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Bilayer Ondansetron Tablet with Eudragit Coating: Toward a Dual-Action Oral Delivery System

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Abstract: ***Backgroun***d: The route of absorption most preferred is oral drug delivery because of its convenience, affordability and patient compliance. Nevertheless, traditional oral pills usually have shortcomings like low bioavailability, ease in drug release and development of frequent dose schedules Introduction - Ondansetron is a short-acting selective 5-HT3 receptor antagonist, combined with nausea and vomiting prevention and has a short half-life; therefore, patient compliance may be decreased with many doses required every day. This review centers on the development and testing of dual-action bilayer tablets. ***Material Method*** - ondansetron which are covered with Eudragit extensible polymers with the aim of creating modified release profiles. The bilayer tablet encloses both the immediate release layer and the sustained release layer within a single tablet to enhance both the timely effect and sustained effectiveness of the therapy by increasing the plasma concentrations steadily and decreasing dosing frequency. ***Result & Discussion*** - The addition of Eudragit coating increases site-specific release and safe release of the drug in the stomach. ***Conclusion*** - All the instruments displayed in the review include formulation strategies, choice of polymers, quality by design (QbD) strategy and assessment approaches to maintain the integrity of the tablet and the controlled drug release. The newer technologies of bilayer tablets and polymer coating offer prospective solutions in improving therapeutic outcomes and compliance with therapy in antiemetic therapy. Future opportunities involve the presence of nanotechnology and individualised medication in assisting in better oral drug delivery systems.

Keywords: Ondansetron, bilayer tablets, dual release, Eudragit coating, modified release.

INTRODUCTION

Oral drug administration is deemed more preferable due to its non-invasiveness, low cost, and the lack of therapeutic side effects in the delivery of oral medication, yet poor bioavailability, instability in the gastrointestinal tract and variable absorption pose important drawbacks that could affect the results of therapy and decrease compliance (Lou et al., 2023; Alqahtani et al., 2021). To overcome these challenges, the pharmaceutical developments in the present area made targeting of drugs via controlled release systems modified or lipid-based system formulations, or mucoadhesive vehicles preventing their degradation, protecting absorption, and enabling targeted or prolonged release (Buya et al., 2020).

Tablet-based technologies are extensively investigated and, in particular, bilayer types because of strong composition and scalability, allowing a more accurate manipulation of drug release profile and an enhancement of therapy efficacy associated with stable plasma concentrations and a decrease in dosing frequency (Alqahtani et al., 2021). More sophisticated techniques including self-nano-emulsifying drug delivery systems (SNEDDS), micro/nanoscale carriers with an even greater efficiency in solubility and stability are being employed mainly when poorly soluble or biologic drugs need to be worked with (Haddadzadegan et al., 2022). Microfabricated devices and site-delivery systems based on mucoadhesives also present targeting uses of the gastrointestinal tract, reliant on site-

selection and long-holding properties of devices (Kumar et al., 2022). On the whole, these novel oral drug delivery technologies are supposed to ensure the maximum bioavailability of drugs, minimal toxicity, and enhanced adherence of patients, that will be a huge breakthrough in surmounting the burden of current oral dosage types (Ahadian et al., 2020).

The technology of bilayer pills has also developed passed the facts by allowing fixed-dose mixtures, and enables advanced control of the drug release profile, including immediate and sustained drug release within one dosage form. This two-layered approach can give one of the layers a rapid onset of action and the other to sustain the therapeutic levels over time, hence reducing how frequently one should dose the patient and achieve compliance, which is particularly useful in the case of chronic conditions (Simão et al., 2023). Optimal formulation and process parameters are essential in order to achieve the desired release kinetics, avoid separation of layers, and ensure quality during the manufacturing of bilayer, a complex task due to many variables in play (Simão et al., 2023).

In the case of ondansetron, a commonly used antiemetic preparation, it has been shown using a dual-release (had two modes) tablet formulation. A bimodal release ondansetron tablet (RHB-102) was shown to significantly improve the stool consistency and symptom relief of patients with diarrhoea-predominant irritable bowel syndrome (IBS-D) in a randomised, double-blind trial, and has a positive safety profile (Plasse et al., 2020). This demonstrates the clinical applicability of bilayer or bimodal release pills to customize ondansetron's ability to certain therapeutic requirements to provide both immediate and prolonged antiemetic impact. These types of innovations are typical representatives of optimisation of existing drugs such as ondansetron in different clinical uses through bilayer tablet technology (Simão et al., 2023).

The short half-life of ondansetron, so far only taken in single-layered oral tablets, means that, in spite of frequent plateau relevant plasma levels, the patient must sustain varying levels in the plasma as the drug is free-flowing in the intestinal lumen, and it has therefore a low level of patient compliance, particularly in chemotherapy patients. Combining an immediate and a slow rate of drug release into a single tablet in bilayer and controlled-release formulations promises a solution to this by improving the consistency of treatment and therapeutic convenience.

