



Unveiling Swelling and Erosion Dynamics: Early Development Screening of Mirabegron Extended Release Tablets

Ana S. Sousa^{1,2} · J. Serra² · C. Estevens² · R. Costa² · António J. Ribeiro^{1,3}

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Abstract

Although the development of extended release (ER) matrices has been extensively investigated, understanding the most appropriate mechanism of drug release to achieve the desired release remains a cost- and time-consuming challenge in the early stages of formulation development. This study aimed to investigate the early stage of developing ER hydrophilic matrix tablets containing mirabegron as a model drug, focusing on the effects of polymer type, diluent type, and polymer amount on critical quality attributes (CQAs), namely, tablet swelling and erosion behavior. A full factorial design was employed to explore the interactions of control factors through multivariate regression analysis, emphasizing the application of quality by design (QbD) principles. The swelling and erosion performances of 72 formulations were evaluated. The swelling data were fitted to the Vergnaud model. Finally, *in vitro* drug release profiles were investigated for four of the formulations studied. The polymer type, diluent type, and polymer amount had distinct effects on the swelling and erosion behavior of the ER matrix tablets. Compared with those with isomalt (G720) or dextrate (DXT), formulations with polyethylene glycol 8000 (P8000) consistently exhibited greater swelling. Additionally, higher molecular weight was correlated with increased swelling within the same polymer type. Hydroxypropylmethylcellulose (HPMC) and polyethylene oxide (PEO)-based formulations showed higher swelling rates, while polyvinyl alcohol (PVA-80) displayed the highest erosion percentage. The findings highlight the significance of incorporating early-stage screening designs to maximize efficiency and optimize time and resource. This approach enables the development of a comprehensive understanding of drug release mechanisms from ER matrix tablets.

Keywords erosion · extended release matrix tablets · formulation screening · quality by design · swelling

Introduction

The pharmaceutical industry has been increasingly focused on the development of extended release (ER) matrix tablets, which offer significant advantages over immediate release formulations in terms of safety and efficacy. ER matrix tablets are particularly promising for drugs characterized by short half-lives [1] or narrow absorption windows [2], as they can modulate drug release, reduce dosing frequency, minimize side effects, and enhance patient compliance and therapeutic outcomes [3].

Among the different types of ER monolithic matrix systems, hydrophilic matrices are the most studied and widely used in ER tablet manufacturing [4]. These systems rely on the homogeneous dispersion of the drug within a polymer-based matrix, with commonly employed hydrophilic polymers including hydroxypropylmethylcellulose (HPMC) [5–7], hydroxypropylcellulose [8, 9], polyethylene oxide (PEO) [10, 11], polyvinyl alcohol (PVA) [12], sodium carboxymethylcellulose (NaCMC) [13], and carbopol [14, 15]. One of the important factors for understanding the functionality of hydrophilic matrices lies in the drug release mechanism that can occur through one or a combination of different mass transport processes, i.e., swelling, erosion, and dissolution of the polymer chains, in addition to drug diffusion and dissolution [16–18].

When the hydrophilic matrix tablets come into contact with water or gastrointestinal fluid, the solvent diffuses into the matrix and acts as a plasticizer, causing a glass-rubber transition. The polymeric chains start to relax and disentangle,

✉ António J. Ribeiro
aribeiro@ff.uc.pt

¹ Faculdade de Farmácia, Universidade de Coimbra, Coimbra 3000-148, Portugal

² Grupo Tecnimede, Quinta da Cerca, Caixaria, Dois Portos 2565-187, Portugal

³ i3S, IBMC, Porto, Rua Alfredo Allen, 4200-135, Portugal



inducing polymer swelling and forming a gel layer that controls drug release. The drug particles homogeneously dispersed in the matrix, diffuse through the hydrated gel layer whereas the drug molecules exposed on the surface dissolve into the surrounding medium. Simultaneously, the matrix surface may erode, exposing more drug particles for release into the medium [19]. This orchestrated interplay of swelling, drug diffusion, dissolution, and matrix erosion contributes to the controlled release of the drug over time. The importance of the swelling mechanism started to be investigated and discussed at the end of the 20th century [5, 17, 20–25]. The matrix swelling process proposed by Siepmann *et al.* [22] is consistent with the findings reported by Colombo *et al.* [20], who identified three distinct fronts in HPMC matrix tablets (swelling front, diffusion front, and erosion front).

