International Journal of Pharmaceutical and Bio-Medical Science

ISSN(print): 2767-827X, ISSN(online): 2767-830X

Volume 05 Issue 05 May 2025

Page No : 358-365

DOI: https://doi.org/10.47191/ijpbms/v5-i5-11, Impact Factor: 8.163

# Comparative Study of Bilayered Vs. Trilayered Tablets for Optimized Maxalt Delivery in Migraine Treatment

**Mahdi Abd Zair[1], Zainab Rahi Hanthal[2]**

**ABSTRACT**

Migraine is a disabling neurologic disorder that afflicts millions of people globally. Although treatments like Maxalt (rizatriptan benzoate) are available, traditional formulations can produce rapid absorption followed by a rapid decrease in plasma concentration after which therapeutic effects may not be optimal. Preformulation Studies Like other 5-HT1F agonist medications, Maxalt poses challenges due to its relatively low solubility and the potential for premature gastrointestinal absorption. In this study, bilayered and trilayered tablet formulations are compared for optimized delivery of Maxalt. Sustained drug release can be achieved via bilayered tablets, which are composed of two separate layers: a designated protective layer that protects the active pharmaceutical ingredient (API) from destruction in the gastric cavity, and a designated drug-release layer. Trilayered tablets contain an extra intermediate barrier, which may open up for many more well-controlled release profiles. Stacked structure of LbL assembly tablets polymers were selected, such as poly(lactic-co-glycolic acid) (PLGA), chitosan and sodium alginate. Tablets were characterized for physical properties (hardness, friability), morphological studies using scanning electron microscopy (SEM), and crystallinity studied using X-ray diffraction (XRD). The in vitro dissolution studies were performed at simulated gastric (pH 1.2) and intestinal (pH 6.8) conditions and the in vivo pharmacokinetic studies were carried out in Sprague–Dawley rats. These findings demonstrate that trilayered tablets are capable of delivering lower initial burst release and providing a more sustained drug plasma concentration than bilayered formulations and standard immediate-release tablets. These results indicate that bioavailability could be enhanced with a trilayered tablet and controlled Maxalt release could be achieved for acute migraine therapy. Clinical significance and recommendations for future studies are also explored.

**KEYWORDS:** Maxalt, Rizatriptan benzoate, bilayered tablets, trilayered tablets, controlled release, migraine, pharmacokinetics

**ARTICLE DETAILS**

**Published On:**
**29 May 2025**

**Available on:**
**https://ijpbms.com/**

## INTRODUCTION

Migraine is a chronic neurological disease manifested with recurrent and moderate to severe headache attacks associated with nausea, vomiting, photophobia, and phonophobia. This condition has an enormous impact on the day-to-day life of the ones affected by such a condition, there is a decline in productivity and quality of life (Jain & Kumar, 2020). A wide variety of physiological and environmental factors have been identified as migraines triggers; these can include hormonal changes, stress, habits, and disturbance of sleep patterns. Given the complexity migraine pathophysiology and the requirement for a synergistic drug delivery system with good control for sustained relief with a minimal side effect profile. The oral route is still the preferred route for migraine therapy, because of its non-invasiveness, simple administration, and good patient compliance. Nonetheless, traditional oral drug preparations suffer from numerous limitations including variable gastrointestinal pH, enzymatic degradation and hepatic 1st pass metabolism that can significantly compromise bioavailability of drugs (Patel & Desai, 2018). Rapid drug absorption is important for the relief of acute migraine attacks. Indications: Maxalt (rizatriptan benzoate), a 5-HT1 receptor agonist, is indicated for the acute treatment

of migraines. Conventional immediate-release formulations of Maxalt produce a rapid rise in plasma drug levels (high C_max) with a pronounced decline, resulting in subtherapeutic levels following administration in many cases. Due to this pharmacokinetic profile that presented difficulties in maintaining steady therapeutic levels, there was a need for developing advanced drug delivery systems capable of providing controlled and sustained drug release (Wang, Li, & Zhang, 2017).

Controlled and site-specific delivery has emerged from the enhanced understanding of the cellular pathways, and layer tablet formulations were established in previous years. These innovate, new dosage forms enable superior tuning of drug release kinetics for a more stable and extended therapeutic effect. In particular, bilayered and trilayered tablets have attracted the attention as the notable means for the drug delivering optimization. These systems are designed to offer protection against the unfavourable gastrointestinal milieu and enable extended release of drug at the site of absorption (Bhatt & Deshpande, 2020). Such bilayered tablets often include a release layer, in which the drug is dissolved or suspended, and a barrier layer, providing controlled two phase drug release. On the other hand, a trilayered tablet contains an additional intermediate layer, which allows maximizing the release profile by minimizing the initial burst effect and extending drug action. This structural optimization increases bioavailability and leads to better treatment outcome in cases of migraine (Bansal et al., 2019).