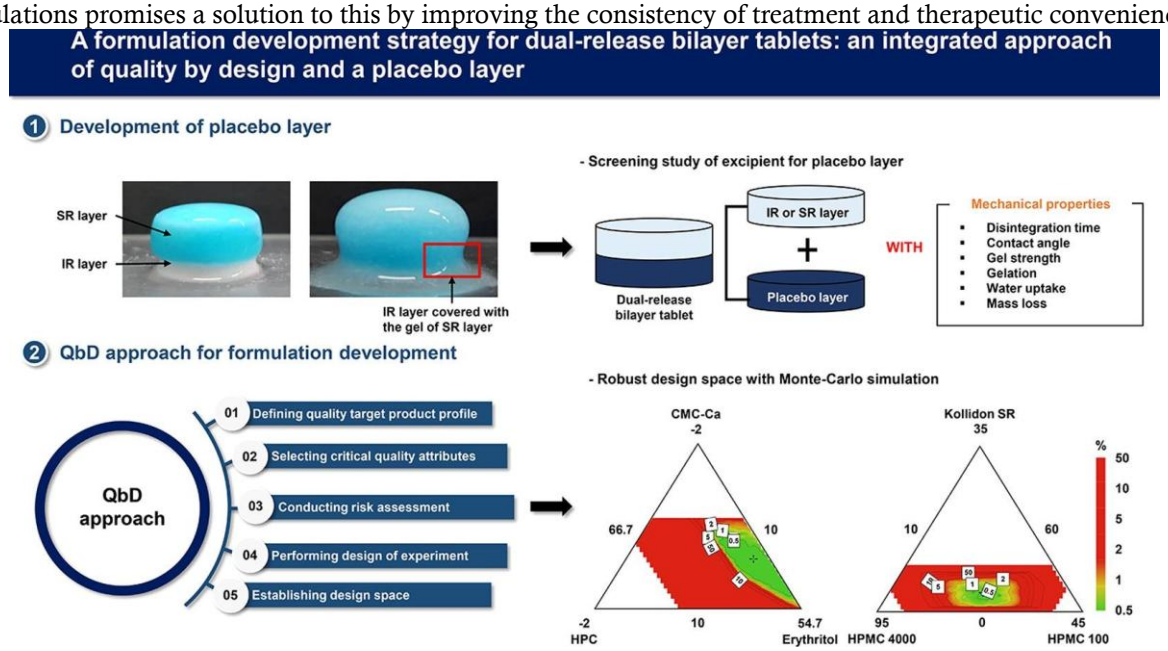

Fig. 1: Dual-release Bilayer Tablet Formulation and QbD Development Workflow
Source: (Han et al., 2022)

This representation shows that the systematic approach to the development of dual-release bilayer tablets is based upon the principles of formulation science and Quality by Design (QbD). In the upper part, the picture illustrates a bilayer system, consisting of a sustained release (SR) layer and an immediate release (IR) layer which were represented by visualizing the concepts before and after the gelation of the SR layer. The technique includes the screening of excipients and optimisation of the placebo matrix, determination of such key mechanical properties as disintegration, gelation, and water uptake. The bottom section contains the workflow of QbD: the target product profiles definition, critical attribute identification, risk analysis, experimental design, and design space. The triangular plots elaborate the strong and robust design space with which the exactly right ratios of excipients can be developed through the Monte-Carlo simulation to assure the end bilayer tablet product of high quality and performance(Han et al., 2022).

Bilayer tablets would be able to provide an initial high dose (immediate release) to reverse acute symptoms as soon as possible, and a later sustained release layer that would maintain therapeutic plasma levels over long durations to avoid the necessity of conducting high-frequency dosing (Simao et al., 2023). Patients may undergo only once-daily or less frequent dosing schedules; this fact is especially important when patients experience fatigue, they may skip doses during their treatment (Plasse et al., 2020). The controlled-release reduces the peaks and troughs in drug concentrations and reduces breakthrough symptoms with the aim of improving efficacy overall (Plasse et al., 2020).

Polymer Coatings (e.g., Eudragit) are also able to offer site-specific release, pH-dependent release, to further optimise drug delivery and stability in the gastrointestinal tract (Allahham et al., 2020).

Ondansetron single-release tablets three times a day, demonstrated bioavailability and efficacy comparable to a bimodal (dual-release) tablet (RHB-102), which showed bioavailability and efficacy with once-daily dosing, resulting in rapid absorption and long effect. This was better tolerated and had an enhanced role in symptom control in a clinical trial (Plasse et al., 2020). Fine-tuning of release profiles and robust production of bilayer tablets is being done using Quality by Design (QbD) methodologies and using advanced polymers (e.g., Eudragit) (Simao et al., 2023).

