery often lead to weak interlayer bonding, capping, and delamination in multilayer tablets.

Layer weight variation and content uniformity

Layer weight variation and content uniformity are critical manufacturing challenges in multilayer tablets, strongly influenced by polymer properties. Poor flowability of polymeric excipients, arising from fine particle size, irregular shape, or high cohesiveness, can lead to inconsistent die filling and uneven layer weights. Variations in polymer density and segregation tendency between layers further contribute to non-uniform distribution of the active pharmaceutical ingredient, adversely affecting content uniformity. Inadequate control

of polymer flow and compressibility may also result in interlayer mixing or incomplete layer formation. Therefore, careful selection of polymers with suitable flow characteristics, along with optimization of granulation and compression parameters, is essential to ensure uniform layer weight, consistent drug content, and compliance with pharmacopeial specifications.

Layer weight variation is directly related to content uniformity in multilayer tablets because inconsistent die filling leads to unequal amounts of drug-containing material in each layer. When polymer flowability and density are not well controlled, variations in layer weight increase the risk of non-uniform drug distribution, resulting in tablets that may fall outside pharmacopeial limits for content uniformity. This relationship is particularly critical in low-dose layers, where even small weight fluctuations can cause significant assay variability. Therefore, controlling polymer flow, granule size distribution, and compressibility is essential to minimize layer weight variation and ensure consistent content uniformity across batches.

Capping, lamination, and delamination

Capping, lamination, and delamination are common mechanical defects encountered during multilayer tablet manufacturing and are closely linked to polymer properties and compression behavior. Capping occurs when the top or bottom portion of a tablet separates due to air entrapment or excessive elastic recovery of polymers after compression. Lamination refers to the splitting of a tablet into two or more horizontal layers, often caused by differences in compressibility, moisture content, or polymer deformation characteristics. Delamination is specific to bilayer and multilayer tablets and results from weak interlayer adhesion due to incompatible polymers or insufficient bonding at the interface. Proper selection of polymers with compatible deformation behavior, along with optimized compression and lubrication conditions, is essential to minimize these defects and ensure tablet integrity.

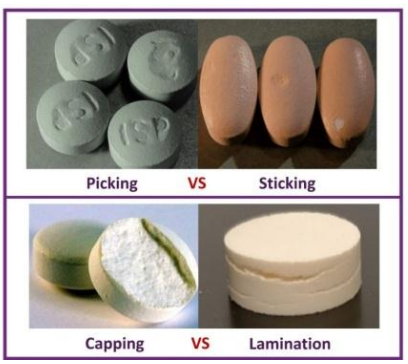

Fig. 3: Shwing different manufacturing challenges.

Scale-up and industrial considerations

Scale-up and industrial considerations are critical when translating multilayer tablet formulations from laboratory to commercial production, particularly with respect to polymer behavior. Polymers that perform well at small scale may exhibit altered flow, compressibility, or lubrication sensitivity under high-speed compression, leading to defects such as layer weight variation, delamination, or capping. Differences in shear exposure, dwell time, and compression force during scale-up can also influence polymer deformation and interlayer adhesion. Therefore, selection of polymers with robust and reproducible mechanical properties, along with optimization of processing parameters and equipment selection, is essential to ensure consistent product quality and manufacturability at an industrial scale.

Table 10: Evalution Parameteers.

Evaluation Parameter	Polymer Property Involved	Influence of Polymer Selection	Impact on Tablet Performance
Flow properties	Particle size, shape, cohesiveness	Determines ease of die filling and layer formation	Layer weight uniformity and content uniformity
Compressibility	Plastic vs elastic deformation	Controls compaction behavior	Tablet hardness and interlayer bonding
Hardness / Tensile strength	Binding capacity, molecular weight	Stronger binding improves strength	Mechanical integrity during handling
Friability	Polymer cohesion and flexibility	Poor binding increases abrasion	Resistance to breakage
Capping / Lamination	Elastic recovery, lubrication sensitivity	High elastic recovery increases defects	Tablet integrity and yield
Interlayer adhesion	Polymer compatibility, deformation behavior	Compatible polymers enhance bonding	Prevention of delamination
Disintegration time	Swelling ability, solubility	Fast-hydrating polymers reduce time	Rapid drug availability (IR layers)
Dissolution / Drug release	Viscosity, permeability, swelling	Governs diffusion, erosion, swelling	Sustained, controlled, or rapid release
Content uniformity	Flow and segregation tendency	Poor flow causes dose variability	Dose accuracy and compliance
Layer weight variation	Density, flowability	Uneven flow causes weight fluctuation	Structural consistency
Swelling index	Hydrophilicity, gel formation	Higher swelling enhances matrix control	Sustained-release performance
Shelf-life assessment	Moisture sensitivity, chemical compatibility, permeability	Polymers influence moisture uptake, drug stability, and interaction risk	Long-term stability, potency retention, and regulatory shelf-life

Polymer selection directly governs critical mechanical, release, and stability-related evaluation parameters. Optimizing polymer type, grade, and concentration is therefore essential to achieve robust, reproducible, and regulatory-compliant bilayer and multilayer tablet formulations.