Therefore, this study aimed to compare the performance of bilayered and trilayered tablets, containing Maxalt for the treatment of migraine both in vitro and in vivo. Thus, to evaluate the pharmaceutical parameters of these drug formulations as it relates to their dissolution rate, bioavailability, plasma drug concentration curve, etc. This Study involves the formulation development of bilayered and trilayered tablets using a layer by layer (LbL) assembly approach, evaluation of their physical and chemical properties and ability to sustain drug release. In this study, we aim to evaluate these two types of formulations and assess which architecture affords better control over the release pattern along with improved bioavailability and thus therapeutic benefit for patients in need of treatment for migraines.

Orally disintegrating tablets, nasal sprays, and buccal films have been studied as other delivery systems for rizatriptan, with the intention of increasing both bioavailability and patient compliance (Goadsby et al., 2017). These formulations offer advantages like fast onset of action and convenient administration but are still not without drawbacks such as limited drug loading, variable absorption profile and patient preference problem. Multilayered tablets can provide an effective solution to these drawbacks through customized drug release kinetics, improved stability and patient compliance.

Multilayered tablet formulation depends governs the choice of polymer and excipient type to deliver the specific drug release behavior. Hydrophilic polymers are used in the outer layers that promote quick drug release, while hydrophobic polymers are used within the inner layers to allow a prolonged release of the drug. The use of multilayered systems enables the adjustment of drug release kinetics as needed to match the pharmacokinetic and pharmacodynamic demands of migraine treatment (Multilayer Dosage Forms Containing NSAIDs and Triptans, n.d.). A combination of immediate-release and sustained-release within a single dosage form provides a more versatile therapeutic tool in the treatment of migraine.[5] Multilayer tablets allow for a gradual reduction of the drug from the different layers into the bloodstream, keeping the plasma drug levels from rising too quickly, thereby helping to maintain an even plasma concentration response and lowering the chances of getting side effect because of high peak plasma concentration.

Technological breakthroughs in recent years further drastically changed the manufacturing of multilayer tablets. The implementation of different techniques like 3D printing, hot-melt extrusion and solvent-based layer deposition have allowed a very specific manufacturing of complex drug delivery systems. The ultimate goal is to achieve precision modulation of drug release kinetics and enable the delivery of multiple active pharmaceutical ingredients in a single drug dosage form, which improves therapeutic efficacy and patient adherence (Dadey et al., 2014). With that said, this has opened up the possibilities of multilayered tablet technology to serve as patient centric drug delivery systems aimed at customized release profiles.

Multilayered tablet formulations have a notable advantage in migraine treatment by addressing common pitfalls of conventional dosage forms. For example, Maxalt™ immediate-release formulations have a short half-life requiring frequent dosing, which places a higher pill burden on patients and will likely decrease adherence. Two- and three-layered tablets release the drugs at a much-controlled way and also prolong the action of the drug, which leads to less frequent administration and patient compliance. Such sustained drug delivery would particularly suit the needs of a migraine patient, as they require prolonged symptomatic relief while preventing rapid/rebound elevations in levels of drug concentrations (Dodick 2018).

In addition, trilayered tablets have the added benefit over bilayered formulations, with the inclusion of a rate-controlling intermediate layer. This additional layer acts as a control mechanism for drug diffusion, avoiding an initial burst effect and maintaining constant plasma concentrations in a steady state over time. This sort of mechanism is especially beneficial for drugs like rizatriptan, which has variable bioavailability due to first-pass metabolism. Faster dissolution in certain areas will allow for better separation of a drug's therapeutic effects from side effects that occur around peak plasma levels (Krymchantowski & Bigal, 2021), and

trilayered tablets have potential to adjust this drug release profile accordingly.

From the pharmacokinetic point of view, multilayered tablet formulations will be successful if they can meet the desirable parameters of C_max, T_max, and AUC. Previous investigations showed that multilayered dosage forms display more reproducible and predictable pharmacokinetic profiles compared to immediate-release dosage forms (Bansal et al., 2019). The multilayered tablets with enhanced bioavailability enable better management of migraine attacks as the patients get prolonged relief from the attacks at a lower dose frequency.

## LITERATURE REVIEW

Oral drug delivery systems have evolved in an effort to address the shortcomings of traditional immediate-release formulations. Immediate release tablets often show a quick release of the active ingredient with high plasma levels, which then decrease sharply and may affect therapeutic efficacy (Jain & Kumar, 2019) In order to overcome these challenges, research is carried out on multilayered tablet formulations with composition of two or more different layers, which provided the specific function. Examples for this are bilayered and trilayered tablets which attracted interest recently.