Thus, the development of the Ondansetron two-layered tablet that is coated with Eudragit is an enormous breakthrough in the science of oral drug delivery. It provides a logical solution to limiting the pharmacokinetics of conventional dosage forms and is in compliance with the larger objective of pharmaceutics to create patient-centric, effective and reliable delivery solutions.

Ondansetron: An Overview

Ondansetron is a selective serotonin, 5-HT3 receptor antagonist typically in the form of ondansetron hydrochloride. It is a white or off-white crystalline water-soluble powder. The drug has a moderate aqueous solubility and this can be improved with a formulation technique, e.g., nanofibers or polymer matrix (Rachmawati, 2025). The pKa of Ondansetron is about 7.4 implying that the drug is predominantly un-ionised in physiological pH, which facilitates its absorption in the gastrointestinal tract. Log P value (lipophilicity) is approximately 2.6, indicating moderate lipid solubility, but implies that the drug is vulnerable to first-pass metabolism. Under standard storage conditions, Ondansetron is observed to be chemically stable although it is subject to influences of extreme PH and extreme temperature.

When the drug is orally ingested, ondansetron is promptly absorbed with peak plasma concentrations usually attained in 1.5 to 2 hours. But it is less absolute bioavailability (approximately 60 percent) because of one of its large metabolism in the hepatic first pass. The drug is extensively spread in the body, its volume of distribution is about 2.5 L/kg and the protein binding is about 70-76%. Ondansetron is covered with extensive hepatic metabolism, mainly through the cytochrome P450 (CYP3A4, CYP2D6 and CYP1A2) enzymes, which form in inactive metabolites. Elimination is mainly conferred via renal dumping of metabolites with terminal half-life of 3 to 5 hours and requires that the dose to be taken several times a day to be effective (Kamranpour et al., 2021).

Ondansetron is also a competitive antagonist to the 5-hydroxytryptamine type 3 (5-HT3) receptors which are peripherally found on vagal nerve endings in the gastrointestinal tract and centrally on the chemoreceptor trigger zone in the brain. Ondansetron interferes with the binding of serotonin at these receptors, which, therefore, suppresses the emetic reflex and is a good preventive and treatment of nausea and vomiting caused by chemotherapy, radiotherapy, and surgery (Zarkadas et al., 2020).

Ondansetron is commonly employed in the prevention and treatment of nausea and vomiting related to cancer chemotherapy (CINV), radiotherapy and in the postoperative (PONV) recovery. It is regarded as one of the first-line antiemetic agents in the field of oncology supportive care and perioperative medicine and may be administered alone or included with corticosteroids and other antiemetic agents to improve their efficacy (Xu et al., 2025). Although effective, other 5-HT3 antagonist drugs (like palonosetron and granisetron) can prove to be more effective in a specific clinical situation, as it was proposed in some studies (Xu et al., 2025).

The traditional forms of ondansetron tablet have low half-life; because of this, multiple doses are administered daily to sustain therapeutic plasma concentrations, consequently making ondansetron lowly compliant by patients, particularly those on intensive chemotherapy. Changes in plasma levels can result in breakthrough symptoms. Also, during pediatric dosage education, the mathematics of preparing tablets can change the drug release profiles (Rachmawati, 2025). To overcome these drawbacks, newer substances have been created (for example, extended-release granules and fast-dissolving sublingual nanofibers), which offer more consistent drug release, enhance patient satisfaction, and offer a flexible dose-response range (Kamranpour et al., 2021).

Bilayer Tablet Technology

The bilayer pills are improved oral dosage forms, which are made by two distinct layers, where each could carry different active pharmaceutical ingredients (APIs) or release levels. In this type of design, drugs can be delivered sequentially or simultaneously inside a single tablet, and either instantly or long-lasting. Different polymers and excipients can then be used to design the layers, allowing the controllability of the release kinetics, degradation protection of sensitive drugs, or separation of incompatible molecules (Simão et al., 2023). Recent advances in manufacturing approaches, including hot-melt extrusion technology, 3D printing, and direct compression, have increased the risks of bilayer tablet design because aside from giving the chance to select the selected drug quantity, the layer density, and paired release properties, it is now feasible to regulate them all in particular and regulate these parameters exactly (Tabriz et al., 2021).