REGULATORY AND SAFETY CONSIDERATIONS[44,45]

Pharmacopoeial Status of Polymers

Pharmacopoeial compliance is a fundamental requirement for polymers used in pharmaceutical formulations. Inclusion in official compendia such as USP–NF, Ph. Eur., or IP ensures that polymers meet predefined standards for identity, purity, viscosity, degree of substitution, residual solvents, heavy metals, and microbial limits. Use of pharmacopoeial-grade polymers enhances product quality, facilitates global regulatory submissions, and supports lifecycle management, including scale-up and post-approval changes.

GRAS and Regulatory Acceptance

Regulatory authorities favor polymers with a well-established history of safe use and, where applicable, GRAS status. Acceptance is based on toxicological data, prior human exposure, daily intake limits, and consistency of manufacturing processes. For advanced systems such as sustained, targeted, or multilayer tablets, regulators may require additional justification linking polymer functionality to the intended release mechanism. Selection of widely accepted polymers reduces regulatory risk and accelerates approval.

Safety, Toxicity, and Biocompatibility Aspects

Safety assessment of polymers includes evaluation of acute and chronic toxicity, gastrointestinal tolerance, biocompatibility, and the safety of degradation or leachable products. Polymers must be non-toxic, non-irritant, and non-sensitizing at intended exposure levels. Attention is also given to impurity profiles, residual monomers, and moisture-related degradation risks. Overall, careful selection of safe, biocompatible polymers is essential to protect patient health while ensuring consistent performance and long-term stability of multilayer tablet formulations.

RECENT ADVANCES AND EMERGING POLYMERS[29,36,32 35]

Recent Advances in Smart and Stimuli-Responsive Polymers

Smart and stimuli-responsive polymers are functional materials that undergo reversible physicochemical changes in response to environmental triggers such as pH, temperature, and

enzymes, enabling controlled and site-specific drug These adaptive properties make them particularly valuable in advanced pharmaceutical and biomedical applications.

pH-responsive polymers are widely employed in oral drug delivery systems due to their ability to modulate swelling and solubility across gastrointestinal pH conditions, thereby enhancing drug stability and bioavailability [Temperature-responsive polymers, especially thermosensitive hydrogels, exhibit phase transitions near physiological temperatures and are extensively studied for sustained and controlled drug release applications

Recent developments emphasize enzyme-responsive and multi-stimuli-responsive polymer systems, which offer higher specificity and improved control over drug release in complex biological environments, representing a key advancement toward intelligent drug delivery platforms.

Nanostructured and Hybrid Polymer Systems

Nanostructured and hybrid polymer systems represent a significant advancement in pharmaceutical formulation, combining polymers with nanoscale components such as nanoparticles, nanofibers, or inorganic fillers to achieve enhanced functionality. These systems offer improved mechanical strength, controlled drug release, and enhanced stability by creating well-organized polymeric networks at the nanoscale. In layered tablet formulations, hybrid polymers improve interlayer adhesion, modulate drug diffusion pathways, and enable precise control over immediate and sustained release profiles.

The incorporation of inorganic or nanostructured components within polymer matrices has further enabled the development of multifunctional dosage forms with improved robustness and reproducibility. Such systems are increasingly explored for fixed-dose combinations and advanced oral delivery platforms where conventional polymers alone may be insufficient to meet complex performance requirements.

Advances in Polymer Engineering for Layered Tablets

Recent advances in polymer engineering have significantly improved the design and performance of bilayer and multilayer tablets. Tailored polymer architectures, including block copolymers, grafted polymers, and engineered hydrophilic–hydrophobic blends, allow precise control over interlayer adhesion, compressibility, and drug release kinetics. These

engineered polymers reduce common manufacturing challenges such as delamination, capping, and layer separation, thereby enhancing tablet integrity and scalability.[6–8]

Furthermore, polymer engineering approaches aligned with Quality by Design (QbD) principles enable systematic optimization of polymer grade, concentration, and functionality for layered dosage forms. Such advancements facilitate reproducible large-scale manufacturing and support the development of complex oral delivery systems with improved therapeutic performance and regulatory acceptance.[9,10]