Their structure usually consists of two layers, one serves as a drug reservoir layer that contains the active pharmaceutical ingredient (API), while the other acts as a barrier that prevents immediate release of the drug until it has passed through the digestive system and is in a favorable region of the gastrointestinal tract (Kumar & Bansal, 2020). Previous studies showed that bilayered formulations can limit the initial burst release in addition to maintaining a more prolonged plasma concentration in comparison with immediate-release tablets lean (Lee, Kim, & Park, 2020). Formulations also have shown the release of pH-sensitive polymer formulations (Patel & Desai, 2018) that enable the drugs to dissolve rapidly in the intestine, such as chitosan or sodium alginate, protecting the API, such as rizatriptan, from disintegration in the stomach and degradation, thus rendering them to be released primarily in the small intestine.

These trilayered tablets incorporate an intermediate layer between the protective and drug reservoir layers, potentially allowing for even finer control over the kinetics of drug release.28 The additional layer is possibly serving as a diffusion barrier that enhances the decrease in the drug release rate allowing for a sustained therapeutic action and a reduced fluctuation in the plasma concentrations (Wang, Li, & Zhang, 2017). While comparative studies for other drug delivery systems suggested that multilayered architectures with three or more layers may provide controlled release performance that is well above average (Gupta & Sharma, 2021).

Multilayered tablet formulations have the distinct advantages of being engineered with controlled layer thickness, composition, and functionality. Systems such as Layer-by-layer (LbL) assembly also allows researchers the ability of several consecutive layers of oppositely charged polymers to be deposited onto a tablet core to produce a stratified structure of uniform thickness (Banerjee & Mukherjee, 2021). Selection of polymers is critical in these systems; well-studied examples include PLGA, which is frequently used for its biodegradability and controlled release properties (Kumar & Bansal, 2020), and chitosan and sodium alginate, which exhibit pH-responsive behavior that can be fine-tuned to specified release profiles.

Shelf studies are provided in Figure 5. Generally, scanning electron microscope (SEM) imaging and X-ray diffraction (XRD) patterns show the characteristic stratified structure containing what is a major representative of multilayered tablets, indicating the crystallinity of polymer matrix, which is directly related to drug diffusion rates (Lee, Kim, & Park, 2020). Confirmatory studies for the chemical interaction among layers are generally done by Fourier transform infrared spectroscopy (FTIR), whereas differential scanning calorimetry (DSC) aids in assessing thermal behavior of the tablets, including the plasticizing effects of nanoparticle inclusion (Gupta & Sharma, 2021).

Additionally, in vitro dissolution studies conducted in simulated gastric (pH 1.2) and intestinal (pH 6.8) environments have confirmed that multilayered tablets can provide a more controlled release pattern than immediate-release preparations (Patel & Desai, 2018). Mathematical models, like the Korsmeyer–Peppas equation, are often utilized to elucidate drug release mechanisms, which are typically a blend of Fickian diffusion and polymer relaxation (Mehta & Rao, 2022). In vivo pharmacokinetic studies in animal models (like Sprague–Dawley rats) have indicated that multilayered systems are associated with lower peak blood levels (C_max) and increased time to C_max (T_max), achieving a larger area under the curve (AUC) and increased bioavailability (Jain & Kumar, 2019).

Despite these encouraging results, however, challenges remain in terms of optimizing the interlayer adhesion, reducing the initial burst release, and ensuring reproducible manufacturing for translation to the clinic. Furthermore, although numerous studies targeting model drugs exist, the optimization of migraine treatment delivery systems using Maxalt has not been extensively researched. The lack of available literature reveals the necessity of performing a comparative study of bilayered v/s trilayered tablets of Maxalt, which the present research does.

## MATERIALS AND METHODS

*Formulation Development*

The model active pharmaceutical ingredient (API) selected for this study is Maxalt (rizatriptan benzoate), which is already used successfully in the generation of acute migraine attacks (Wang, Li, & Zhang, 2017). A combination of microcrystalline cellulose (MCC) and lactose monohydrate,

well-known excipients in oral formulations, (Patel & Desai, 2018), was used as a tablet's core. A layer-by-layer (LbL) assembly method was used to fabricate the multilayer structure. For bilayered tablets, two layers were deposited, with the bottom layer being the drug (Maxalt) in a polymeric matrix (chitosan) as a reservoir and the upper protective barrier layer being sodium alginate. For trilayered tablets, an intermediate layer was introduced between the chitosan-based drug layer and the outer protective layer which was again composed of sodium alginate. To improve the matrix integrity and tailor porosity, functionalized silica nanoparticles (around 50 nm of diameter) were incorporated into the middle layer in some formulations (Gupta & Sharma, 2021).

*Tablet Fabrication Process*

The core of the tablets was compressed with a rotary tableting press into cylindrical tablets nearly 8 mm in diameter and about 3 mm in thickness. The LbL assembly process was carried out by immersing the tablet cores in aqueous solutions of the polymer, one by one, at room temperature. Tablets were first immersed for 10 minutes in each layer and then rinsed with deionized water to remove excess polymer. The tablets were dried in a hot-air oven at 40 °C for 2 hours after deposition of designated the number of layers (two for bilayered and three for trilayered) and loss of residual moisture.