Tablets made in bilayers have a number of strengths over traditional single-layer tablets. The most important is the capability to implement sequential goal of delivering an instantaneous dose to activate rapid onset and the latter delivers an alternative efficient goal of having an extended or delayed outcome of therapeutic effects (Crişan et al., 2023). This method can decrease the rate of dosing, which comes especially in handy in chronic conditions, and can increase patient adherence, by making medications easier (Israr et al., 2022). Bilayer neoparticles can also enable drug-drug and drug-API incompatibilities to be separated or it is possible to load drugs that have varying release needs into the same neoparticle, increasing the efficacy and safety levels of therapeutic dosages (Janczura et al., 2022). Also, they are able to reduce the drug-drug and drug-excipient interactions through physically isolating ingredients inside the pill (Janczura et al., 2022).

Bilayer tablets present special issues in their manufacture, despite its advantages. Avoidance Layer separation (delamination) may take place when the layers have less-than-optimal adhesion, or compression parameters are not tuned (Simão et al., 2023). Blending and compression may pose a potential risk of cross-contamination between the layers, particularly when APIs or excipients move between the layers (Simão et al., 2023). The process is more complicated than that of single-layer tablets because it is necessary to visually monitor material characteristics, granulation, and compression and make sure that the tablet looks similar in all its aspects: uniformity, mechanical strength, and drug delivery rate (Janczura et al., 2022). To design and prevent such risks, more advanced quality control measures are implemented like Quality by Design (QbD) techniques, which implement checks to control manufactured goods leading to a robust product performance (Arshad et al., 2021).

Bilayer pills are particularly efficient in controlled-release systems, where this allows biphasic release of drugs both in the short dose (ensuring filling the first peak) and in the long one (seen in typically in medicines of pain management, sleep disorders and gastrointestinal illnesses), (Bassetto et al., 2024). Also useful in fixed-dose combination therapy, two or more drugs can be administered simultaneously with characteristics of their respective release profiles to minimise interactions with each other (Ullah et al., 2023). As one example, the cardiovascular disease (rosuvastatin and acetylsalicylic acid) and the treatment of tuberculosis (isoniazid and rifampicin) and of Helicobacter pylori (clarithromycin and esomeprazole or pantoprazole) are a few application areas of bilayer tablets (Junqueira et al., 2024).

A number of bilayer pills currently exist or were previously considered for clinical activity. Notable examples include:

Tuberculosis Bilayer tablets: The combination of isoniazid (immediate release), then rifampicin (sustained release) so that the two could be maximised and reduce drug destruction (Tabriz et al., 2021).

H. pylori, Floating bilayer tablets: Clarithromycin with esomeprazole (or pantoprazole) are used together to treat gastrointestinal secretion and controlled-release (Ghazali et al., 2021).

Melatonin bilayer tablet: It aims to assist in the treatment of sleeping disorders, achieving both rapid and prolonged release (to simulate somatomelanotrop hormone secretion into the circulation) (Bassetto et al., 2024).

Cardiovascular combinations: Bilayer tablets of rosuvastatin and acetylsalicylic acid to be used in the context of a dual-action use (Junqueira et al., 2024).

Altogether, bilayer tablet technology has important therapeutic and practical benefits over single-layer tablets, such as personalised drug delivery, better compliance and combination therapy, but it necessitates cautious design and fabrication to address the technical difficulties.

Role of Polymers in Modified Release

In the experimental design of modified release drug delivery systems, polymers are inevitants in being able to determining the rate, duration and location of drug release. They are versatile and thus can result in the formulations that can safeguard drugs against the unfavourable gastrointestinal conditions, increase bioavailability, and fit a given therapeutic profile to particular clinical requirements. As a matrix former, coating or carrier, polymers may be utilized, and

their choice is of paramount importance in achieving the needed characteristics of release (Ghasemiyeh& Mohammadi-Samani, 2021).

There are pharmaceutical polymers that are natural (e.g., cellulose derivatives, gums, alginates), and those that are synthetic (e.g., polyacrylonitrile, polyvinylpyrrolidone, Eudragit, PLGA). Natural polymers are frequently biocompatible and biodegradable, and thus, it can be used in sustained and target delivery, whereas synthetic polymers have more tunability in chemical structure, mechanical strength, and release forces (Marco, 2023). This can be enhanced by combining both natural and synthetic polymers to increase the carrier stability and release of the drug as in interpenetrating polymer networks (IPNs) and core-shell (Lohani et al., 2024). Direct physicochemical characteristics of polymers like solubility, swelling capacity and permeability, impact on the kinetics of drug release. The hydrophilic polymers (e.g., polyvinylpyrrolidone, cellulose ethers) expand in the aqueous medium, create gels which regulate rates of drug diffusion and erosion, and the hydrophobic ones (e.g., polyacrylonitrile, Eudragit RS) delay the water permeation and maintain release (Lv et al., 2021). Crosslinking, molecular weight and polymer-drug interactions also influence the integrity of the matrix, drug encapsulation, and release pixels. An example is that phase-separated blends between hydrophilic and hydrophobic polymers can form porous networks that tune release rates (Olsson et al., 2024). Diffusion, swelling or erosion processes of diffusion, incorporating matrix polymers throughout the dosage form are used to regulate pharmacokinetic release of drugs. Coating polymers on the other hand, offer a shield or coating around the drug core or pellets, which delays, provides sustained or localised release by altering permeability, or reacts to environmental factors, such as pH (Al-Hashimi et al., 2025). The decision of using matrix and coating strategies relies on the desired profile of release, characteristics of drug and target site.