The journey from concept to market-ready ER matrix tablets is a complex and highly regulated process that has benefited from the paradigm shift guided by the application of the principles of Quality by Design (QbD). QbD offers a systematic framework for pharmaceutical development, focusing on defining the quality target product profile (QTPP), critical quality attributes (CQAs), and critical process parameters (CPPs) [26, 27]. The context of ER matrices emphasizes a comprehensive understanding of the formulation and manufacturing processes with the aim of reducing variability and optimizing product quality and performance while ensuring the controlled release of drugs over an extended period of time. Considering the complex mechanisms of oral ER delivery systems, additional development challenges in fulfilling quality-related regulatory requirements should be considered to increase efficiency and improve time and cost-effectiveness [28]. Many studies have applied the QbD approach in the design and development of ER matrix tablets [29–33]. Nevertheless, despite the increasing daily implementation of QbD concepts in drug product design and development, screening experimental designs continues to fall short in recognizing their importance [28]. Employing QbD-based screening designs in the early stage of pharmaceutical development allows pharmaceutical companies to enhance scientific understanding and achieve drug products with the required quality profile while optimizing resources efficiently. These screening designs systematically explore a wide range of variables and their interactions, which is especially valuable when drug quantities are limited. This approach helps identify high-risk factors that impact product quality and process performance [34].

This article delves into the early stage of ER matrix tablet development, with a particular focus on understanding the release mechanisms of mirabegron, a potent and selective beta-3 adrenergic receptor agonist widely used for overactive bladder (OAB) syndrome. Although previous studies have explored mirabegron formulation and process optimization [35–37], none have specifically addressed the importance of screening in early development. A holistic approach will

be applied to evaluate the impact of diverse input materials (matrix agents and diluents) on the mechanisms governing the behavior of mirabegron ER formulations – swelling and erosion – through a full factorial DoE. Although *in vitro* dissolution tests play a crucial role in predicting the *in vivo* performance of a drug product, the existing United States Pharmacopeia (USP) methods for ER drug products are intrinsically slow, labor intensive, time consuming and expensive [38]. Additionally, during early drug product development, when the amount of drug substance available is limited and the formulation is not completely defined, only a limited number of experiments can be carried out. As a result, it may not be possible to develop a dissolution method that establishes the most appropriate conditions for controlling product performance. In this work, eight polymers with different properties (PEO, HPMC, PVA, and carbopol) were combined with different diluents to modulate drug release from the ER tablets. While lactose, mannitol, and dicalcium phosphate are more commonly used diluents in the design of hydrophilic matrices [39], alternative soluble diluents from different sources, such as isomalt [35], dextrans [40] and polyethylene glycol (PEG) [41], deserve to be investigated. The aim of this study was to develop a valuable screening strategy for ER formulation development, considering the matrix former and diluent properties as critical variables, to achieve a comprehensive understanding of the mechanisms of drug release from oral ER matrix tablets and to better support a QbD approach. To the best of our knowledge, this study shows for the first time the application of screening designs in the initial stages of ER matrix tablet development, uniquely investigating the complex effects of diverse polymers and diluents on drug release mechanisms. This intends to be a useful approach that addresses a significant gap in ER matrix tablet formulations by significantly enhancing cost and resource optimization through a streamlined and science-driven process.