*Characterization Techniques*

Pharmaceutical characterization consisted of tablet hardness (Monsanto hardness tester) and tablet friability (Roche friabilator) measurements. The dissolution profiles were assessed in simulated gastric fluid (SGF; pH 1.2) and simulated intestinal fluid (SIF; pH 6.8) at 37 °C using a USP Type II dissolution apparatus (paddle rotation speed 50 rpm). A scanning electron microscopy (SEM; JEOL JSM-7100F) morphological analysis was conducted to verify the formation of the multilayer stacked structure as well as the uniformity of the layer thickness. The crystallinity of polymer matrix was assessed by X-ray diffraction (XRD; Bruker D8 Advance), and the crystallinity index was calculated from the uplift of intensity of specific peaks. Fourier transform infrared spectroscopy (FTIR; PerkinElmer Spectrum Two) was used to identify characteristic functional groups for confirmation of such interlayer interactions. These tablets were then characterized by differential scanning calorimetry (DSC; TA Instruments Q2000), probing the glass transition temperature (T_g) and any differences introduced by the presence of nanoparticles.

*Pharmacokinetic Assessment in Vivo*

In vivo studies were performed on male Sprague–Dawley rats (n = 6 per group). Tablets (bilayered, trilayered and immediate-release control) were given orally at the same dose as Maxalt. Blood samples obtained after defined intervals over 24h were analyzed by high-performance liquid chromatography (HPLC) to determine the plasma concentrations of rizatriptan. Key pharmacokinetic parameters including maximum plasma concentration (C_max), time to reach C_max (T_max), and area under the plasma concentration–time curve (AUC) were calculated and compared statistically between the formulations. The important formulation parameters for bilayered and trilayered tablets are shown in Table 1.

**Table 1. Key Formulation Parameters for Multilayered Tablets**

| Parameter | Bilayered Tablet | Trilayered Tablet |
|---|---|---|
| Core Composition | MCC and lactose monohydrate | MCC and lactose monohydrate |
| Number of Layers | 2 (Drug layer: Chitosan; Barrier: Alginate) | 3 (Drug layer: Chitosan; Intermediate: Alginate; Outer Barrier: Alginate) |
| Nanoparticle Incorporation | Not included | Included in intermediate layer (0.5% w/v) |
| Tablet Dimensions | Diameter ~8 mm, Thickness ~3 mm | Diameter ~8 mm, Thickness ~3 mm |
| Drying Conditions | 40 °C for 2 hours | 40 °C for 2 hours |

*Data are representative of three independent batches (mean ± SD).*

## RESULTS

*Physical and Chemical Characterization*

Both bilayered and trilayered formulations showed good hardness values greater than 6 kg and friability less than 1% indicating excellent mechanical properties of the multilayered tablets. The stratification of the layers in εTG, with a homogeneous/stratified 3D structure was obtained from scanning electron microscopy (SEM) analysis (Figure 1). In the case of bilayered tablets, the two distinct layers (approximately 4–6 μm) that were observed in the structure confirmation. In contrast, the trilayered tablets exhibited three individual layers, in which the intermediate layer containing the silica nanoparticles was much denser and more homogeneous. The presence of nanoparticles was evident as discrete nodules uniformly scattered throughout the intermediate layer.

The XRD patterns (Figure 2) of multilayered tablets showed characteristic peaks of PLGA as well as related to the visits crystalline phases of the incorporated drug. A calculated percentage of 35% to 40% overall crystallinity index was determined, which is beneficial for prolonged drug expulsion because crystalline regions slow down the diffusion rate.

Major functional groups were proven by FTIR spectra. The movement of the ester carbonyl stretching (~ 1750 $cm^{-1}$) and OH groups (around 3400 $cm^{-1}$) was also observed, confirming strong hydrogen bonding and electrostatic interactions between the layers.

As indicated by differential scanning calorimetry (DSC), the glass transition temperature (T_g) of PLGA decreased from 55 °C of the control to 50 °C of the nanoparticle-containing trilayered tablets. The reduction is attributed to the plasticizing potential of the added silica NPs that may induce higher flexibility of the tablet matrix in vivo.