The Eudragit of copolymers synthesized are a series of methacrylate compound-oriented synthetic copolymers that is based on functional groups along with solubility depending on the pH level. Eudragit RS and RL: Water-insoluble, permeable [su]nascent polymers are also used as sustained release systems, whereas NE grades are neutral and can be used as aqueous dispersions; L and S grades are anionic and dissolve at a higher pH value (L at pH >6, S at pH >7) and are therefore preferable to enteric coats (Al-Hashimi et al., 2025). Solvility and permeability of the polymer can be decoded by the chemical structure, namely ratio of ethyl acrylate, functional groups and methyl methacrylate and thus enables a perfect choice of regions in the gastrointestinal tract in which drugs can be released (Al-Hashimi et al., 2025).

Eudragit polymers have extensive uses in the determination of enteric protection, sustained release, and site-directed drug delivery. As an example, Eudragit L100 may slow down release in the stomach which is acidic, and release instantly in the intestine as reported in indomethacin oral disintegrating capsules (Al-Hashimi et al., 2025). Formulators can adjust the proportion of particular Eudragit grades and particle size to achieve a conditional release profile to ensure drugs are not readily degraded in the stomach, lower the patient price, and mitigate the characteristics of twins to cure the consequences of gastrointestinal gastric exposure. Eudragit-coated systems are additionally provided in multiparticulate or in pellet form to deliver pH-stimulated or timed release, to facilitate the manufacturing of novel oral dosage forms of an extensive scope of treatment options (Al-Hashimi et al., 2025).

Formulation Aspects of Ondansetron Bilayer Tablets

To achieve both immediate action and sustained action, the development of the ondansetron bilayer tablet involves the consideration of the distinction between IR and SR layers. The IR layer is optimised to disintegrate fast and release drugs at a high dose with rapid therapeutic plasma concentration, whereas the SR layer is formulated to provide slow drug release in the body, reducing the need to dose and variability of plasma concentrations. This profile of dual-release requires a strict choice of the excipients, polymers, and technology, close attention to the essential material qualities, and parameter regulation during processing, which ensures the integrity of the layers and predictable behaviour (Simão et al., 2023).

To achieve a quick break-up of the tablets upon coming into contact with the gastrointestinal fluids, superdisintegrants are normally incorporated in the IR coating, which includes croscarmellose sodium, sodium starch glycolate or crospovidone. Bulk is added with diluents, such as microcrystalline cellulose or mannitol, and lubricants, such as magnesium stearate or sodium stearyl fumarate, are used to decrease friction on the pill at ejection and increase the ease of manufacturability, respectively. These excipients are selected and combined in a manner that favours a rapid collapse in addition to a high rate of drug release and high mechanical strength (Simão et al., 2023; Allahham et al., 2020). The SR layer is based on hydrophilic and/or hydrophobic polymers in the regulation of drug release. The most popular polymers are Eudragit (with different grades to deposit, depending on pH) or hydrogen-propyl methylcellulose (HPMC) to use as gel-forming matrices, polyvinylpyrrolidone (PVP) to bind and sustained release, and Carbopol to swell

and mucoadhere (Ferreira et al., 2022). Polymer type, molecular weight, ratio are also chosen, leading to a change in the rate of release and a mixture of the two can be used to adjust the dissolution profile. Other excipients like fillers, binders, and plasticisers are selected in such a way that they maximise the hardness of the tablets, minimise their friability and attain even drug distribution.

The compatibility tests are necessary, so that the ondansetron and the chosen excipients cannot interact negatively, as it might interfere with its stability, activity, or even safety. Secondary techniques used are Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD), to establish the presence of chemical / physical in reactive systems. The investigations would aid in determining effective excipient mixtures, avoiding polymorphic, degradation processes, and stepping towards robust formulation, in particular, in the case of the complex polymer mixtures or the introduction of new manufacturing techniques (Ferreira et al., 2022).

