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Design of Functionalized Bi-Layered Swellable PCL/Eudragit-Based Matrix Tablets for Controlled Drug Release: Crank's Diffusion, Kinetic Modeling and Mechanistic Insights

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Abstract

Bi-layered functionalized swellable matrix Tablets were prepared by direct compression using either Eudragit RL100 (MS) or Eudragit RL100/poly(ϵ -caprolactone) (PCL) blends (MM) as matrix-forming polymers. Depending on the formulation, the functional component consisted of either a synthesized Schiff base (Im) or its corresponding copolymeric carrier (Cp), incorporated into the polymer matrix at a 1:1 (w/w) ratio. Formulations were designed to investigate the effects of polymer matrix composition and dissolution medium pH on the diffusion-controlled release of *p*-anisidine and the transport mechanisms. Drug release studies were performed under simulated gastrointestinal conditions (pH 1.2, 4.0, and 8.0). The results demonstrate that the highest release was achieved under simulated gastric conditions (pH 1.2) and the drug release could be modified by means of these formulations. Moreover, the incorporation of PCL into the Eudragit RL matrix significantly enhanced *p*-anisidine release compared with Eudragit RL alone. This enhancement was attributed to the semi-crystalline nature of PCL, which modified the internal microstructure of the polymer matrix and facilitated molecular diffusion. Although the calculated diffusion coefficients using Crank's analysis remained within the same order of magnitude for all formulations, Kinetic analysis indicated that drug release was predominantly governed by Fickian diffusion. The overall release process resulted from the combined effects of pH-dependent Schiff base hydrolysis, matrix hydration, and diffusion through the swollen polymeric matrix. These findings highlight the potential of functionalized PCL/Eudragit RL blend Tablets as promising polymeric matrices for the design of tunable diffusion-controlled drug delivery systems by integrating pH-responsive hydrolysis with polymer matrix engineering.

Keywords: Bi-Layered Tablets, Swellable Polymeric Matrices; Poly(ϵ -caprolactone); Controlled Drug release; Crank's Diffusion; Kinetic Modeling.

1. Introduction

The advancement of natural and synthetic polymers as carriers or excipients in drug delivery systems has transformed the landscape of modern therapeutics. [1–4] These materials offer significant advantages, including modulated and controlled drug release, improved pharmacokinetic profiles, tunable biodegradability, enhanced stability, surface functionalization for targeted delivery, increased therapeutic

efficacy, and reduced dosing frequency. [1,2,5] Among these systems, polymeric matrices have emerged as one of the most versatile platforms for controlling drug release through the modulation of matrix composition, swelling behavior, and diffusional properties. [2,4,6] Their physicochemical properties, including composition, hydrophilicity, swelling behavior, and permeability, strongly influence water absorption, drug diffusion, and ultimately the release performance of the dosage form. [4,6]

The versatility of synthetic polymers allows for the design of delivery systems that respond to different physiological stimuli, such as pH or temperature. [2] Polymeric drug delivery systems are generally classified into two categories: polymers exhibiting intrinsic pharmacological activity and biologically inert polymers used as drug carriers. [2,3] Our study focuses on the latter category, in which the active agent is covalently linked to the polymeric carrier through a hydrolyzable Schiff-base (imine, C=N) linkage. [7,8] Such pH-sensitive bonds represent an attractive approach for controlling the release of primary amine-containing drugs, since drug release depends on the hydrolysis of the imine bond under physiological conditions. [8] Among pH-responsive drug delivery systems, Schiff bases have continued to attract considerable interest in organic and medicinal chemistry because their reversible imine bond undergoes hydrolysis under physiological conditions, enabling controlled release of bioactive compounds. [7-9] Their hydrolyzable imine linkage has also been exploited in polymer-based drug delivery systems as a potentially cleavable linker for controlled release. [7,8] The pioneering studies of Hammett, Jencks, and Layer established the mechanistic basis of imine hydrolysis [11-13], while more recent investigations have highlighted the influence of molecular structure, substituent effects, supramolecular environments, and reaction medium on the hydrolytic stability and kinetics of Schiff base linkages. [7,14-16] Early kinetic studies by Kamogawa *et al.* [17] and Huang *et al.* [18] demonstrated that Schiff base hydrolysis is strongly influenced by both molecular architecture and reaction medium.

Building on these pioneering studies, Mesli *et al.* carried out a series of systematic investigations, elucidating the effects of substituents, molecular structure, and reaction medium on hydrolytic hydrolysis stability, kinetics and reaction mechanisms of Schiff bases. [19-23] Liu *et al.* further clarified the influence of substituent effects on Schiff base hydrolysis through combined kinetic and computational studies, providing additional mechanistic insights into imine stability and reaction. [24] Moreover, Schiff's bases generally exhibit faster hydrolysis than their polymer-bound counterparts, highlighting the stabilizing effect of their incorporation into polymeric carriers on the imine bond and their potential as polymer-carrier Schiff-base systems for controlled drug delivery applications. [25] Previous studies demonstrated that the hydrolysis kinetics of Schiff base copolymers are strongly influenced by both the polymeric carrier and the reaction medium, with hydrolysis following apparent first-order kinetics in homogeneous solutions, [26,27] whereas kinetic modeling indicated that drug release in heterogeneous media is predominantly governed by Fickian diffusion. [27,28] These modeling approaches have also been applied in previous investigations of polymeric drug-delivery systems. [29-32] More recently, we systematically investigated the hydrolysis behavior of these Schiff base copolymers in heterogeneous media, demonstrating that pH and polymer molecular weight significantly influence the drug release kinetics and diffusion behavior. [28] Based on

these findings, the present study investigates the combined effects of poly(ϵ -caprolactone) (PCL) incorporation into Eudragit RL matrices and dissolution medium pH on the diffusion-controlled release of *p*-anisidine from bi-layered swellable matrix Tablets.

However, the combined influence of swellable polymeric matrices and pH-dependent imine hydrolysis on diffusion-controlled drug release under simulated gastrointestinal conditions has received limited attention. Among the polymers commonly employed for controlled drug delivery, Eudragit RL is widely used because of its high permeability resulting from the presence of quaternary ammonium groups, whereas poly(ϵ -caprolactone) (PCL) is a biocompatible and biodegradable polymer characterized by its semi-crystalline structure, excellent film-forming ability, and favorable swelling properties. The combination of these polymers in a swellable matrix offers an effective strategy for modulating matrix hydration, liquid penetration, and drug transport, thereby enabling tailored release profiles.

To address this gap in our research, the previously synthesized *p*-anisidine-functionalized imine monomers (Im) and copolymers (Cp) were incorporated into bi-layered swellable PCL/Eudragit RL matrix tablets. Initially, solid dosage forms (discs) were prepared based on Eudragit RL100 (Eud) and mixtures of Eudragit RL100 and poly(ϵ -caprolactone) (PCL) at two different proportions. Subsequently, the effects of polymer matrix composition and dissolution medium pH on the diffusion-controlled release of *p*-anisidine under simulated gastrointestinal conditions were investigated. Furthermore, Crank's diffusion analysis, together with the Higuchi and Korsmeyer–Peppas kinetic models, was applied to elucidate the drug transport behavior and the predominant release mechanism.

2. Materials and Methods

2.1. Chemicals

p-Anisidine ($\geq 99\%$ purity) was purchased from Merck (Germany), Eudragit[®] RL100 ($M_w = 150000$) from Röhm Pharma (Germany). Poly(ϵ -caprolactone) (PCL, $M_w = 7286 \text{ g}\cdot\text{mol}^{-1}$) was synthesized from ϵ -caprolactone (2-oxepanone) and decanedioic acid and characterized as previously described by Belarbi *et al.* (2009).³³

For the kinetic studies, the pH 1.2 buffer solution was prepared by dissolving 80 mL of 1.0 M hydrochloric acid (HCl; Cheminova International, Spain) and 2.0 g of sodium chloride (NaCl; Merck, Germany) in deionized water and adjusting the final volume to 1 L. The pH 4.0 acetate buffer was prepared by mixing appropriate amounts of acetic acid and sodium acetate and diluting to a final volume of 1 L with deionized water. The pH 8.0 buffer solution was prepared by mixing 500 mL of 0.025 M sodium tetraborate decahydrate (Fluka, Switzerland) with 205 mL of 0.1 M hydrochloric acid, followed by dilution to a final volume of 1 L with deionized water. All buffer solutions were freshly prepared prior to use.