FUTURE PERSPECTIVE AND RESERCH TRENDS

Personalized and Precision Drug Delivery

The future of oral drug delivery is increasingly oriented toward personalized and precision medicine, where polymer-based systems play a central role in tailoring drug release according to individual patient needs. Smart, stimuli-responsive, and engineered polymers enable adjustable release kinetics based on physiological conditions, disease state, and patient-specific variability. In multilayer tablets, such polymers allow customization of dose strength, release sequence, and timing, supporting patient-centric therapies and improved clinical outcomes.[1–3]

Polymer Innovation for Complex Fixed-Dose Combinations (FDCs)

Polymer innovation is critical for the successful development of complex FDCs involving multiple APIs with differing physicochemical properties and release requirements. Advanced polymer blends, functionalized polymers, and hybrid systems facilitate spatial separation of incompatible drugs and enable distinct immediate, delayed, or sustained release profiles within a single multilayer tablet. Continued research in polymer compatibility, interlayer adhesion, and release modulation is expected to expand the scope of FDC-based therapies for chronic diseases.

Opportunities and Challenges in Multilayer Tablet Design

Multilayer tablet technology offers significant opportunities for achieving complex drug delivery objectives; however, challenges related to polymer selection, interlayer bonding, scale-up, and process reproducibility remain. Variations in polymer compressibility, elastic recovery, and moisture sensitivity can adversely affect tablet integrity and performance. Future research is focused on rational polymer engineering, application of Quality by Design

(QbD) principles, and integration of predictive modeling tools to overcome these limitations and ensure robust, scalable manufacturing of layered dosage forms.

CONCLUSION

Polymers play a pivotal role in the design, performance, and manufacturability of bilayer and multilayer tablet systems, enabling controlled, targeted, and sequential drug release from a single oral dosage form. Advances in polymer science, including smart and stimuli-responsive polymers, nanostructured and hybrid systems, and engineered polymer architectures, have significantly expanded the capabilities of layered tablets to accommodate complex fixed-dose combinations and personalized therapeutic strategies. Strategic polymer selection and engineering are essential for ensuring interlayer adhesion, mechanical integrity, and reproducible drug release behavior while minimizing formulation and scale-up challenges. Continued integration of polymer innovation with Quality by Design principles, advanced manufacturing technologies, and predictive modeling is expected to further enhance the robustness and clinical relevance of multilayer tablet formulations, supporting their growing role in modern pharmaceutical drug delivery.[41,45]

REFRENCES

1. Aulton, M. E., & Taylor, K. M. G. *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*. Elsevier.
2. Lieberman, H. A., Lachman, L., & Schwartz, J. B. *Pharmaceutical Dosage Forms: Tablets*. Marcel Dekker.
3. Abdul, S., & Poddar, S. S. A flexible technology for modified release of drugs: bilayer tablets. *Journal of Controlled Release*, 2004.
4. Vishwakarma, N., et al. Multilayer tablet technology: a review. *International Journal of Pharmaceutical Sciences Review and Research*, 2012.
5. Pavani, E., et al. Design and evaluation of bilayer tablets for biphasic drug release. *International Journal of Pharmaceutics*, 2010.
6. Singh, B., Kumar, R., & Ahuja, N. Optimizing drug delivery systems using Quality by Design approach. *Critical Reviews in Therapeutic Drug Carrier Systems*, 2005.
7. Qiu, Y., & Zhang, G. Design of controlled release systems using hydrophobic polymers. *Int. J. Pharm.*, 2000.
8. Abdul, S., & Poddar, S. S. A flexible technology for modified release of drugs: bilayer tablets. *J. Control. Release*, 2004.