The processing technique used is an important determinant of the quality and performance of bilayer tablets. The SR layer is frequently wet granulated in order to add to the flow of the powder mixture, a uniformly distributed exposure to drugs and mechanical strength. The IR layer would be easier to compress using direct compression because it is simpler and would not alter the speed of disintegration. Elaborated techniques like 3D printing, hot-melt extrusion are being followed as methods of customized and intricate formulations and provide accurate control over layer structure and drug content (Allahham et al., 2020). The optimisation of the process parameters (e.g., granule size, compression force, moisture content, etc.) is necessary in each technique, preventing the development of such problems with the use of the technique as segregation, variation of weight, and delamination of layers.

A significant problem is exploring the physical integrity of bilayer tablets. The compressibility and flow characteristics of the blend of each phase, the layer sequence and press order, and compatibility of excipients between layers are some of the key parameters. Weak bonding among layers can result in separation/delamination, whereas the variance in mechanical characteristics can result in capping/lamination on ejection. Quality by Design (QbD) methods are becoming increasingly employed to evaluate and control critical material attributes (CMAs) and critical process parameters (CPPs) in a systematic way, which is necessary to assure efficient bilayer formation and to predict or reproducible drug release (Polak et al., 2024). These parameters are critical parameters to be optimised and tracked during development and scale-up to ensure regulatory compliance and product success.

Coating of Bilayer Tablets with Eudragit

Bilayer tablet coating is a key approach towards modified drug release, especially in site-directed delivery and preservation of active drugs against the hostile gastrointestinal environment. A proper coating will ensure that premature release of drugs in the stomach is prevented, minimise gastrointestinal side effects and that the drug release in the gastrointestinal tract is as desired, e.g.colon or small intestine. It is particularly applicable to all those drugs which are unstable in the acidic environment or that need to act locally in the lower gut, such as during inflammatory bowel disease or arthritis-related IBD treatment (Jadiya et al., 2024).

Polymer Coating can be done by either solvent-based or aqueous-based applications. In solvent-based coatings, Eudragit polymers can be dissolved in organic solvents, which can provide both fast drying and easy film formation, but could be a considerable safety and environmental hazard. Aqueous coating techniques that dissolve Eudragit in water have become more popular since they are less toxic and they also reduce environmental impact although they might need fine-tuning of process factors which can result in cracking or incomplete coverage (Al-Hashimi et al., 2025). The two processes demand the optimisation of both the spray rate and atomization and drying conditions to a uniform and functional coating be obtained.

The uniformity and thickness of the coating of Eudragit is very important in order to create consistency in the release of drugs and resistance to gastric failures. The essential parameters are the rate of penetration and the consistency of the coating solution, rate of spray, pressure inside the atomization, temperature of the tabbed bed, and time taken to coating. Poor control may cause uneven coating and this may cause dose dumping or underdosing. Homogeneous finishes guarantee the actualisation of pH-susceptible qualities of Eudragit leading to trusted site-precise liberation (Al-Hashimi et al., 2025).

The ability of Eudragit polymers to be soluble at specific pH allowing the targeted drug release is widely applied. As an illustration, Eudragit S-100 and L-100 dissolve at pH values above 7 and 6 because it provides safety to the drug in the stomach and release it in the colon or small intestine (Doggwiler et al., 2023). This property can be used in bilayer tablets to induce delayed or colon-targeted drug release, which is shown in sulfasalazine foodstuffs with no release of the drug under acidic

and neutral pH, whereas there was release at colonic pH (Jadiya et al., 2024). Coatings and other triggers can also be used in combination with Eudragit to even more directly target the delivery point (Varum et al., 2020).

Tables coated with Eudragit release very low quantities of drug in the stomach, with the release rate of the drug being influenced to be either slow or swift, depending on contact with the intestinal pH of the target. This translates to the extended treatment plasma levels, a decreased dosage rate, and elevated adherence to treatment in patients (Doggwiler et al., 2023). Projects in vivo and in vitro evidence to demonstrate that these types of coats offer high gastric toughness and can be used to release in bolus or pulses, as needed in vivo, and driven by formulation design (Aldawsari et al., 2022). The integrity and stability of the coating is preserved during gastrointestinal transit such that the drug is released at only the intended location, which maximises efficacy and reduces systemic side effects.

Current Research and Case Studies

More recent research on ondansetron has investigated novel oral delivery strategies, such as bimodal (dual 3D-release) and 3D-printed formulations, but has not specifically investigated bilayer ondansetron-coated adhesive tablets using Eudragit bilayer. An interesting example is the creation of an investigational bimodal release ondansetron tablet (named RHB-102) that is intended to be received once per day in case of diarrhoea-predominant irritable bowel syndrome (IBS-D). This formulation was found to be much better than placebo, exhibited considerable improvements in stool consistency and symptom management, had a favourable safety profile and mild, transient constipation as the only side effect. The clinical efficacy of dual-action ondansetron delivery in the management of chronic gastrointestinal conditions has been presaged by the bimodal type of release approach that replicates the effect of a bilayer tablet by giving an individual immediate and sustained drug release (Plasse et al., 2020). Further, oral dose has been 3D printed orodispersible ondansetron printlets selectively using selective laser sintering (SLS) 3D printing to produce printlets with vehicles that release the drug similarly to commercial orally disintegrating tablets by rapidly dispersing directly in the cavity but provides the benefit of individualised dosing (Allahham et al., 2020).