2.2. Preparation of Matrix Tablets

The functionalized matrix Tablets for controlled release were prepared by direct compression using a laboratory hydraulic press (Perkin–Elmer, Germany). Depending on the Tablet formulation, the functional component consisted of either the synthesized Imine Im (Schiff Base) or the corresponding Copolymer Carrier Cp. Poly(ϵ -caprolactone) (PCL) / RL100 blends (MM) or either Eudragit RL (MS) were used as

matrix-forming polymers to control the release behavior. The amounts of the functional active agent (Im or Cp) and the selected polymeric matrices were accurately weighed at a 1:1 (w/w) ratio. The powder mixture was further blended manually in an agate mortar to ensure homogeneous distribution of all components. A small amount of absolute ethanol (2–3 sprays) was added to obtain a slightly cohesive mass suitable for compression. The resulting blend was transferred into a 12 mm stainless-steel die and compressed using a laboratory hydraulic press to obtain cylindrical matrix Tablets. Tablets were prepared by sequential compression to ensure intimate interfacial contact between the immediate-release and sustained-release layers while minimizing delamination. Compression pressure was selected to obtain mechanically robust Tablets without inducing structural damage to the polymeric matrices. This procedure ensured reproducible Tablet geometry and minimized variability in diffusion path length, thereby improving the reliability of the subsequent kinetic analyses. The Tablets were subsequently dried at room temperature in a desiccator until constant weight was achieved prior to physicochemical characterization and *in vitro* release studies.

2.3. Physical Characterization of the Matrix Tablets

The weight of each matrix Tablet was determined using an analytical balance with a precision of ± 0.1 mg. The Tablet diameter (d) and thickness (h) were measured using a digital Vernier caliper (Mitutoyo, Japan; accuracy ± 0.01 mm). The prepared Tablets exhibited a diameter of approximately 1.20–1.23 cm and a thickness ranging from 0.18 to 0.19 cm, depending on the formulation. The compositions and physicochemical characteristics of all prepared formulations are summarized in Table 1.

2.4. *p*-Anisidine Release and Hydrolysis Kinetics

The hydrolysis kinetics of the Schiff-base monomer (Im) and copolymers (Cp) were investigated in heterogeneous simulated gastric media (pH 1.2 and 4.0) and intestinal (pH 8.0) medium using a UV–Vis spectrophotometer, previously calibrated at the maximum absorption wavelength (λ_{max}) of *p*-anisidine. The release experiments were conducted in a closed flask maintained at 37 ± 0.5 °C and under controlled stirring at 500 rpm. The tablets were placed in a permeable fiberglass basket and soaked in 100 mL of the corresponding simulated fluid (pH 1.2, 4.0, or 8.0). The dissolution medium was stirred magnetically at a rotation speed of 500 min^{-1} to achieve good homogenisation. Samples (1 mL) of the solution were collected for analysis at different time intervals. After an appropriate dilution, the sample was analysed using a UV-VIS spectrophotometer. The released *p*-anisidine was quantified at $\lambda_{\text{max}} = 272$ nm in acidic medium (pH 1.2 and 4.0), with molar extinction coefficients (ϵ) of 1200 and 1280 $\text{L mol}^{-1} \text{cm}^{-1}$, respectively, and at $\lambda_{\text{max}} = 295$ nm with $\epsilon = 2100$ $\text{L mol}^{-1} \text{cm}^{-1}$ in alkaline medium (pH 8.0).

3. Results and Discussion

3.1. *In Vitro* Drug Release profile of Bilayered Im–PCL/Eudragit-Based Tablets

The *in vitro* release behavior of *p*-anisidine from bilayered functionalized PCL/Eudragit-based matrix Tablets incorporating Im and Cp carriers was investigated under physiological conditions (37 ± 0.5 °C) in three simulated dissolution media (pH 1.2, 4.0, and 8.0). The corresponding release profiles and kinetic parameters are presented in Figures 1 and Table 2, respectively.

Table 1. Composition and physicochemical characteristics of the prepared bilayered functionalized PCL/Eudragit-based matrix tablets.

Formulation	Carrier	Matrix type	Matrix composition	Carrier/Matrix ratio (w/w)	Tablet weight (mg)	Theoretical drug loading (mg)	Diameter (cm)	Thickness (cm)	Release medium pH
T1	Im	MM	Eudragit RL/PCL (50/50)	50/50	210.0	53.08	1.20	0.18	1.2
T2		MS	Eudragit RL	50/50	212.3	54.26	1.21	0.18	1.2
T3		MM	Eudragit RL/PCL (50/50)	50/50	215.0	54.95	1.21	0.18	4.0
T4		MS	Eudragit RL	50/50	214.3	54.80	1.21	0.19	4.0
T5		MM	Eudragit RL/PCL (50/50)	50/50	220.0	56.23	1.23	0.19	8.0
T6		MS	Eudragit RL	50/50	220.0	56.23	1.23	0.19	8.0
C1	Cp	MM	Eudragit RL/PCL (50/50)	50/50	210.0	28.78	1.20	0.18	1.2
C2		MS	Eudragit RL	50/50	212.3	29.09	1.21	0.18	1.2
C3		MM	Eudragit RL/PCL (50/50)	50/50	215.0	29.46	1.21	0.18	4.0
C4		MS	Eudragit RL	50/50	214.3	29.36	1.21	0.19	4.0
C5		MM	Eudragit RL/PCL (50/50)	50/50	220.0	30.14	1.23	0.19	8.0
C6		MS	Eudragit RL	50/50	220.0	30.14	1.23	0.19	8.0

MS: single Eudragit RL matrix. MM: mixed Eudragit RL/PCL matrix (50:50 w/w). All formulations contained 50 w % polymeric matrix and 50 w % functionalized carrier.

As shown in Figure 1, the release behavior of *p*-anisidine from Tablets was markedly influenced by the polymeric matrix composition. Formulations prepared with the mixed Eudragit RL/PCL matrix (MM) exhibited different release profiles from those prepared with the Eudragit RL matrix alone (MS), despite identical drug loading. The corresponding Higuchi plots (% cumulative release versus the square root of time) are presented in Figure 2.

At acidic pH, *p*-anisidine is released in its protonated form (H_3N^+-R'), whereas at basic pH it is released in its neutral form (H_2N-R'). All formulations exhibited a progressive release profile characterized by an initial rapid release stage followed by a slower and more sustained liberation phase until approaching equilibrium. Such behavior is typical of matrix-controlled delivery systems, where the release process is governed by the combined effects of medium penetration, carrier hydrolysis and diffusion through the hydrated polymeric matrix.

Unlike the homogeneous hydrolysis previously reported for Im and Cp, incorporation of the functionalized carriers into polymeric matrices significantly modified the release behavior. The surrounding polymeric environment acted as an additional diffusion barrier, resulting in prolonged release and improved control of

drug liberation. Consequently, the release mechanism no longer depended exclusively on the hydrolysis of the Schiff-base linkage but also on solvent diffusion, matrix hydration and drug transport through the polymer network.

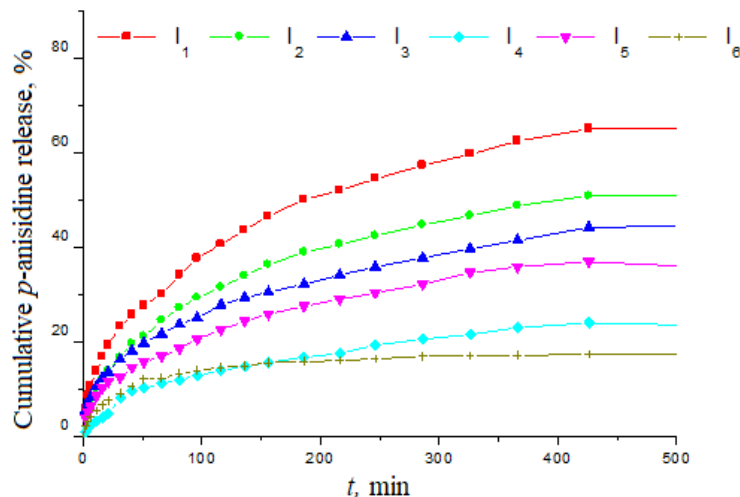


Fig. 1. Cumulative *p*-anisidine release profiles from Im-loaded bilayered PCL/Eudragit-based matrix Tablets prepared with MS and MM matrices in simulated dissolution media (pH 1.2. 4.0. and 8.0).