Materials and Methods

Materials

Mirabegron was used as a model drug and was purchased from Dr. Reddys Laboratories Ltd., Hyderabad, India. The excipients were purchased from or provided by Dow Chemical Company (Midland, MI, USA), Lubrizol (Westerlo, Belgium), Merck & Co. (Kenilworth, New Jersey, USA), BENE0 (Mannheim, Baden-Wurttemberg, Germany), JRS Pharma (Rosenberg, Baden-Wurttemberg, Germany), DuPont (Dartford, UK) and UNDESA (Barcelona, Spain). Table 1 summarizes the excipients used in the study. Four grades of PEO, namely N-750, 1105, N-60 K and 303, were used with a viscosity range at 25 °C of 600–1200 mPa.s (5% solution), 8800–17,600 mPa.s (5% solution), 2000–4000 mPa.s (2%

Table 1 Excipients Used in the Study and Their Function in Formulation

Abbreviation	Excipient name	Commercial name	Function in formulation	Manufacturer
PEO N-750	Polyethylene oxide	POLYOX™ WSR N750	Matrix former	DuPont
PEO 1105	Polyethylene oxide	POLYOX™ WSR 1105	Matrix former	DuPont
PEO N-60 K	Polyethylene oxide	POLYOX™ WSR N-60 K	Matrix former	DuPont
PEO 303	Polyethylene oxide	POLYOX™ WSR 303	Matrix former	DuPont
HPMCK4M	Hydroxypropyl methylcellulose	Methocel™ K4M Premium	Matrix former	DuPont
HPMCK100M	Hydroxypropyl methylcellulose	Methocel™ K100M Premium CR	Matrix former	DuPont
CAR-71G	Carbomer homopolymer type A	Carbopol® 71G NF Polymer	Matrix former	Lubrizol
PVA-80	Polyvinyl alcohol	Parateck® SRP80	Matrix former	Merck & Co.
G720	Isomalt	galenIQ™ 720	Diluent	BENEO
DXT	Dextrates	EMDEX®	Diluent	JRS Pharma
P8000	Polyethylene glycol 8000	CARBOWAX™ SENTRY™ NF Powder	Diluent	DOW
MgSt	Magnesium stearate	Kemilub EM-F-V	Lubricant	UNDESA

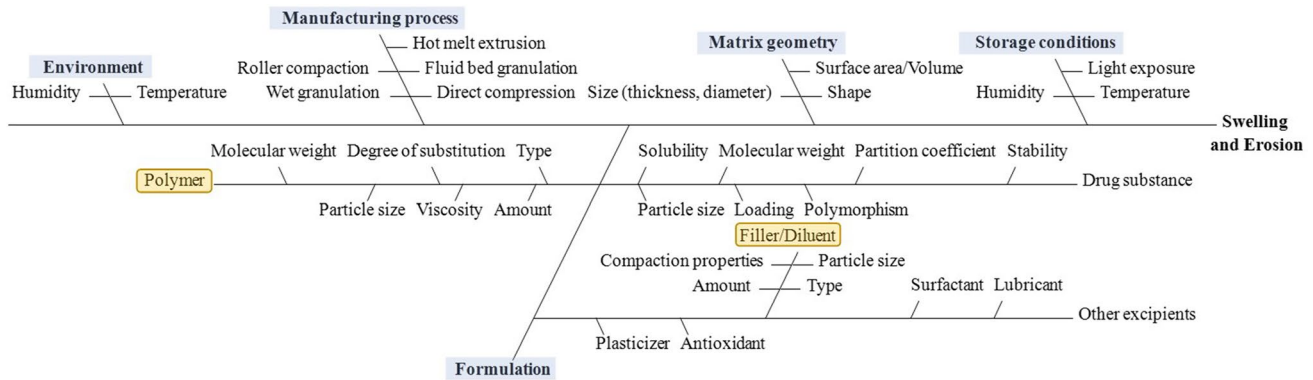


Fig. 1 Cause–effect diagram illustrating the critical parameters affecting ER matrix tablet development

solution) and 7500–10,000 mPa.s (1% solution), respectively. Two grades of HPMC (USP type 2208), K4M and K100M, were used with viscosities ranging from 2663 to 4970 mPa.s and 75,000–100,000 mPa.s, (2% w/w aqueous solution at 20 °C), respectively. A complete table regarding the excipients’ batch numbers, unique ingredient identifiers and manufacturers is provided in supplementary material Table S1.