Other than ondansetron, bilayer and Eudragit-coated tablet forms have been independently deployed with numerous other drugs, with the need to be formulated with modified release or site-specific release. Eudragit-coated bilayer pills, such as of sulfasalazine, could also be developed in such a way that the drug does not release at the gastric and small intestinal mucosa but can release at colonic pH (Allahham et al., 2020). The application of this method is possibly effective with therapeutic agents of inflammatory bowel disease or agents that are additional unstable under acidic environments. Addition of Eudragit polymers with their pH-sensitive solubility enables the site and timing to possess exact control of the drug release that is essential in achieving maximum effect in the therapeutic approach and reducing side effects.

The in vitro and in vivo studies indicate that dual-release systems, bilayer systems, have the potential to generate more stable plasma drug concentrations, less affected dose rate, and enhanced patient compliance than the traditional single-layer systems or immediate-release systems. RHB-102, the bimodal release profile has shown better symptom control compared to IBS-D patients in the case, and the results supported by in vivo measurements indicate that the sustained therapeutic action has been achieved in vitro (Plasse et al., 2020). Likewise, 3D-printed ondansetron pills exhibited the same rate and complete release of the drug, as the conventional commercial products do (Allahham et al., 2020). These results indicate the importance of state-of-the-art development technologies in the optimization of drug delivery and therapeutic results.

The opportunities of personalised and combination therapies are growing alongside the development of novel technologies of drug delivery in the form of 3D printing, hot-melt extrusion, or complex methods of coating. Such technologies allow an accurate dosage, release dynamics, and tablet pill format control, which facilitates the creation and building of personalised medicines by asking various patient requirements, or by responding to complex disease conditions (Allahham et al., 2020). Bilayer and Eudragit-coated systems may further increase the efficacy, safety, and convenience of the oral administration of drugs such as ondansetron and many others with wider-ranging therapeutic applications as they build up research, as well as be integrated (Plasse et al., 2020).

Regulatory and Industrial Perspectives

The Quality by Design (QbD) model is widely used in designing bilayer tablets in order to provide strong product quality and universal regulatory control. QbD focuses on a rational realisation of validity on how critical material characteristics (CMAs) and critical process characteristics (CPPs) impact the critical quality characteristics (CQAs) of final product. When making a bilayer tablet formulation, this includes careful risk assessment and optimisation at the main phase including blending, granulation, pre-compression, and main compression. QbD assists in ensuring and managing variables that may

influence weight variability, segregation and delamination amongst layers, that is typical of bilayer tablet production. With QbD, the manufacturers are able to develop more robust processes and to produce consistently performing products as mandated by the regulatory officials (Simão et al., 2023).

Good Manufacturing Practices (GMP) is of paramount importance in the manufacture of bilayer and modified-release tablets. The guidelines of GMP mandate a thorough control of the quality of raw materials used, equipment calibration, environment and documentation during the manufacturing process. In the case of bilayer tablets, particular concern with cross-contamination between layers to avoid, content uniformity, and retaining the physical integrity of the tablet should also be taken into consideration. In-process testing as the thickness, hardness, and weight of the tablets, though, is essential in order to comply with the regulations and provide patients with safety (Israr et al., 2022).

The FDA and EMA regulatory bodies have certain regulations that govern the designing of bilayer formulas and modified-release formulas approval. These recommendations focus on the comprehensive characterisation of the drug product, such as dissolution, stability testing, and proving the in vitro-in vivo correlation (IVIVC) where needed (Kim et al., 2025). The regulatory review exercise also evaluates the reason behind the selected release profiles, how sound the manufacturing regime is, and how sufficient the controls are to provide consistency between batches. The use of QbD and risk management practices may need to be documented to provide support when submitting regulation (Simao et al., 2023).

The laboratory-scale preparation of bilayer tablets to an industrial scale encounters a number of difficulties. Holding layer uniformity, delamination prevention, and repeatable drug release behaviour can be harder when operating at larger scale because of the limitations of equipment and variability of process at the larger scale. Bilayer tablet production is even more complex, which increases the potential loss of control over the process and the failure of products. To accomplish these challenges, it is important to pay much attention to optimising the process, developing strong quality control mechanisms, and continuing a risk evaluation during commercialisation. These risks can be guarded against with the help of state-of-the-art production procedures and regular observation that will contribute to successful market penetration (Ebrahimi et al., 2024).