The corresponding Higuchi plots (Figure 2) did not pass exactly through the origin and a slight curvature was observed during the initial stage of release. This deviation can be attributed to the time required for the dissolution medium to penetrate the Tablet, hydrate the polymeric matrix, and establish a hydrated diffusion layer surrounding the dosage form before Fickian diffusion becomes the dominant release mechanism. Once hydration is established, diffusion through the hydrated polymer matrix governs the release process, regardless of the dissolution medium. Although slight differences in medium viscosity may influence the initial hydration stage.

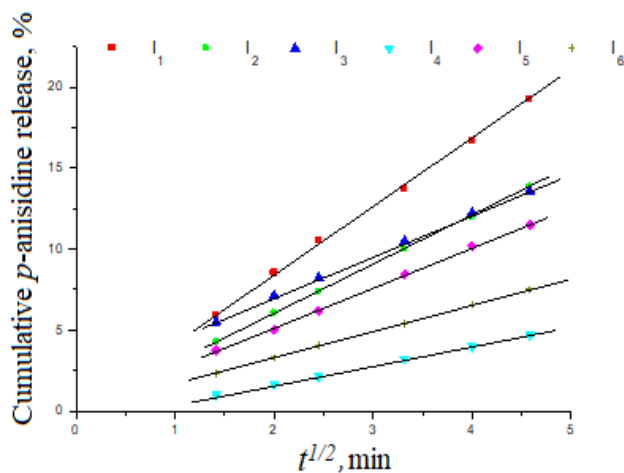


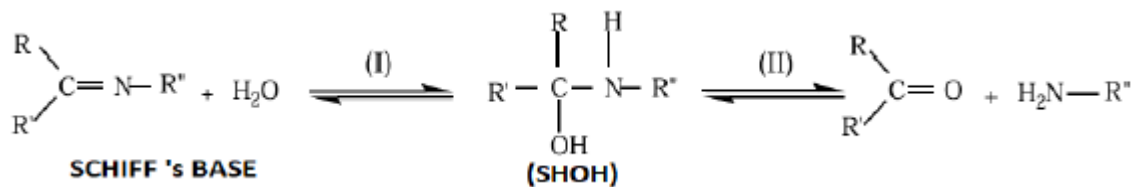
Fig. 2. Higuchi plots of cumulative *p*-anisidine release versus the square root of time in different dissolution media (pH 1.2. 4.0. and 8.0) at 37 ± 0.5 °C and 500 rpm.

The linearity of the Higuchi plots after this initial period indicates that both liquid uptake and drug release are predominantly governed by a Fickian diffusion-controlled process. This observation justifies the application of Crank's analytical solutions to determine the apparent diffusion coefficients of *p*-Anisidine in the different dissolution media.

3.1.1. Effect of polymeric matrix composition

To evaluate the influence of the polymeric carrier on drug release, formulations prepared with the mixed Eudragit RL/PCL matrix (MM) were compared with those prepared using exclusively of the Eudragit RL matrix (MS) under identical experimental conditions.

As shown in Figure 1, matrix composition significantly affected both the release rate and the cumulative amount of drug released. At the same simulated dissolution medium pH, the mixed PCL/Eudragit matrices consistently exhibited higher cumulative release than the corresponding Eudragit-only formulations, whereas the MS formulations T4 and T6 showed particularly low equilibrium release percentages. The effect of matrix composition was particularly evident under gastric conditions (pH 1.2). At equilibrium (420 min), the mixed Eudragit RL/PCL matrix (MM) released 78.4% of the incorporated *p*-anisidine, compared with 59.8% for the corresponding Eudragit RL matrix (MS), corresponding to an absolute increase of 18.6 percentage points (approximately 31% relative improvement) following PCL incorporation. This enhancement can be attributed to the incorporation of PCL. The incorporation of PCL increased drug release compared with Eudragit RL alone by modifying the internal morphology and hydration behavior of the polymeric matrix, thereby altering solvent penetration and drug diffusion pathways. The increase in drug release following PCL incorporation can be interpreted in terms of the physicochemical characteristics of the polymer blend. The semi-crystalline nature and partial hydrophobicity of PCL alters the internal microstructure and hydration behavior of the matrix, thereby influencing solvent penetration through the matrix while simultaneously modifying the tortuosity of the diffusion pathways and increasing the effective diffusional pathways, and facilitating drug transport through the polymer matrix. Consequently, the increased matrix hydration and structural modifications enhance drug diffusion while preserving the dominant controlled-release mechanism, which remained Fickian according to the Higuchi and Korsmeyer–Peppas analyses. These observations demonstrate that PCL acts as a release-modulating component, primarily modulates the effective diffusional resistance rather than changing the governing transport mechanism, in meaning, improving molecular diffusion while maintaining the controlled-release characteristics of the matrix. The increase in liquid absorption facilitates solvent penetration and promotes hydrolysis of the grafted Schiff-base linkage (Scheme 1); and thereby increasing the amount of *p*-anisidine available for diffusion through the hydrated polymer matrix.



Scheme 1. Hydrolysis reaction of Schiff's base.

A similar trend was observed at pH 4.0 and pH 8.0. At pH 4.0, the cumulative release increased from 21.7% for the MS formulation to 53.6% for the MM formulation, corresponding to an increase of 31.9 percentage points. Notably, at pH 8.0, the cumulative release increased from 19.7% to 55.5%, representing an increase of 35.8 percentage points. These results indicate that presence of PCL consistently enhances drug release over the entire investigated pH range. The more pronounced relative improvement observed at pH 4.0 and 8.0 suggests that the mixed matrix compensates for the slower hydrolysis kinetics under less acidic conditions by promoting greater matrix hydration and facilitating drug diffusion.

The equilibrium liquid absorption measurements further support this interpretation, showing that the mixed matrices generally exhibited greater liquid uptake than the single-polymer matrices. Enhanced medium penetration facilitates hydrolysis of the grafted Schiff-base bonds while simultaneously increasing the amount of drug available for diffusion. Therefore, drug release results from the combined contribution of hydrolysis and diffusion rather than from a purely diffusion-controlled process.

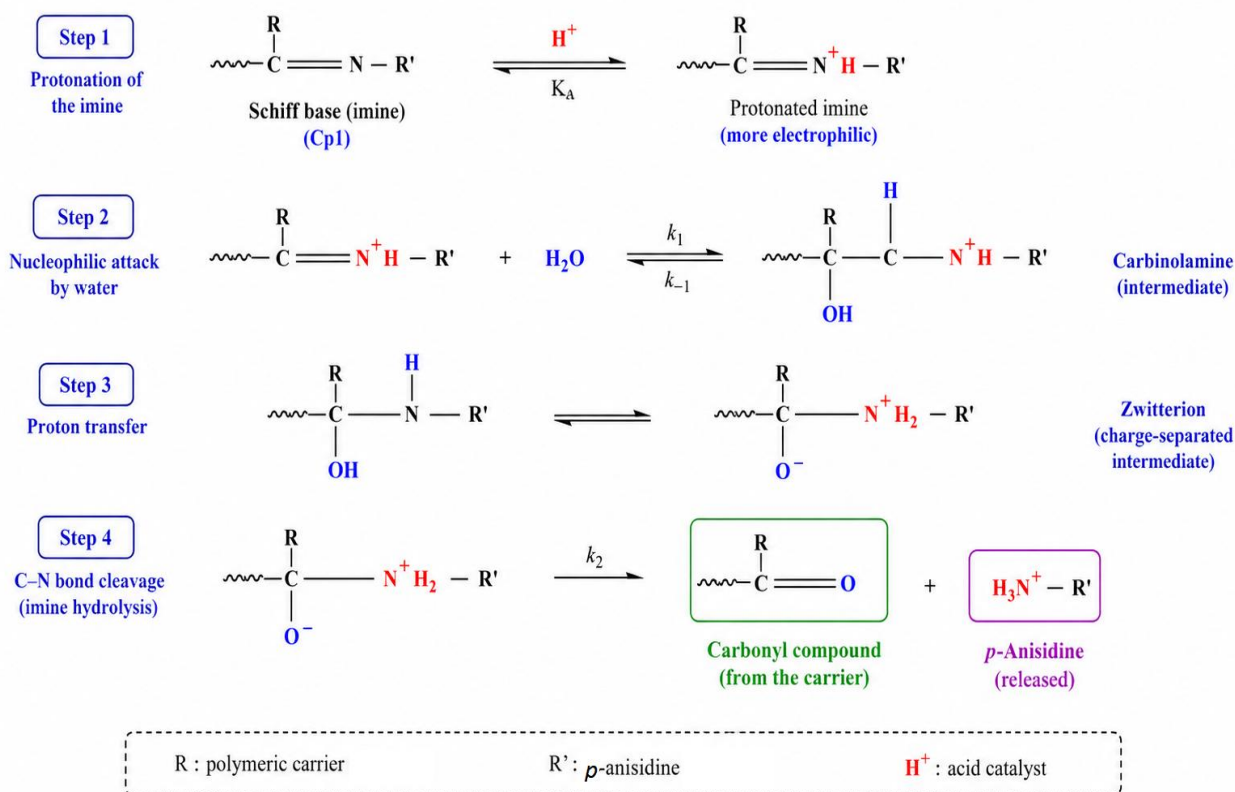


Fig. 3 Mechanism of acid-catalyzed hydrolysis of the imine (Schiff-base) linkage.