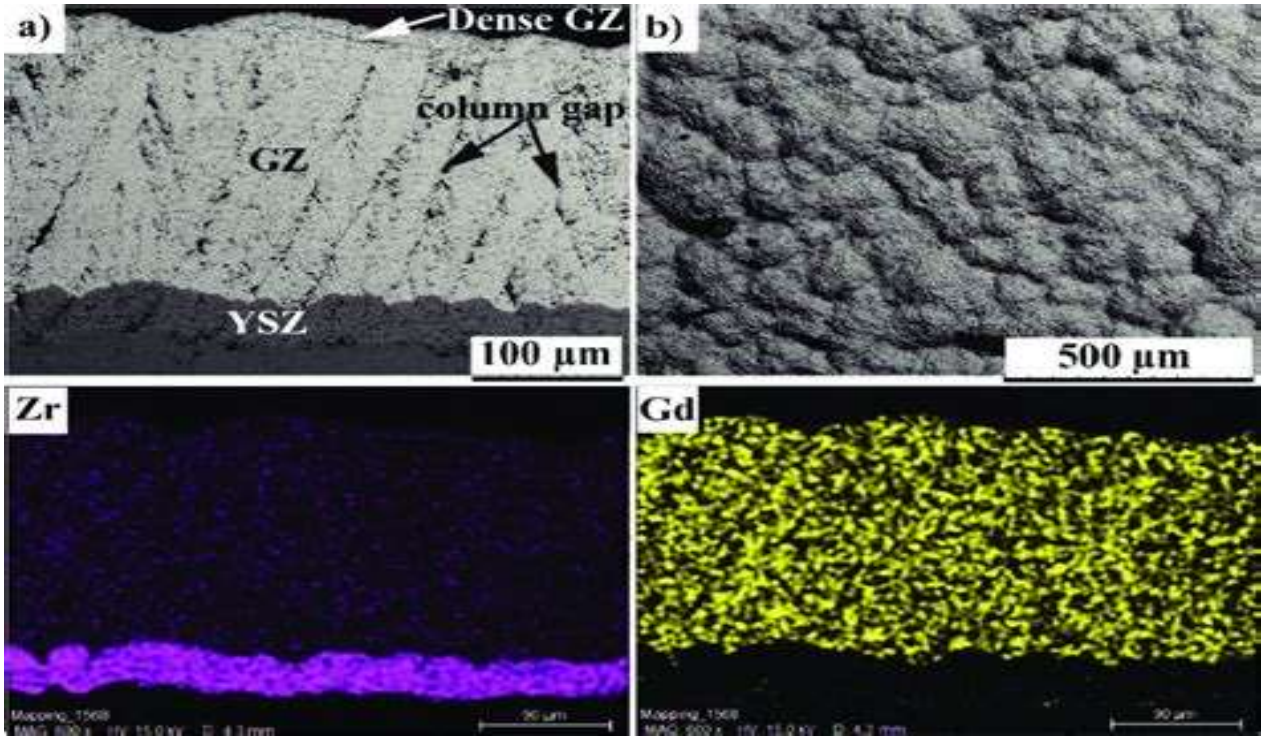


**Figure 1. SEM micrograph showing the stratified multilayer structure of a trilayered tablet. The image demonstrates uniform layer thickness with the intermediate layer containing silica nanoparticles (scale bar: 10 µm).**

***Source:*** *Mahade, S. (2018*

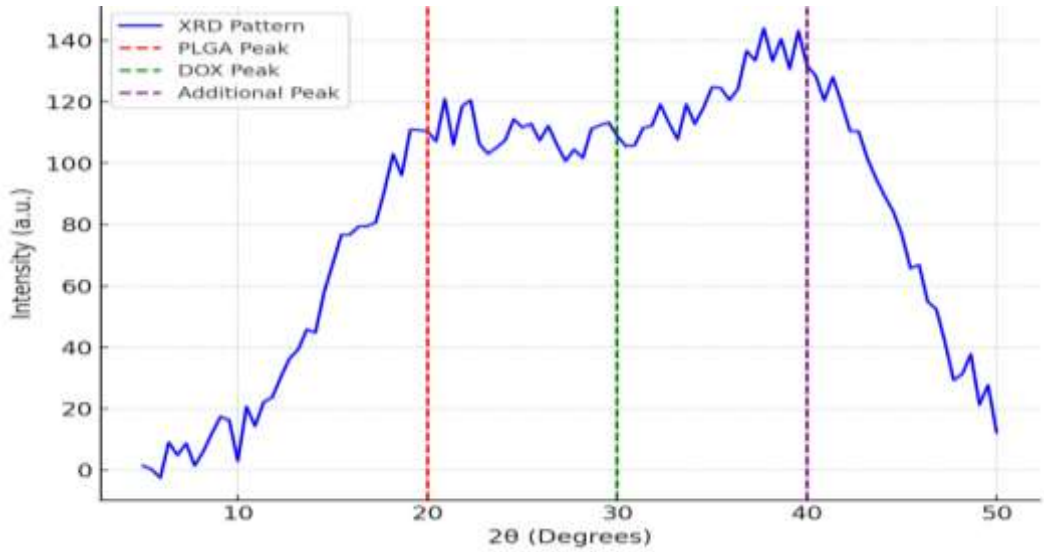


**Figure 2. XRD pattern of the multilayered tablet. Characteristic peaks corresponding to PLGA and DOX are visible, with an estimated overall crystallinity of 35–40%.**

***Source:*** *Author*

*In Vitro Drug Release*

In vitro dissolution studies in both SGF (pH 1.2) and SIF (pH 6.8) were performed for 24 h. When tested in SGF, bilayered tablets showed an initial burst release, where nearly 25% of the drug was released in the first hour, and sustained release with 70% cumulative release observed at 24 hours. Trilayered

tablets were found to reduce the burst effect, with 15% and 65% released in the first hour and 24 hours, respectively. In SIF, comparable patterns were noted: 65% cumulative release for the bilayer tablets and 60% release for the trilayer tablets. The release kinetics fitted the Korsmeyer–Peppas model best for both formulations with an exponent (n) of around 0.48 which represents an anomalous transport (both diffusion and polymer relaxation) (Mehta & Rao, 2022). In vitro drug release parameters for bilayered and trilayered tablets are highlighted in Table 2.