Future Perspectives

Controlled drug release has been revolutionised as of recently through advances in polymer sciences and nanotechnology, it is now possible to do more precise, steady and targeted drug delivery. Examples of polymers which are considered non-toxic, specifically natural (e.g., chitosan, cellulose) and synthetic (e.g., PLGA, PLA) inspired the creation of drugs carriers with greater biocompatibility, biodegradability, and release profiles. Those nano-blended systems have the potential to solve the problems in targeting controlled delivery of drugs and genes to therapeutic benefits and minimized side effects (Maghsoudi et al., 2020). The toolkit can also be further expanded by nanoengineered polysaccharides and nanogels that differentiate in response to certain stimuli (such as pH, temperature, enzymes) to release drugs on demand, and the released kinetics of nanoengulfing can be easily modelled and predicted to increase the ability to translate research findings to clinical practice (Nguyen et al., 2023).

To this end, polymer based hydrogels and nanocomposites are now being engineered to be compatible with personalized medicine since they can be customized to meet the needs of particular patients i.e. particular drug release rates, drug combinations, and locations (Nguyen et al., 2023). In combination with sophisticated polymers and nanotechnology, bilayer tablets can represent the option of dual or controlled drug release to accommodate individual dosage and enhance therapeutic results. Engineering and capability of designing drugs delivery systems in the nanocosmos enable the individualization of pharmacokinetic and disease profile-specific therapies (Eltaib, 2025).

Other release-modifying agents, including nanogels, nanoparticles and smart polymers, are being combined with eudragit polymers to form even more advanced control of drug release. As an example, modifying Eudragit with stimuli-responsive nanogels or nanoparticles can allow using multi-triggered release, with the drug being protected in the stomach and becoming activated only in the conditions of certain stimuli in the intestine or in response to external pulling factors (Gleason, 2021). This delivery improves site specific delivery, and may be especially useful in drugs that degrade in the gut or drugs that penetrate to the colon.

Although face-to-face laboratory developments on polymer and nanotechnology-based drug delivery are encouraging, there is still a challenge in the expansion of such systems to clinical applications. Reproducibility, stability, toxicity, and regulatory considerations issues have to be put down to make sure that translation is safe and effective. But strong disease release kinetic modeling, enhanced fabrication strategies (initiated chemical vapor deposition and electrospinning) and a better grasp of

polymer-drug interactions are contributing to closing the divide between experimental devices and actual therapies (Bayer, 2023). The future of controlled release and personalized medicine is expected to become dependent on the further combination of advanced polymers, nanotechnology, and smart agents to regulate release (Maghsoudi et al., 2020).

CONCLUSION

Recent studies show that the drugs available in a device that shows a number of bilayer tablets (two layers of instantaneous release and sustained application) would allow exact regulations of the spontaneous disclosure curves. There are a wide range of successful remedies that have been 3D-printed with regard to drug assortments, including atorvastatin/ezetimibe, rosuvastatin/atenolol and tramadol, along with high-tech 3D-printed and floating tablet remedies (Mubeen et al., 2022). Determined in both in vitro and in vivo research, bilayer tablets can provide quick onset of action release of the IR layer, and long-term therapeutic benefit at the SR layer, making bilayer-tablets superior in their capacity to provide improved efficacy and reduced dosing cadence with enhanced control of chronic disorders (Israr et al., 2022).

Bilayer tablets overcome some of the constraints of the more traditional single-layer formulations. They can either physically separate otherwise incompatible drugs or give them sequential release to permit otherwise difficult-to-realise combination therapies. Studies involving atorvastatin/ezetimibe, rosuvastatin/atenolol, and tramadol bilayer tablets have demonstrated a high level of effectiveness of this technique in the reduction of lipids, foaming pressure, and related pain (Shinkai et al., 2023). Customisation of the drug release kinetics also helps ensure increased patient adherence and reduce side effects through more stable plasma drug concentrations (Elsayed et al., 2022).

Eudragit coatings with their ability to become pH receptive is applied to further improve the performance of the bilayer pills, protect drugs such as ondansetron against gastric destruction and release drugs in the intestine. This not only enhances bioavailability and prolonged action but also has minimal side effects on the gastrointestinal tract and long-term treatment. Another valuable addition to oral drug delivery is the incorporation of the Eudragit coatings with the incorporation of bilayer technology, which provides better gastric protection and localized, targeted drug delivery (Israr et al., 2022).

Finally, in terms of enhancing therapeutic performance, patient comfort, and sustaining overall treatment compliance to diverse ailments, we find that dual-action bilayer pills, particularly those with sophisticated polymerisation such as Eudragit, are indeed a poignant milestone in better living.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to improve readability and grammar. After using ChatGPT, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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