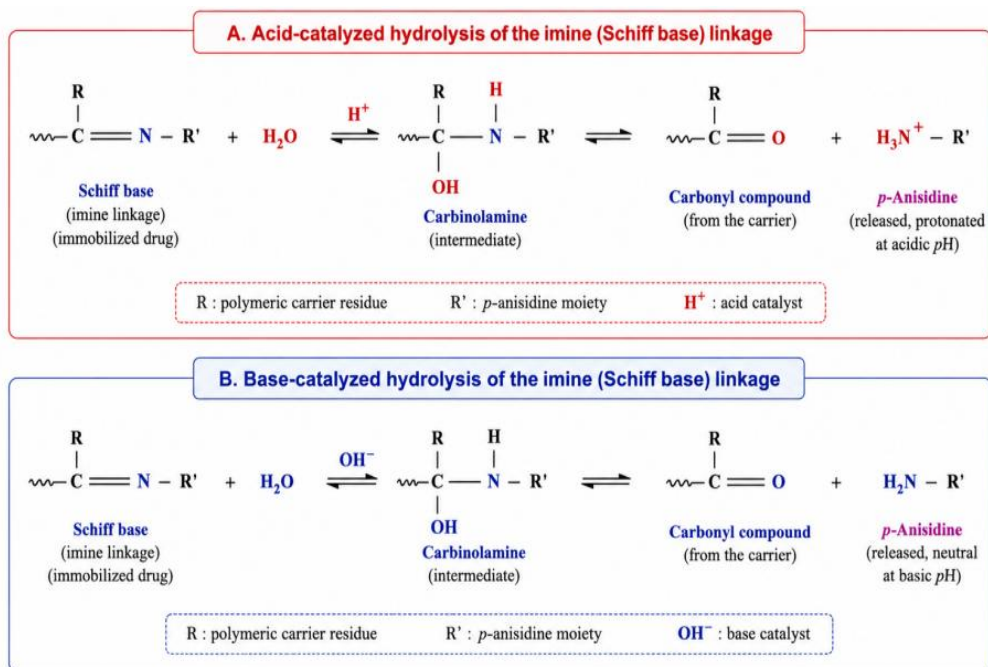
The Figure 3 clearly shows the proposed hydrolysis mechanism of the grafted imine (Schiff-base) linkage involving the following sequence: protonation of the imine linkage → addition of H₂O → formation of the α-amino alcohol intermediate → cleavage of the C=N bond → formation of the carbonyl compound and protonated *p*-anisidine.

3.1.2. Effect of pH on Drug Release

The influence of the release medium was investigated under acidic (pH 1.2), mildly acidic (pH 4.0) and alkaline (pH 8.0) conditions. The release profiles clearly demonstrate that the surrounding pH plays a principal role in controlling drug liberation from the matrix Tablets (Figure 1).

For both polymeric matrices, the highest cumulative release was consistently observed under gastric conditions (pH 1.2). At equilibrium (420 min), the cumulative release from the mixed Eudragit RL/PCL matrix (MM) reached 78.4%, whereas, lower values of 53.6% and 55.5% were obtained at pH 4.0 and pH 8.0, corresponding to decreases of 24.8 and 22.9 percentage points, respectively. A similar trend was observed for the Eudragit RL matrix (MS), where the cumulative release decreased from 59.8% at pH 1.2 to 21.7% at pH 4.0 and 19.7% at pH 8.0, representing reductions of 38.1 and 40.1 percentage points, respectively.

These results indicate that gastric conditions markedly promote drug release, irrespective of the matrix composition. This behavior is consistent with the acid-catalyzed hydrolysis of the grafted Schiff-base linkage, which accelerates cleavage of the carrier–drug bond and consequently increases the amount of free *p*-anisidine available for diffusion through the hydrated polymer network (Scheme 2).



Scheme 2. Mechanisms of acid / base-catalyzed hydrolysis of the Schiff-base linkage leading to *p*-anisidine release.

Despite the differences in drug release, the equilibrium liquid absorbed remained relatively similar over the investigated pH range, suggesting that the observed differences in drug release arise primarily from variations in hydrolysis kinetics rather than from substantial changes in matrix swelling. These findings demonstrate that both the physicochemical characteristics of the polymeric matrix and the pH-dependent hydrolysis of the functionalized carriers jointly govern the overall drug release performance.

3.2. In Vitro Drug Release profile of Bilayered Cp –PCL/Eudragit-Based Tablets

Following the investigation of the directly incorporated Im system, the release behavior of *p*-anisidine from Cp-based matrix Tablets was evaluated to assess the influence of its incorporation within the functionalized polymeric carrier. Six formulations (C1–C6) were prepared using either a mixed Eudragit RL/PCL matrix (MM) or a single Eudragit RL matrix (MS) and evaluated in dissolution media at pH 1.2, 4.0 and 8.0. The corresponding release profiles are presented in Figure 4.

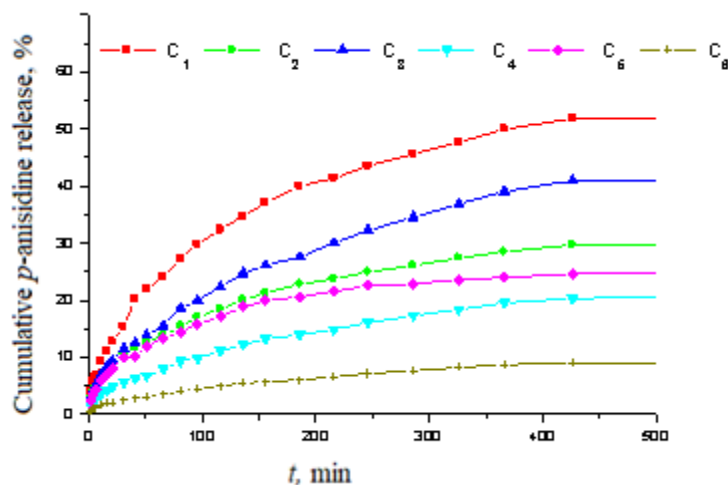


Fig. 4. Cumulative *p*-anisidine release profiles from Cp-loaded bilayered PCL/Eudragit-based matrix Tablets prepared with MS and MM matrices in simulated dissolution media (pH 1.2, 4.0, and 8.0).

Based on these experimental results, the following conclusions can be drawn:

- By plotting the percentage of drug released versus the square root of time for the different Cp matrix tablet formulations, a linear relationship was observed during the initial stage of the release kinetics process (Figure 5). This behavior indicates that drug transport from the Cp copolymeric carriers is predominantly governed by Fickian diffusion.

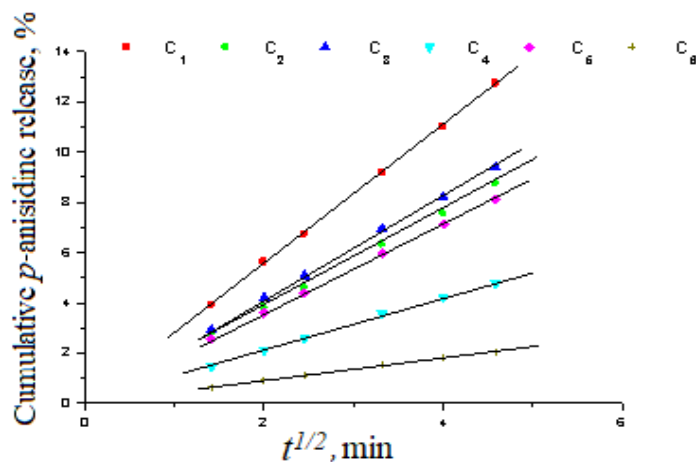


Fig. 5. Higuchi plots of cumulative *p*-anisidine release versus the square root of time in different dissolution media (pH 1.2, 4.0, and 8.0) at 37 ± 0.5 °C and 500 rpm.