QbD Approach for Screening of ER Matrix Tablets

Initial Risk Assessment

Considering that the development of ER formulations is inherently associated with several critical factors that can compromise the quality of the final product, an overall risk assessment of CMAs and CPPs that can potentially impact the quality of ER matrix tablets was developed by using a cause-and-effect diagram. This risk assessment aimed to identify high-risk formulation and process components to improve drug product quality based on prior knowledge, corporate experience,

and literature reports. An overall risk evaluation is depicted in Fig. 1, which shows the formulation and process parameters that can influence the swelling and erosion behavior of ER matrix tablets. In ER matrix tablet development, variations in matrix former properties can significantly impact the CQAs of the drug product. Although extensive literature focuses on *in vitro* drug release as a primary CQA, research addressing swelling and erosion behavior within a QbD approach remains limited. In fact, the degree of swelling of hydrophilic matrix tablets is a fundamental property that significantly impacts drug diffusion rates. Nonetheless, the relationship between swelling and drug release kinetics is complex and depends on multiple factors, including drug and polymer properties [42]. For water-soluble drugs, release is primarily influenced by the water penetration rate into the matrix and the diffusion of drug molecules through the hydrogel layer [5, 43]. In contrast, for poorly water-soluble drugs, matrix erosion becomes the rate-limiting step.

As drug solubility decreases, the release rate within the gel layer slows, affecting drug transport near the erosion front and reducing matrix swelling and resistance of the gel to erosion

[44]. Adjusting polymer choice, concentration, and other formulation factors can modulate swelling behavior and achieve desired drug release kinetics. A linear relationship between swelling and drug release was found in tablets containing binary combinations of three different polymers, indicating the role of swelling in controlling drug release by diffusion [45]. A number of studies have demonstrated that factors such as drug solubility [43], polymer amount, grade, degree of substitution [8, 46–48], and filler type [49, 50] can influence the rate of swelling and the release of the drug from hydrophilic matrices. A comparative study of HPMC matrices with different water soluble and insoluble excipients at varying concentration revealed that formulations containing lactose exhibited significantly greater water uptake than those containing microcrystalline cellulose or dicalcium phosphate. As lactose is a water-soluble excipient, it creates pores in polymer matrices, leading to enhanced water penetration and a higher swelling capacity [50]. While the manufacturing process significantly impacts the physical characteristics of tablets, including compressibility, compactibility, porosity, gel layer thickness, and *in vitro* drug release [47, 51–53], these aspects are beyond the scope of this article due to the multitude of process parameters involved. In this article, we delve into the primary components of oral ER formulations, emphasizing polymer and diluent properties as critical variables. The discussion centers on the key components highlighted in Fig. 1, exploring their impact on the CQAs of ER matrix tablets.

Screening Study – Full Factorial Design

During the initial screening phase, selecting an appropriate experimental design is crucial, considering the number of variables and the available resources. This study focused on three key factors: polymer type (X_1), polymer amount (X_2), and diluent type (X_3), based on an initial risk assessment. Screening studies aim to efficiently identify the most significant factors among a large set of potential factors with the least number of experiments and in a cost- and time-effective manner. In this study, since laboratory work is not overly limiting and time-consuming, a full factorial design with 72 runs was employed to investigate how these formulation parameters affect tablet swelling and erosion dynamics. The percentage of polymer and diluent was fixed at 79%, while mirabegron and magnesium stearate amounts remained constant. The swelling percentage at three time points (Y_1 , Y_2 , Y_3) and the erosion percentage (Y_4) were selected as dependent variables. Y_1 was set as 0.5 h, Y_2 as 2 h, and Y_3 as 4 h. An overview of the independent (factors) and dependent (responses) variables studied is given in Table II. To minimize the impact of potential biases and foster statistical validity, all experiments were randomized. The formulation compositions used in the experiments are provided in Table S2 in the supplementary material.

Preparation of Tablets

Tablets were prepared by direct compression. Ingredients were sieved through a 500 μm mesh, while magnesium stearate was sieved through a 250 μm mesh. To expedite the tableting process and due to the limited amount of drug substance, 10 g of each blend was mixed in a 75 mL high-density polyethylene wide-mouth bottle using a high-frequency agitator, CryoMill (Retsch GmbH, Haan, Germany), for 30 s at a maximum speed of 30 Hz, which promoted mixture homogeneity. The formulations were compressed to a thickness of 2.5 mm using a single-station compaction simulator (STYL'One, Medel'Pharm, France), simulating a S rotary press-TSM D compaction cycle with a pitch circle diameter of the turret of 370 mm. The compaction simulator was tooled with a standard EU-D 11.28 mm round flat-faced punch and die. The samples were prepared by manually pouring the weighed powder (400 mg \pm 5% range) into the die.