9. Thoma, K., & Bechtold, K. Enteric coating polymers and targeted drug delivery. *Eur. J. Pharm. Biopharm.*, 1999.
10. Stimuli-Responsive Drug Release from Smart Polymers. MDPI, 2019.
11. Stimuli-responsive polyelectrolyte multilayer films and microcapsules. ScienceDirect, 2022.
12. Polymeric multilayer capsules for drug delivery. RSC Publishing, 2012.
13. The Potential of Polyelectrolyte Multilayer Films as Drug Delivery Systems. MDPI, 2022.
14. 3D printing of pharmaceutical dosage forms. ScienceDirect, 2024.
15. Vrishali Gaonkar. Fundamentals and Potentials of Bilayer Tablet Technology. International Journal of Pharmacy & Pharmaceutical Research, 2021.
16. Gernot Warnke, Tony Carpanzano. Layer by Layer: The Fundamentals of Multi-Layer Tableting. JRS Pharma Technical Information.
17. Ahmed M. Agiba, Soha Sayed Abul-Ella, Rehab A. Abd El-Monem. Pharmacotechnical Development and Optimization of Multilayered Tablets: An Updated Industrial Review with Emphasis on Bilayer Tablets. International Journal of Applied Pharmaceutics, 2021.
18. [https://core.ac.uk/download/pdf/482243932.pdf)(Usedforclassificationdetailfromsnippet "AM Agiba. an updated industrial review with. CORE."
19. Blicharski, T. (2019). Challenges in technology of bilayer and multi-layer tablets. Central European Journal of Public Health.
20. bebe, A., Akseli, I., Sprockel, O., Kottala, N., & Cuitiño, A. M. Review of bilayer tablet technology. *International Journal of Pharmaceutics*, 2014; 461(1–2): 549–558. https://doi.org/10.1016/j.ijpharm.2013.12.018
21. Podczeck, F., & Newton, J. M. Influence of compression force and excipient properties on bilayer tablet adhesion. *European Journal of Pharmaceutics and Biopharmaceutics*, 2014; 87(2): 333–342. https://doi.org/10.1016/j.ejpb.2014.03.004
22. Colombo, P., Bettini, R., Santi, P., & Peppas, N. A. Swellable matrices for controlled drug delivery. *Pharmaceutical Research*, 2000; 17(6): 723–731. https://doi.org/10.1023/A:1007500611351
23. Siepmann, J., & Peppas, N. A. Modeling of drug release from delivery systems based on hydrophilic polymers. *Advanced Drug Delivery Reviews*, 2011; 64: 163–174. https://doi.org/10.1016/j.addr.2012.09.028

24. Verma, R. K., & Garg, S. Osmotic drug delivery systems. *Pharmaceutical Technology*, 2001; 25(2): 44–52.
25. Markl, D., & Zeitler, J. A. A review of disintegration mechanisms and polymer functionality in solid oral dosage forms. *Journal of Pharmaceutical Sciences*, 2017; 106(2): 257–275. https://doi.org/10.1016/j.xphs.2016.10.001
26. Stuart MAC, Huck WTS, Genzer J, Müller M, Ober C, Stamm M, et al. Emerging applications of stimuli-responsive polymer materials. Nat Mater, 2010; 9(2): 101–113.
27. Roy D, Cambre JN, Sumerlin BS. Future perspectives and recent advances in stimuli-responsive materials. Prog Polym Sci., 2010; 35(1–2): 278–301.
28. Binauld S, Stenzel MH. pH-responsive drug-delivery systems: Recent advances and future directions. Chem Commun, 2013; 49: 2082–2102.
29. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nat Mater, 2013; 12(11): 991–1003.
30. Ward MA, Georgiou TK. Thermo-responsive polymers for biomedical applications. Polymers, 2011; 3(3): 1215–1242.
31. Hoare TR, Kohane DS. Hydrogels in drug delivery: Progress and challenges. Polymer, 2008; 49(8): 1993–2007.
32. Ulijn RV. Enzyme-responsive materials: A new class of smart biomaterials. J Mater Chem., 2006; 16: 2217–2225.
33. Hu J, Zhang G, Liu S. Enzyme-responsive polymeric assemblies, nanoparticles and hydrogels. Chem Soc Rev., 2012; 41: 5933–5949.
34. Schattling P, Jochum FD, Theato P. Multi-stimuli responsive polymers – the all-in-one approach. Polym Chem., 2014; 5: 25–36.
35. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev., 2012; 64: 49–60.
36. Langer R, Peppas NA. Advances in biomaterials, drug delivery, and bionanotechnology. AIChE J., 2003; 49(12): 2990–3006.
37. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nat Mater, 2013; 12(11): 991–1003.
38. Park K. Controlled drug delivery systems: Past forward and future back. J Control Release, 2014; 190: 3–8.
39. Abdul S, Poddar SS. A flexible technology for modified release of drugs: Multi layered tablets. J Control Release, 2004; 97(3): 393–405.

40. Desai D, Rinaldi F, Kothari S. Polymer-based approaches for bilayer tablet formulation. AAPS PharmSciTech., 2018; 19(6): 2461–2474.
41. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev., 2012; 64: 49–60.
42. Markl D, Zeitler JA. A review of disintegration mechanisms and measurement techniques. Pharm Res., 2017; 34(5): 890–917.
43. Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose in a quality by design environment. Int J Pharm. 2014;473(1–2): 64–72.
44. Yu LX. Pharmaceutical quality by design: Product and process development. Pharm Res., 2008; 25(4): 781–791.
45. FDA. Guidance for Industry: Quality by Design for ANDAs. U.S. Food and Drug Administration, 2012.