- A slight curvature was observed at short times in the same plots. This release pattern can be explained by the establishment of equilibrium between the matrix Tablet and the dissolution medium, together with the release of drug molecules initially located at the surface of the Tablet.
- It should be noted that drug release was faster from the matrix Tablets based on the Eudragit RL/PCL matrix than from those prepared the with Eudragit RL alone, regardless of the dissolution medium.

3.2.1. Effect of polymeric matrix composition

All formulations of Cp-based matrix Tablets exhibited a progressive increase in cumulative *p*-anisidine release versus time, followed by a gradual approach toward equilibrium (Figure 4). However, both the extent and the rate of drug release were strongly affected by the pH of the dissolution medium and the polymeric matrix composition. At the equilibrium (420 min), the MM formulations consistently exhibited higher cumulative release than their corresponding MS formulations. Specifically, cumulative release reached 62.64% for C1 compared with 43.92% for C2 at pH 1.2. 53.99% for C3 compared with 26.96% for C4 at pH 4.0 and 31.17% for C5 compared with 14.07% for C6 at pH 8.0.

For the mixed Eudragit RL/PCL matrix, this behavior suggests that incorporation of PCL into the Eudragit RL matrix provides a more favorable environment for liquid penetration and matrix hydration, thereby facilitating the transport of the released drug molecules through the hydrated polymeric network. Unlike conventional matrix tablets, *p*-anisidine remains covalently linked to the polymeric carrier through a pH-sensitive Schiff-base linkage before being released into the dissolution medium. Consequently, the amount of drug available for diffusion also depends on the hydrolytic cleavage of the imine bond. However, the higher release observed for the MM formulations cannot be attributed exclusively to diffusion, since drug release also depends on the hydrolysis of the grafted Schiff-base linkage.

Indeed, the overall enhanced release observed for the MM systems results from the combined contributions of pH-dependent bond hydrolysis, improved matrix hydration, greater accessibility of the imine linkage to the aqueous medium, and diffusion of the released *p*-anisidine through the polymeric matrix.

3.2.2. Effect of dissolution medium pH

As shown in Figure 4, the dissolution medium markedly influenced the release behavior of *p*-anisidine from the Cp-based Tablets. The equilibrium release percentages ranged from 14.07% to 62.64%, indicating a pronounced influence of the formulation and dissolution conditions on the release behavior of the Cp-based Tablets. For both matrix systems, the highest cumulative release was obtained under acidic conditions (pH 1.2), whereas progressively lower release was observed at pH 4.0 and pH 8.0.

For the mixed Eudragit RL/PCL matrices (MM), the cumulative amount of *p*-anisidine released at the equilibrium release after approximately 426 min decreased from 62.64% at pH 1.2 (C1) to 53.99% at pH 4.0 (C3) and 31.17% at pH 8.0 (C5). A similar trend was observed for the single Eudragit RL matrices (MS), for which the corresponding release percentages decreased from 43.92% for C2 at pH 1.2 to 26.96% for C4 at pH 4.0 and 14.07% for C6 at pH 8.0.

These results demonstrate that acidic conditions (pH 1.2) favor the release of *p*-anisidine from the Cp-based Tablets, regardless of matrix composition. The pH-dependent behavior, confirmed by the substantially

higher release observed under acidic conditions, is consistent with the acid-sensitive character of the grafted imine linkage and its susceptibility to acid-catalyzed hydrolysis (Scheme 2). At pH 1.2, protonation of the imine facilitates its hydrolytic cleavage, thereby increasing the amount of *p*-anisidine available for subsequent diffusion through the hydrated polymeric matrix.

As the pH increased, the lower cumulative amount released may reflect reduced hydrolysis of the grafted linkage and, consequently, a smaller fraction of *p*-anisidine becoming available for release and a larger fraction remaining associated with the carrier.

The effect of pH was especially noticeable for the MS Tablets, with equilibrium release decreasing from 43.92% at pH 1.2 to only 14.07% at pH 8.0 (Table 2). Nevertheless, the same overall pH-dependent trend was maintained in the MM Tablets, indicating that the chemical response of the Cp carrier to the dissolution environment remains a major determinant of *p*-anisidine availability for release.

Interestingly, despite the similar liquid absorption capacity reported for most Tablets, the C3/C6 pair showed a different behavior, where the release difference was not directly correlated with absorbed liquid. This observation suggests that, under basic conditions, the limited hydrolysis of the Schiff-base linkage becomes the predominant factor controlling *p*-anisidine availability, thereby reducing the impact of matrix hydration on the overall release process.

Overall, these findings indicate that the release of *p*-anisidine from Cp-based Tablets exhibited a clear pH-dependent behavior.

Table 2. Effect of dissolution medium pH on the hydrolysis of the grafted Schiff-base linkage and the cumulative *p*-anisidine release from Cp-based MM and MS formulations at equilibrium.

Dissolution pH	Chemical environment	Expected behavior of the Schiff-base linkage	Experimental release
1.2	Strongly acidic	Strong protonation and susceptibility to acid-catalyzed cleavage	C1: 62.64%; C2: 43.92%
4.0	Moderately acidic	Imine linkage remains susceptible to hydrolysis	C3: 53.99%; C4: 26.96%
8.0	Basic	Reduced acid-catalyzed hydrolysis of the imine linkage	C5: 31.17%; C6: 14.07%

3.3. Diffusion analysis based on Crank's model

To obtain a deeper understanding of the diffusion process governing drug release from the prepared bilayered functionalized PCL-based matrix Tablets, the experimental data were further analyzed according to Crank's diffusion model.³⁴ Unlike empirical kinetic models, Crank's theory provides a physically meaningful description of mass transport by allowing the determination of both the equilibrium releasable drug content and the apparent diffusion coefficients of the drug and the dissolution medium.

3.3.1. Determination of the equilibrium mass of released *p*-anisidine (m_{∞})

a. Calcul of (m_{∞} , drug) from of Bilayered Im-Based Tablets

The equilibrium drug mass released (m_{∞} , drug) and the equilibrium absorbed liquid mass (m_{∞} , liq) were determined according to Crank's approach³⁴ by linear extrapolation of the logarithmic plots of $\ln (mt/m_{\infty})$

versus $1/t$ for cumulative *p*-anisidine release and $\ln (mt/m_0)$ versus $1/t$ for liquid absorption. A representative example corresponding to formulation T1 (MM, pH 1.2) is shown in Figure 6, whereas the calculated values for all investigated formulations are summarized in Table 3.

The equilibrium released drug content varied markedly among the investigated formulations, confirming that complete drug release was not achieved under the experimental conditions. Depending on the formulation and release medium, a significant fraction of *p*-anisidine remained entrapped within the polymeric matrix, indicating that drug transport was controlled not only by hydrolysis of the grafted Schiff-base linkage but also by diffusion through the hydrated matrix.

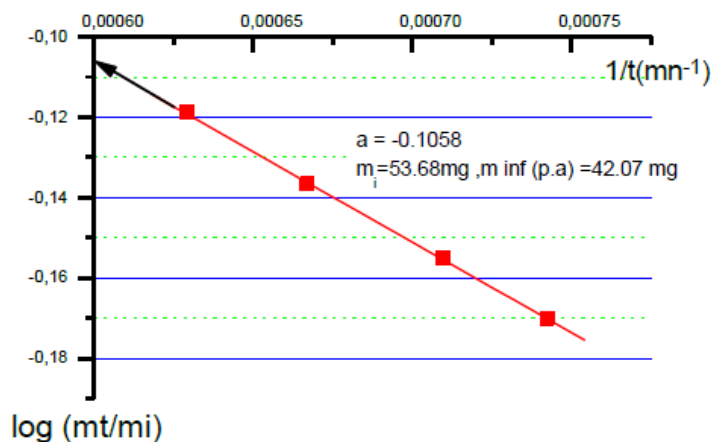


Fig. 6 Determination of the equilibrium released drug content ($m_{\infty, \text{drug}}$) according to Crank's model by linear extrapolation of $\log(mt/m_i)$ versus $1/t$ for T1 formulation at pH 1.2 (37 °C, 500 rpm).