Development of ER Matrix Tablets QTPP

The main goal of pharmaceutical development is to successfully design a quality product aligned with the developed QTPP. The QTPP for an ER matrix tablet is a prospective summary of the desired quality attributes that should be present in the final drug product. This may include elements such as dosage form, delivery system, route of administration, and drug release [27]. QTPP is usually defined early in development, based on prior knowledge and relevant literature, ensuring that the final drug product meets the desired quality, safety, and efficacy standards while enhancing patient convenience and compliance. Table III provides an example of a QTPP for a hydrophilic ER matrix tablet. It is important to note that in establishing the QTPP for an ER swellable matrix tablet, defining a dosage strength that provides adequate release kinetics without the risks of dose dumping [54], pharmacobezoars [55], or compromised therapeutic outcomes is essential for ensuring patient safety and efficacy.

Swelling Studies

The rate of tablet water uptake (swelling) was determined by gravimetric analysis methods using an analytical balance (Sartorius, CPA225D, Germany). The dry matrix tablets were accurately weighed (W_i) in a glass vial, and 10 mL of deionized water was added to the vial. The vials with the samples were incubated in an orbital agitator (IKA KS 4000 ic control, Staufen, Germany) at $37 \pm 0.5^\circ\text{C}$ with rotation at 100 rpm. The samples were withdrawn until water uptake reached the maximum, where water was discarded, and each vial was carefully inverted for approximately 30 s to remove the excess liquid from around the swollen tablets

Table II Experimental Matrix for Screening Study on the Formulation Variables of ER Matrix Tablets

Independent variables	Value
X ₁ : Polymer type	PEO N-750 PEO 1105 PEO N-60K PEO 303 HPMC K4M HPMC K100M CAR-71G PVA-80
X ₂ : Polymer amount (%)	10 20 30
X ₃ : Diluent type	P8000 DXT G720
Dependent variables	
Y ₁ : percentage of swelling at 0.5 h	
Y ₂ : percentage of swelling at 2.0 h	
Y ₃ : percentage of swelling at 4.0 h	
Y ₄ : percentage of erosion	

and reweighed (W_s). Once again, 10 mL of deionized water was added, and the samples were rapidly reincubated until the next sampling point. The degree of swelling was determined from the mean of three replicates. The weight (%) increase due to water uptake was calculated at each time point from (1).

$$\text{Swelling (\%)} = \frac{W_s - W_i}{W_i} \times 100 \quad (1)$$

Erosion Studies

The erosion of the matrix tablets was also determined by a gravimetric technique. The wet samples used in the swelling studies were allowed to dry in an oven at 60°C and weighed until a constant weight was achieved (final dry weight, W_t). The eroded material was quantified by subtracting the dry weight of the tablet core from the initial tablet weight. The degree of erosion was estimated using (2):

$$\text{Erosion (\%)} = \frac{W_i - W_t}{W_i} \times 100 \quad (2)$$

Swelling Kinetics

To determine the water uptake kinetics, swelling data were fitted to a mathematical model described by Vergnaud [56]. Several authors have used this model to elucidate the mechanism of swelling [9, 48, 57]. The generalized equation of the Vergnaud model is shown in (3):

$$M = kt^n \quad (3)$$

where M is the amount of liquid transferred at time t and k is the swelling constant, which depends on the amount of liquid transferred after infinite time, the porosity of the matrix and the diffusivity. The exponent n indicates the mechanism of water uptake. A value of $n < 0.5$ indicates a diffusion-controlled mechanism in which the rate of diffusion of the liquid is much slower than the rate of diffusion of the polymer. A value of $n = 1$ suggests that the water diffuses through the polymer matrix at a constant velocity, indicating an advancing front that marks the limit of liquid penetration into the matrix. A value of $0.45 < n < 1$ indicates anomalous or complex behavior, where the rates of liquid diffusion and polymer hydration are of similar magnitude [58].