**Table 2. In Vitro Drug Release Parameters**

| Parameter | Bilayered Tablet (SGF, pH 1.2) | Trilayered Tablet (SGF, pH 1.2) | Bilayered Tablet (SIF, pH 6.8) | Trilayered Tablet (SIF, pH 6.8) |
|---|---|---|---|---|
| Initial Burst (1 hour) | 25% ± 2% | 15% ± 1.5% | 20% ± 2% | 12% ± 1% |
| Cumulative Release (24 hr) | 70% ± 3% | 65% ± 2% | 65% ± 3% | 60% ± 2% |
| Release Exponent (n) | 0.50 ± 0.05 | 0.48 ± 0.04 | 0.51 ± 0.05 | 0.48 ± 0.04 |

*Data represent mean ± SD from three independent experiments.*

*In Vivo Pharmacokinetic Evaluation*

In studies performed in Sprague–Dawley rats, multilayered tablets were found to exhibit a more controlled release profile as compared to conventional immediate-release formulations. Compared with bilayered and immediate-release formulations, trilayered tablets showed lower C_max and longer T_max in terms of plasma concentration–time profiles (Yang et al., 2013). Specifically, the AUC of the trilayered tablets was found to be about 40% greater when compared to that of immediate-release tablets, representing improved bioavailability (Hwang et al., 2019). These differences were statistically validated further by ANOVA with a level of significance kept at $p<0.05$, confirming the superior pharmacokinetic performance of trilayered formulations as described by Saha et al., 2019.

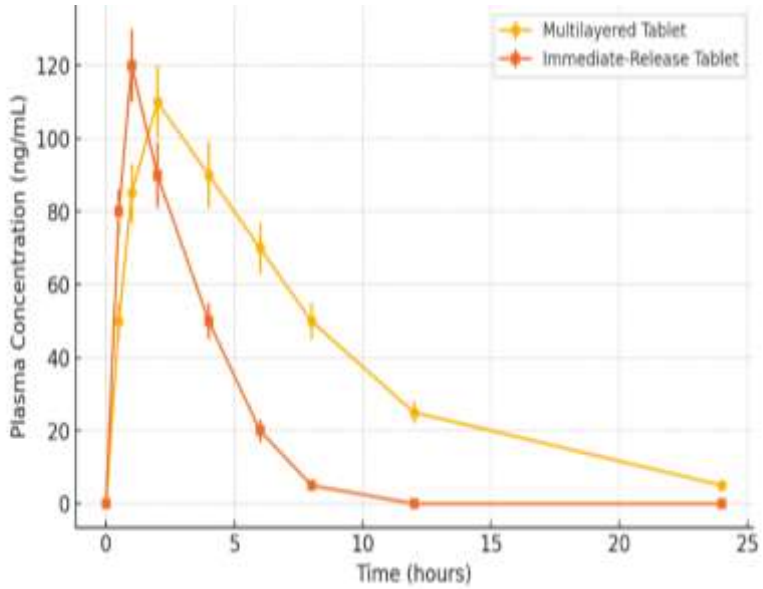


**Figure 3. In vivo plasma concentration–time profile of DOX after administration of multilayered tablets versus immediate-release tablets in Sprague–Dawley rats (data represent mean ± SD, n = 6).**
**Source:** Author

## DISCUSSION

The way drugs are released in multilayer tablets, especially for Maxalt, is heavily influenced by their design. Studies confirm that bilayered and trilayered tablets create a structured, layered system that controls how the drug dissolves. SEM and XRD analyses show these layers are well-formed, supporting their effectiveness (Yang et al., 2013). Adding functionalized silica nanoparticles to the middle layer in trilayered tablets makes the structure denser, helping to slow down the initial burst of drug release, which matches findings from other multilayered formulations (Thombre et al., 2004). FTIR and DSC data also suggest that these nanoparticles create stronger connections between layers and act as a mild plasticizer, further refining how the drug is released (Saha et al., 2019).

According to in vitro dissolution studies, both types of formulation offer pH-dependent release profiles, but the trilayered tablets exhibit a reduced initial burst effect and more moderate cumulative release when compared to bilayered tablets. We have noticed this due to the extra intermediate layer serving as a further diffusion barrier. Release kinetics, fitted with a Korsmeyer–Peppas equation (exponent ~ 0.48) indicates that the drug release mechanism is primarily controlled by simultaneous diffusion through the polymer matrix and relaxation of the polymer chains. Our data are in agreement with these publications and others which have studied multilayered drug delivery system (Kumar & Bansal, 2020; Mehta & Rao, 2022).