Conversely, the equilibrium absorption of dissolution medium was considerably higher than the amount of released drug for all formulations. This result demonstrates that penetration of the release medium into the polymeric matrix proceeds faster than drug diffusion. Such behavior is characteristic of swellable polymeric matrices, in which rapid matrix hydration is followed by a slower diffusion of the released molecules through increasingly tortuous diffusion pathways.

Table 3. Equilibrium masses of released *p*-anisidine and absorbed liquid determined by Crank's model for prepared formulations.

Tablets	($m_{\infty, \text{drug}}$), mg	($m_{\infty, \text{Liquid}}$), mg
T1	42.07	148.74
T2	32.45	87.95
T3	29.47	151.54
T4	11.89	143.88
T5	31.19	169.21
T6	11.08	145.35

Table 3 shows the equilibrium released mass of *p*-anisidine ($m_{\infty, \text{drug}}$) together with the equilibrium absorbed liquid mass ($m_{\infty, \text{liquid}}$) obtained from Crank's analysis. For all formulations, the absorbed liquid mass was substantially higher than the released drug mass, indicating that water penetration into the matrix

preceded drug release. However, differences in equilibrium liquid absorbed were not directly correlated with the amount of *p*-anisidine released, suggesting that matrix hydration alone cannot account for the observed release behavior. The availability of *p*-anisidine also depends on the hydrolysis of the grafted Schiff-base linkage prior to diffusion through the hydrated matrix.

The equilibrium amount of *p*-anisidine released (m_{∞} , drug) varied according to the pH of the dissolution medium and remained lower than the initial incorporated amount in all cases, indicating that complete release was not achieved under the investigated pH conditions. In contrast, substantial absorbed liquid was observed, with the percentage of absorbed liquid exceeding 100% in some cases, highlighting the high absorption capacity of the polymeric matrix. These results suggest that extensive liquid penetration into the matrix does not necessarily lead to complete drug release, as a fraction of the incorporated compound remains unreleased at equilibrium.

b. Calcul of (m_{∞} , drug) from Cp-based Tablets

The equilibrium released amount of *p*-anisidine (m_{∞} , drug) was determined for all Cp-based Tablets formulations using Crank's analysis and the obtained values are summarized in Table 4. The comparison of these values revealed that the amount of released *p*-anisidine was strongly dependent on both the dissolution medium and the polymeric matrix composition.

Conversely, the equilibrium absorbed liquid from dissolution medium was generally higher than the amount of released *p*-anisidine for all Cp-based Tablets. This observation indicates that water penetration into the polymeric matrix occurs more rapidly than the release and diffusion of the active agent. Such behavior is characteristic of hydrated polymeric systems, where matrix hydration precedes the release process and provides the aqueous environment required for both hydrolysis of the grafted Schiff-base linkage and subsequent diffusion of the released *p*-anisidine molecules.

The difference between absorbed liquid and released drug content highlights that the release process is not controlled exclusively by diffusion. Indeed, in Cp-based formulations, *p*-anisidine remains covalently attached to the polymeric carrier through a pH-sensitive imine linkage. Therefore, the availability of the active agent depends on the accessibility and hydrolysis cleavage of this linkage, followed by diffusion through the hydrated polymer matrix.

3.3.2. Determination of apparent diffusion coefficients

3.3.2.1. Short-time diffusion analysis for Im-based Tablets

The apparent diffusion coefficients at short release times were determined using Crank's short-time approximation according to the following equation³⁴:

$$D = \frac{P^2 h^2 \pi}{16}$$

Where P is the slope of the linear relationship between the normalized mass fraction (m_t/m_{∞}) and the square root of time ($t^{1/2}$), while h represents the characteristic diffusion length of the matrix. This approach was applied to both *p*-anisidine release and absorbed liquid. As a representative example, the linear plots

obtained for formulation T1 at pH 1.2 and 37 °C are presented in Figure 7. Excellent linearity was observed for both *p*-anisidine release and absorbed liquid, with R^2 values ranging from 0.9997 to 0.9996.

The diffusion coefficients of both the drug and the dissolution medium values at short-time are presented in Table 3. For all investigated formulations, the excellent linearity obtained from the Crank plots ($R^2 > 0.98$) confirms the applicability of the diffusion model to the present delivery systems.

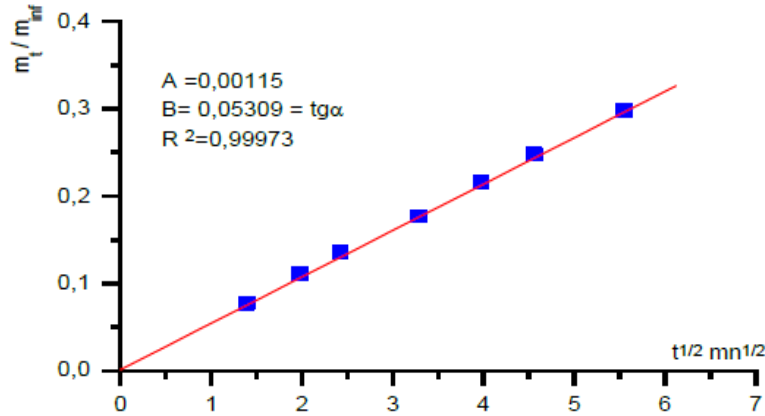


Fig. 7. Representative determination of the diffusion coefficient using Crank's short-time approximation.

Table 4. Results of Release Kinetics with apparent Diffusion coefficients of *p*-anisidine (D_{Drug}) and dissolution medium (D_{Liq}) at Short-time release for T1– T6 and C1–C6 Tablets, calculated using Crank's short-time diffusion; equilibrium released fraction m_{∞} , and absorbed liquid.

Tablet		Mt/M _∞ =f(t ^{1/2})	%m _∞	D _{Drug} (cm ² s ⁻¹)	R ²	Mt'/M _∞ =f(t ^{1/2})	D _{Liq} (cm ² s ⁻¹)	%liq _∞ abs [*]
Im	T1	0.053 t ^{1/2} +1.10 × 10 ⁻³	78.37	1.79 × 10 ⁻⁵	0.9997	0.036 t ^{1/2} +1.40 × 10 ⁻³	8.24 × 10 ⁻⁶	53.09
	T2	0.051 t ^{1/2} +4.91 × 10 ⁻⁴	59.80	1.65 × 10 ⁻⁵	0.9999	0.062t ^{1/2} +2.40 × 10 ⁻³	2.44 × 10 ⁻⁵	39.00
	T3	0.052 t ^{1/2} +1.80 ×10 ⁻²	53.63	1.72 × 10 ⁻⁵	0.9892	0.047 t ^{1/2} +3.30 × 10 ⁻³	1.40 × 10 ⁻⁵	54.52
	T4	0.048 t ^{1/2} –1.30 × 10 ⁻²	21.70	1.63 × 10 ⁻⁵	0.9884	0.035 t ^{1/2} +2 × 10 ⁻⁴	8.68 × 10 ⁻⁶	49.95
	T5	0.045t ^{1/2} +1.00 × 10 ⁻³	55.47	1.43 × 10 ⁻⁵	0.9995	0.045t ^{1/2} +9 × 10 ⁻⁴	1.43 × 10 ⁻⁵	55.22
	T6	0.043 t ^{1/2} +1.00 × 10 ⁻³	19.70	1.31 x 10 ⁻⁵	0.9997	0.0353 t ^{1/2} +8 × 10 ⁻⁴	8.78 × 10 ⁻⁶	48.86
Cp	C1	0.044 t ^{1/2} + 1.06 × 10 ⁻⁴	62.64	1.23 × 10 ⁻⁵	0.9999	0.043 t ^{1/2} + 2 × 10 ⁻³	1.17 × 10 ⁻⁵	57.60
	C2	0.052 t ^{1/2} +1.10 × 10 ⁻³	43.92	1.72 × 10 ⁻⁵	0.9997	0.037 t ^{1/2} +1.40 × 10 ⁻³	8.70 × 10 ⁻⁶	54.75
	C3	0.038 t ^{1/2} +9.81 × 10 ⁻⁴	53.99	9.18 × 10 ⁻⁶	0.9998	0.041t ^{1/2} +7.37 × 10 ⁻⁴	1.07 × 10 ⁻⁵	55.80
	C4	0.038 t ^{1/2} +1.70 × 10 ⁻³	26.96	1.02 × 10 ⁻⁵	0.9993	0.042 t ^{1/2} +6.97 × 10 ⁻⁴	1.25 × 10 ⁻⁵	49.90
	C5	0.057 t ^{1/2} +1.70 × 10 ⁻³	31.17	2.06 × 10 ⁻⁵	0.9998	0.049 t ^{1/2} +2.00 × 10 ⁻³	1.53 × 10 ⁻⁵	36.05
	C6	0.039 t ^{1/2} +5.31 × 10 ⁻⁴	14.07	9.67 × 10 ⁻⁶	0.9996	0.032 t ^{1/2} +2.00× 10 ⁻³	6.51 × 10 ⁻⁶	53.20

Footnote: *Drug release and liquid uptake values correspond to equilibrium conditions after 426 min.*

The apparent diffusion coefficients of *p*-anisidine ranged from 1.31×10^{-5} to $1.79 \times 10^{-5} cm^2 s^{-1}$. The highest value was obtained for T1 ($1.79 \times 10^{-5} cm^2 s^{-1}$), whereas T6 exhibited the lowest value ($1.31 \times 10^{-5} cm^2 s^{-1}$).