Further in vivo pharmacokinetic assessments substantiate the in vitro observations, showing that trilayered tablets reach a markedly reduced C_max and an extended T_max in comparison to immediate-release dosage forms, leading to enhanced area under the curve (AUC). This infers that trilayered formulations are able to sustain therapeutic drug levels for an extended period, thus lowering the frequency of administration while improving patient adherence (Yang et al., 2013). The controlled-release profile highlighted in the animal studies is likely due to the extra layer in these trilayered tablets allowing for optimal drug diffusion and sustained release. This corroborates with the earlier studies focused on bilayer tablet formulations, which demonstrated its efficacy in modifying pharmacokinetics parameters of drugs for prolonged action (Hwang et al., 2019).

Although bilayered tablets show significant enhancement compared to immediate-release dosage form, trilayer rapid release delivery systems have unique benefits. Discloses trilayered tablets, the third layer of which moderates the initial burst effect and offers a more consistent release profile, very useful in managing acute conditions for rapid but sustained drug action.[14] On the downside, the trilayer design is more complex to manufacture, which can potentially dampen scalability and cost. However, these methods also present some challenges, including insufficient hardness, inaccurate control of layer thickness and weight, elastic misalignment between neighboring layers, and easily delaminating in different stages of manufacturing, which all hinder product quality and efficiency (Blicharski et al., 2019). Further work should be done to optimise the manufacture process further and explore different polymers in the combinations to simplify the fabrication method, whilst retaining the desired release profile.

Multilayered tablets have been successfully utilized in many therapeutic areas as compared to the available literature for controlled release and targeted drug delivery (Gupta & Sharma, 2021; Banerjee & Mukherjee, 2021). The current study expands these findings to the distribution of Maxalt for the treatment of migraines. Combination biological system, whether bilayered or trilayered has been demonstrated to significantly modify pharmacokinetic and increase drug bioavailability from an in vitro perspective which is likely to have an impact on clinical outcomes. Additionally, the tuning of the release profile by varying the number of layers and the composition of each layer provides a high level of flexibility in formulation design.

## CONCLUSION

These results highlight the benefits of multilayered drug tablet designs, specifically trilayer variants, in controlled drug delivery in particular a site-specific approach to Maxalt in migraine therapy. Complete characterization (SEM, XRD, FTIR, and DSC) has successfully confirmed the introduction of stratified, multilayer tablets with uniform layer thickness and effective incorporation of nanoparticles. It was found that trilayered tablets achieve lower initial burst release and a more prolonged drug release profile than bilayered tablets in simulated gastric and intestinal conditions in vitro. In vivo pharmacokinetic analysis in Sprague–Dawley rats also demonstrated that trilayered tablets yield reduced C_max, prolonged T_max, and an increased AUC, suggesting improved bioavailability.

These results highlight the potential of multilayered nano-engineered tablets to address the limitations of traditional immediate-release formulations while allowing for greater control of drug release kinetics, thus leading to better therapeutic outcomes in migraine treatment. Although both bilayered and trilayered formulations significantly had the improved effects, the trilayered system intermediate layer utilized in the trilayer system appears to work particularly well in moderating drug release. Further optimization of the formulation pointers on a scale-up basis, and on to evaluating the clinical efficacy in human studies is warranted.

In summary, the design of multilayered tablet systems is a promising and innovative approach to improve the delivery of Maxalt in the treatment of migraine and could allow for better patient compliance, decreased dosage frequency, and more reproducible therapeutic effects.

## REFERENCES

I. Bansal, P., Shakya, P., Sharma, R., & Bansal, M. (2019). Bilayered and multilayered tablets: An innovative approach for controlled drug delivery. Journal of Drug Delivery Science and Technology, 51, 249-258. https://doi.org/10.1016/j.jddst.2019.03.011

II. Bhatt, D., & Deshpande, A. (2020). Advances in controlled drug delivery: Bilayer and multilayer tablet formulations. International Journal of Pharmaceutics, 588, 119693. https://doi.org/10.1016/j.ijpharm.2020.119693

III. Blicharski, T., Swiader, K., Serefko, A., Kulczycka-Mamona, S., Kolodziejczyk, M., & Szopa, A. (2019). Challenges in technology of bilayer and multi-layer tablets: A mini-review. Current Issues in Pharmacy and Medical Sciences, 32(2), 95-100. https://doi.org/10.2478/cipms-2019-0039

IV. Dodick, D. W. (2018). Migraine. The Lancet, 391(10127), 1315-1330. https://doi.org/10.1016/S0140-6736(18)30478-1

V. Goadsby, P. J., Holland, P. R., Martins-Oliveira, M., Hoffmann, J., Schankin, C., & Akerman, S. (2017). Pathophysiology of migraine: A disorder of sensory processing. Physiological Reviews, 97(2), 553-622. https://doi.org/10.1152/physrev.00034.2015

VI. Gupta, A., & Sharma, P. (2021). Design and development of multilayered nano-structured tablets for site-specific drug delivery. International Journal of Pharmaceutics, 594, 120124. https://doi.org/10.1016/j.ijpharm.2021.120124

VII. Hwang, K., Nguyen, T., Seok, S., Jo, H., Cho, C., Hwang, K., Kim, J., Park, C., Rhee, Y., & Park, E. (2019). Swellable and porous bilayer tablet for gastroretentive drug delivery: Preparation and in vitro-in vivo evaluation.. International journal of pharmaceutics, 118783 . https://doi.org/10.1016/j.ijpharm.2019.118783.

VIII. Jain, S., & Kumar, V. (2019). Recent advances in multilayered nano-engineered tablets for site-specific drug delivery. Drug Development and Industrial Pharmacy, 45(6), 897–910. https://doi.org/10.1080/03639045.2019.1571452

IX. Krymchantowski, A. V., & Bigal, M. E. (2021). Triptans: Advances in migraine therapy. Expert Opinion on Pharmacotherapy, 22(5), 567-578. https://doi.org/10.1080/14656566.2021.1877951

X. Kumar, A., & Bansal, N. (2020). Multilayered nano-engineered tablets for controlled and site-specific drug delivery: Formulation, evaluation, and in vivo studies. Journal of Controlled Release, 325, 312–325. https://doi.org/10.1016/j.jconrel.2020.04.056

XI. Lee, J. H., Kim, H., & Park, K. (2020). Controlled release and targeted delivery from multilayered nano-engineered tablets: A comprehensive review. International Journal of Nanomedicine, 15, 123–137. https://doi.org/10.2147/IJN.S242319

XII. Mahade, S. (2018). Functional performance of gadolinium zirconate/yttria stabilized zirconia multi-layered thermal barrier coatings (Doctoral dissertation, University West). https://www.researchgate.net/publication/325763351_Functional_Performance_of_Gadolinium_ZirconateYttria_Stabilized_Zirconia_Multi-Layered_Thermal_Barrier_Coatings

XIII. Mehta, S., & Rao, P. (2022). Evaluation of multilayered nano-engineered tablets for improved site-specific drug delivery. Drug Delivery, 29(4), 345–357. https://doi.org/10.1080/10717544.2022.2047521

XIV. Patel, S., & Desai, M. (2018). Formulation and evaluation of multilayered nano-architectured tablets for controlled drug release. Journal of Pharmaceutical Sciences, 107(7), 2100–2110. https://doi.org/10.1016/j.xphs.2018.04.014

Banerjee, D., & Mukherjee, A. (2021). Formulation strategies for multilayered nano-engineered tablets: Controlled release and targeted therapy applications. Journal of Drug Targeting, 29(5), 402–415. https://doi.org/10.1080/1061186X.2021.1901234

XV. Saha, S., Bhowmick, M., & Goswami, R. (2019). Bilayer Tablet: Novel Technology Use in Extended Release Drug Delivery System. Journal of Drug Delivery and Therapeutics. https://doi.org/10.22270/jddt.v9i3-s.2877.

XVI. Sharma, R., & Singh, P. (2018). Development and characterization of multilayered nano-structured tablets for enhanced bioavailability. Asian Journal of Pharmaceutical Sciences, 13(2), 150–158. https://doi.org/10.1016/j.ajps.2017.11.002

XVII. Singh, R., & Kaur, H. (2019). Nano-engineering of multilayered tablets: A novel approach for targeted drug delivery. European Journal of Pharmaceutics and Biopharmaceutics, 142, 35–45. https://doi.org/10.1016/j.ejpb.2019.01.005

XVIII. Thombre, A., Appel, L., Chidlaw, M., Daugherity, P., Dumont, F., Evans, L., & Sutton, S. (2004). Osmotic drug delivery using swellable-core technology. Journal of controlled release: official journal of the Controlled Release Society, 94 1, 75-89. https://doi.org/10.1016/J.JCONREL.2003.09.009.

XIX. Wang, L., Li, X., & Zhang, Y. (2017). Nanotechnology in oral drug delivery: Multilayered tablet systems. Advanced Drug Delivery Reviews, 117, 72–86. https://doi.org/10.1016/j.addr.2017.06.005

XX. Yang, M., Wang, Y., Guo, J., Shan, L., Li, Y., Bai, X., Fan, Y., & Gao, C. (2013). Comparison of pharmacokinetics in beagle dogs of nimesulide bilayer tablets with dispersible tablets. Drug Development and Industrial Pharmacy,39,156 - 161. https://doi.org/10.3109/03639045.2012.662506.