The fraction of *drug* released at the end of the investigated period also varied considerably from 19.7% for T6 to 78.37% for T1.

In comparison, the apparent diffusion coefficients of the penetrating liquid showed greater variability, ranging from 8.24×10^{-6} to $2.44 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$. The percentage of liquid absorbed after 426 min ranged from 39.00% to 55.22%. These results indicate that the transport behavior of *p*-anisidine and the dissolution medium depends on the formulation and experimental conditions. Interestingly, a higher liquid diffusion coefficient was not systematically associated with a higher extent of *p*-anisidine release, suggesting that liquid penetration alone does not fully govern the release process.

Since the objective of this work is to investigate the effect of the active agent formulation on its release behavior, the results are presented according to the influence of two key parameters, namely the nature of the polymeric matrix and the pH of the release medium.

Comparison of paired MM and MS formulations at the same pH showed diffusion coefficient ratios of *p*-anisidine close to unity ($D_{\text{MM}}/D_{\text{MS}} \approx 1$), indicating that PCL incorporation had only a limited effect on the apparent short-time diffusion of *p*-anisidine. Despite this similarity in diffusivity, substantial differences were observed in the extent of *p*-anisidine release between the two matrix systems, suggesting that the overall release behavior is not governed by apparent diffusivity alone.

Other formulation-dependent processes, including matrix hydration and pH-dependent hydrolysis of the grafted linkage, may influence the amount of *p*-anisidine available for diffusion, in agreement with the mechanisms discussed in *Section 3.1.2*. Comparison of the different formulations reveals that both the polymeric matrix composition and the release medium significantly influence the diffusion behavior. At identical pH values, incorporation of PCL into the Eudragit-based matrix modified solvent penetration and consequently altered the apparent diffusion coefficients. Likewise, variations in pH values affected the hydrolysis rate of the functionalized carrier, thereby influencing the amount of drug available for diffusion.

3.3.2.2. Short-time diffusion analysis for Cp-based Tablets

The linear relationship obtained between the normalized released fraction and the square root of time confirms the applicability of Crank's diffusion model for describing the initial transport process. Similarly, the apparent diffusion coefficients and the release kinetic parameters for the Cp-based Tablets are summarized in Table 4.

The diffusion coefficients of *p*-anisidine varied from 9.18×10^{-6} to $2.06 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$. The highest value was obtained for C5 $2.06 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, whereas C3 exhibited the lowest value $9.18 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$. The fraction of drug released at the end of the investigated period also varied considerably, ranging from 14.07% for C6 to 62.64% for C1.

In comparison, the apparent diffusion coefficients of the penetrating liquid ranged from 6.51×10^{-6} to $1.53 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, while the percentage of liquid absorbed after 426 min varied between 36.05% and 57.60%. These results indicate that both *p*-anisidine transport and liquid penetration are strongly influenced by the formulation. However, the extent of drug release did not correlate directly with either the apparent diffusion coefficient of *p*-anisidine or that of the penetrating liquid. For example, C3 exhibited the highest apparent

diffusion coefficient with only 31.17% of *p*-anisidine released, whereas C1 achieved the highest cumulative release (62.64%) despite a lower diffusion coefficient. Similarly, higher absorbed liquid or faster liquid diffusion did not systematically result in greater drug release. These observations suggest that drug release from Cp-based tablets is governed not only by diffusion but also by the hydrolysis of the grafted Schiff-base linkage, which controls the availability of free *p*-anisidine for diffusion through the hydrated polymeric matrix.

Overall, the calculated diffusion coefficients remained within the same order of magnitude for all Cp-based Tablets, indicating comparable diffusional mobility among the different formulations. However, the differences observed in cumulative release between MM and MS Tablets cannot be explained solely by diffusion. Instead, the release behavior results from the combined effects of matrix hydration, hydrolysis of the pH-sensitive Schiff-base linkage, and diffusion of the released free *p*-anisidine through the hydrated polymeric matrix.

3.4. Release Kinetic Modeling Using the Higuchi and Korsmeyer–Peppas Models

To investigate the drug release mechanism, the experimental release profiles were fitted to the Higuchi and Korsmeyer–Peppas models.³⁵⁻³⁷

The Higuchi model assumes that drug release is primarily governed by Fickian diffusion through a hydrated matrix and predicts a linear relationship between the cumulative drug released and the square root of time. Consequently, a good linear fit indicates that diffusion is the dominant release mechanism during the initial stage of release. The Higuchi model describes drug release from a homogeneous matrix as a diffusion-controlled process and is expressed as:

$$m_t = k_H t^{1/2}$$

Where m_t is the cumulative amount of drug released at time t ; k_H is the Higuchi release constant; and t is the release time. The calculated kinetic parameters including the regression coefficients (R^2) and model constants are summarized in Table 5.

The results obtained from the Higuchi model showed that the Higuchi release constant (k_H) ranged from 1.051 min^{-1/2} to 4.176 min^{-1/2}. The study of *p*-anisidine release from the T1/T2, T3/T4, and T5/T6 formulations showed that the incorporation of PCL into the coating matrix increased the Higuchi release constant (k_H) compared with Tablets containing the Eudragit RL coating matrix, as evidenced by the following values: 4.176 (T1) > 3.009 (T2), 2.807 (T3) > 1.051 (T4), and 2.516 (T5) > 1.634 (T6).

It was observed that the intercept (c) was positive for the majority of the release profiles, indicating the presence of the active compound on the surface of the investigated dosage forms. This surface-associated drug accelerated the initial release upon contact with the dissolution medium, resulting in the burst effect.

The values of the Higuchi release constant further confirmed the previously observed influence of pH on drug release from Tablets T1, T2 and T3, where drug release was faster under simulated gastric fluid conditions (pH 1.2) than at pH 4.0 or pH 8.0.

The correlation coefficients (R^2) were close to 0.99 during the initial stage of release, corresponding to release fractions (m_∞) not exceeding 10%.

Table 5. Correlation coefficients (R^2) and release kinetic parameters obtained from the Higuchi and Korsmeyer–Peppas models for *p*-anisidine release from Im and Cp Tablets.

Tablets	Higuchi's Equation	Korsmeyer–Peppas's Equation			
	$Q = at^{1/2} + c$	R^2	n	$k \text{ (min}^{-n}\text{)}$	R^2
T₁	$y = 4.176x + 0.063$	0.9996	0.492	0.0030	0.9995
T₂	$y = 3.009x + 0.001$	0.9999	0.498	0.0025	0.9999
T₃	$y = 2.807x + 0.993$	0.9892	0.392	0.0015	0.9991
T₄	$y = 1.051x - 0.284$	0.9884	0.651	0.0048	0.9985
T₅	$y = 2.516x + 0.066$	0.9995	0.484	0.0018	0.9986
T₆	$y = 1.634x + 0.004$	0.9998	0.497	0.0067	0.9997
C₁	$y = 2.762x + 0.012$	0.9998	0.498	0.0019	0.9996
C₂	$y = 1.893x + 0.019$	0.9997	0.490	0.0026	0.9994
C₃	$y = 2.053x + 0.049$	0.9996	0.493	0.0014	0.9997
C₄	$y = 1.053x + 0.001$	0.9994	0.497	0.0015	0.9997
C₅	$y = 1.773x + 0.040$	0.9998	0.490	0.0031	0.9999
C₆	$y = 0.450x + 0.006$	0.9999	0.495	0.0015	0.9999

Although the Higuchi model provides information on diffusion-controlled release, a more comprehensive understanding of the release mechanism was obtained using the Korsmeyer–Peppas model. This model is a semi-empirical model widely used to analyze drug release from polymeric matrices when the release mechanism is not fully understood or when more than one release process may be involved. It allows the identification of the predominant release mechanism through the value of the release exponent (n).

$$\frac{m_t}{m_\infty} = k_{KP} t^n$$

The release exponent (n) provides information about the transport mechanism. For cylindrical matrices, the release mechanism can be interpreted according to the value of n , as summarized in Table 6.

Table 6. Interpretation of the release exponent (n) according to the Korsmeyer–Peppas model for cylindrical matrices.³⁵⁻³⁷

n^*	Release mechanism	Description
$n \leq 0.45$	Fickian diffusion	Drug release is governed primarily by diffusion.
$0.45 < n < 0.89$	Anomalous (non-Fickian) transport	Drug release is controlled by the combined effects of diffusion and polymer relaxation/swelling.

$n = 0.89$	Case II transport	Drug release is governed mainly by polymer relaxation.
$n > 0.89$	Super Case II transport	Drug release is dominated by polymer relaxation and swelling, leading to accelerated release.

* n is the release exponent. The interpretation of n is based on cylindrical matrices.

The results obtained from the Korsmeyer–Peppas model showed that the values of the kinetic constant k_{KP} cannot be directly compared because they depend on the value of the release exponent (n), which is not the same for all the release profiles investigated. Furthermore, the value of n provides information about the diffusion mechanism, allowing it to be identified as Fickian or non-Fickian transport. The kinetic parameters obtained from both models are summarized in Table 5.

The values presented in Table 5 show that the release exponent (n) ranged from 0.484 to 0.497 for the Eudragit RL/PCL and Eudragit RL Tablets (T1 and T2) in the acidic medium and (T5 and T6) in the basic medium, values that are close to 0.5. In contrast, n values of 0.392 and 0.651 were obtained for Tablets (T3 and T4) containing Eudragit RL/PCL and Eudragit RL matrices, respectively.

Finally, modeling based on the Korsmeyer–Peppas equation showed that drug release from formulations T1, T2, T5, and T6, containing Eudragit RL/PCL and Eudragit RL as the matrix, followed a Fickian diffusion mechanism. In contrast, drug release from formulations T3 and T4, containing Eudragit RL/PCL and Eudragit RL matrices, respectively, followed a non-Fickian diffusion mechanism.

Following the kinetic analysis of *p*-anisidine release from Im-based Tablets, the release behavior of Cp-based Tablets was investigated using the same analysis.

The Higuchi release constant (k_H) ranged from 0.450 min to 2.762 min for the different Cp Tablets. The study of *p*-anisidine release from the different Cp formulations at various pH values showed that the incorporation of PCL into the coating matrix increased the Higuchi release constant compared with formulations containing Eudragit RL as the coating matrix. It was observed that the intercept (c) was positive for all release profiles, indicating the presence of the drug on the surface of the investigated dosage forms. The drug located at the surface was released rapidly upon the first contact of the dosage form with the dissolution medium, resulting in the characteristic burst effect.

The Higuchi release constants further confirmed the previously observed influence of pH on the release of the active agent from both Cp-based Tablets. Drug release was faster under acidic conditions (pH 1.2) than at pH 4.0 and pH 8.0. Indeed, the correlation coefficients (R^2) were close to 0.99 during the initial stage of release, where the m_∞ values did not exceed 10%, indicating an excellent fit of the experimental data to the Higuchi model.

According to the Korsmeyer–Peppas model, the values of the kinetic constant (k_{KP}) cannot be directly compared because they depend on the release exponent (n), which was close to 0.5 for all Tablets formulations (Table 5).

Finally, modeling according to this equation indicated that drug release from all formulations containing either Eudragit RL/PCL or Eudragit RL as the matrix followed a Fickian diffusion mechanism.

3.5. Comparative Release Behavior of Im- and Cp-Based Tablets formulations

The release mechanism of *p*-anisidine differs markedly between the Im and Cp-based Tablets owing to the different structural organization of the functionalized systems. In the Im-based Tablets, *p*-anisidine is directly incorporated into the functionalized imine-containing monomer structure; consequently, the release behavior is mainly governed by the hydrolysis of the Schiff-base linkage and the subsequent release of the active molecule. As reflected by the diffusion analysis, the apparent diffusion coefficients remained within the same order of magnitude among the different formulations, indicating that variations in cumulative drug release mainly originate from differences in the extent of hydrolysis rather than from diffusional mobility. In contrast, for the Cp-based Tablets, *p*-anisidine remains covalently attached to a polymeric carrier through an imine linkage. Therefore, its release involves a more complex process resulting from the combined contribution of:

- (i) hydrolytic cleavage of the imine linkage.
- (ii) hydration and swelling of the polymeric matrix.
- (iii) and therefore, diffusion of the released *p*-anisidine molecules through the hydrated polymer matrix.

This distinction highlights the different release mechanisms governing the two systems:

- **Im:** the **chemical release mechanism** primarily governed by hydrolysis of the imine linkage dominates.
- **Im** → **chemically dominated release (imine hydrolysis)**
- **Cp :** a **controlled release mechanism** results from the combined contributions of imine-linkage hydrolysis, polymeric matrix effects (including hydration), and diffusion through the polymeric network.
- **Cp** → **matrix-controlled release** involving hydrolysis + hydration/matrix effects + diffusion

Accordingly, the diffusion coefficients also remained within the same order of magnitude, the higher cumulative release observed for MM formulations compared with MS formulations cannot be explained solely by diffusional mobility. Overall, these findings demonstrate two distinct release mechanisms : Im-based Tablets exhibit a predominantly chemically controlled release governed by imine hydrolysis, whereas Cp-based tablets display a matrix-controlled release in which hydrolysis, matrix hydration/swelling and diffusion act synergistically to regulate drug release.

3.6. Mechanistic Insights into Drug Release: Drug release mechanism

This section integrates the experimental findings obtained from the release studies, diffusion analysis, and kinetic modeling to provide a comprehensive interpretation of the overall drug release mechanism. Particular emphasis is placed on the combined roles of Schiff-base hydrolysis, matrix hydration, polymeric matrix composition, and diffusion in controlling *p*-anisidine release.

The overall release behavior cannot be explained by a single transport process. Instead, *p*-anisidine release results from the sequential and synergistic contributions of pH-dependent hydrolysis of the grafted Schiff-base linkage, hydration and swelling of the polymeric matrix, and subsequent diffusion through the swollen

matrix. Drug release was consistently higher under acidic conditions, reflecting the greater hydrolytic susceptibility of the imine bond, whereas release gradually decreased with increasing pH.

The incorporation of PCL into the Eudragit RL matrix enhanced matrix hydration and liquid penetration, thereby increasing drug release rates compared with Eudragit RL alone while preserving the predominant Fickian diffusion mechanism identified by the Higuchi and Korsmeyer–Peppas kinetic models. However, the similar apparent diffusion coefficients obtained for most formulations indicate that diffusion alone cannot fully explain the observed release behavior.

Consequently, Im-based formulations exhibited a chemically controlled release mainly governed by imine hydrolysis, whereas Cp-based formulations provided a matrix-controlled release resulting from the combined contributions of hydrolysis, matrix hydration, and Fickian diffusion.

CONCLUSION

This study investigated the effects of polymeric matrix composition and dissolution medium pH on *p*-anisidine release from functionalized Im- and Cp-based swellable PCL/Eudragit matrix Tablets. The results demonstrated that the incorporation of PCL into the Eudragit RL matrix significantly enhanced *p*-anisidine release, whereas release was higher in simulated gastric fluid than in neutral and basic media and gradually decreased as the pH increased due to the higher hydrolytic susceptibility of the Schiff-base linkage. Diffusion analysis and kinetic modeling further demonstrated that Fickian diffusion was the predominant mechanism controlling *p*-anisidine release from all Tablet formulations. However, the overall release behavior resulted from the combined contributions of pH-dependent imine hydrolysis, matrix hydration, and diffusion through the swollen polymeric matrix. Although the incorporation of PCL significantly enhanced drug diffusion without altering the dominant Fickian release mechanism, highlighting its role in improving drug transport while preserving the overall release behavior.

These findings demonstrate the potential of functionalized swellable PCL/Eudragit polymer blend matrix Tablets as promising platforms for the controlled and tunable release of bioactive compounds through the combined modulation of polymer composition and environmental pH.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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