In Vitro Drug Release Studies

Dissolution studies of the mirabegron matrix tablets were conducted to correlate different swelling and erosion behaviors with the actual drug release. *In vitro* drug release studies

Table III Example of a QTPP for a Hydrophilic ER Matrix Tablet. The Establishment of This QTPP Was Based On Relevant Literature

QTPP element	Target	Justification
Pharmaceutical dosage form	Tablet	Widely accepted dosage form
Dosage design	ER tablet	Patient convenience and compliance by reducing the dosing frequency and side effects
Route of administration	Oral	Most preferred route of administration increasing patient compliance
Dosage strength	80 mg	Required for desired therapeutic efficacy of the drug product
Drug product quality attributes	Physical attributes Assay Content uniformity Drug release	Influence pharmacokinetics of drug
Alcohol induced dose dumping	No dose dumping	The drug release profile in alcohol is critical to patient safety
Pharmacokinetics	ER enabling a controlled release over an extended period	Required for desired efficacy of the drug product
Stability	Quality requirement	Ensure shelf-life and influence the quality of the drug product
Container and closer system	Appropriate for the dosage form	Assurance product quality up to the target shelf-life and ensure the tablet integrity during commercialization

were performed in triplicate on hydrophilic matrices using a USP dissolution apparatus 2 (Sotax AT7 Smart, Sotax AG, Aesch, Switzerland), interfaced with an off-line automatic sampler, with 900 mL of pH 6.8 sodium phosphate buffer at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and 100 rpm. Samples were withdrawn (5 mL) after 30, 60, 120, 240, 360, 480, 600, and 720 min, filtered through a 1.4 μm glass filter, and analyzed for drug content at 250 nm using a UV/Vis spectrophotometer (Evolution 300, Thermo Fisher Scientific, Waltham, MA, USA).

Statistical Analysis

To construct and analyze the full factorial experimental design, JMP[®] 17 (SAS Institute, Inc., NC, USA) statistical analysis software was used. The statistical significance of differences between mean values of other responses under study was assessed with one-way analysis of variance. The confidence level was 95% for all statistical analyses reported.

Results and Discussion

Screening DoE for Setting up the Formulation Components

Statistical Analysis and Summary of Fit

A full factorial model was used to investigate the influence of the input factors and their interactions (linear, 2-factor interaction, and quadratic) on tablet swelling and erosion. Unlike the traditional one-factor-at-a-time (OFAT) approach, which often results in lengthy experimentation and inconclusive results by varying one factor while keeping others

constant, the application of DoE statistical methods has enabled the capture of complex interactions among factors. This approach allows us to find the best solutions by fully exploring and understanding the effects of all factors [59]. In early drug product development, extensive *in vitro* dissolution tests are often impractical due to their cost- and time-consuming nature. Swelling studies provide a faster alternative for preliminary insights into drug release mechanisms, especially when drug substance availability is limited. This work demonstrates our capability to concurrently analyze 72 runs, optimize resources, and accelerate product development. Table S2 (supplementary material) summarizes the matrix design, where rows denote the experiments and their achieved responses at the designated levels of the variables investigated in this study. Multivariate regression analysis and ANOVA were performed to evaluate model fitness and identify causal relationships between the factors and CQAs. A standard least squares model was chosen, with each response fitted separately. Actual by predicted plots are depicted in Fig. 2. The alignment of all data points within the 95% confidence interval region (the faded shade surrounding the red line) not only indicates good data fitting but also implies a high level of reliability in the predicted model's correlation with the actual data. The horizontal blue line corresponds to the null hypothesis (where a given response is factor independent), showing that the desired value is not contained within the red region. Then, if the curve crosses the line, the effect is significant at the $\alpha = 0.05$ level, as observed for all the responses. Figure 2 also summarizes the coefficients of the model terms and associated p values for Y1 – Y4. A p value less than 0.05 ($p < 0.05$) indicated that the factor significantly affected the response. To simplify the regression model, non-significant terms ($p > 0.05$) were not considered. High R^2 values confirmed robust data fitting. In

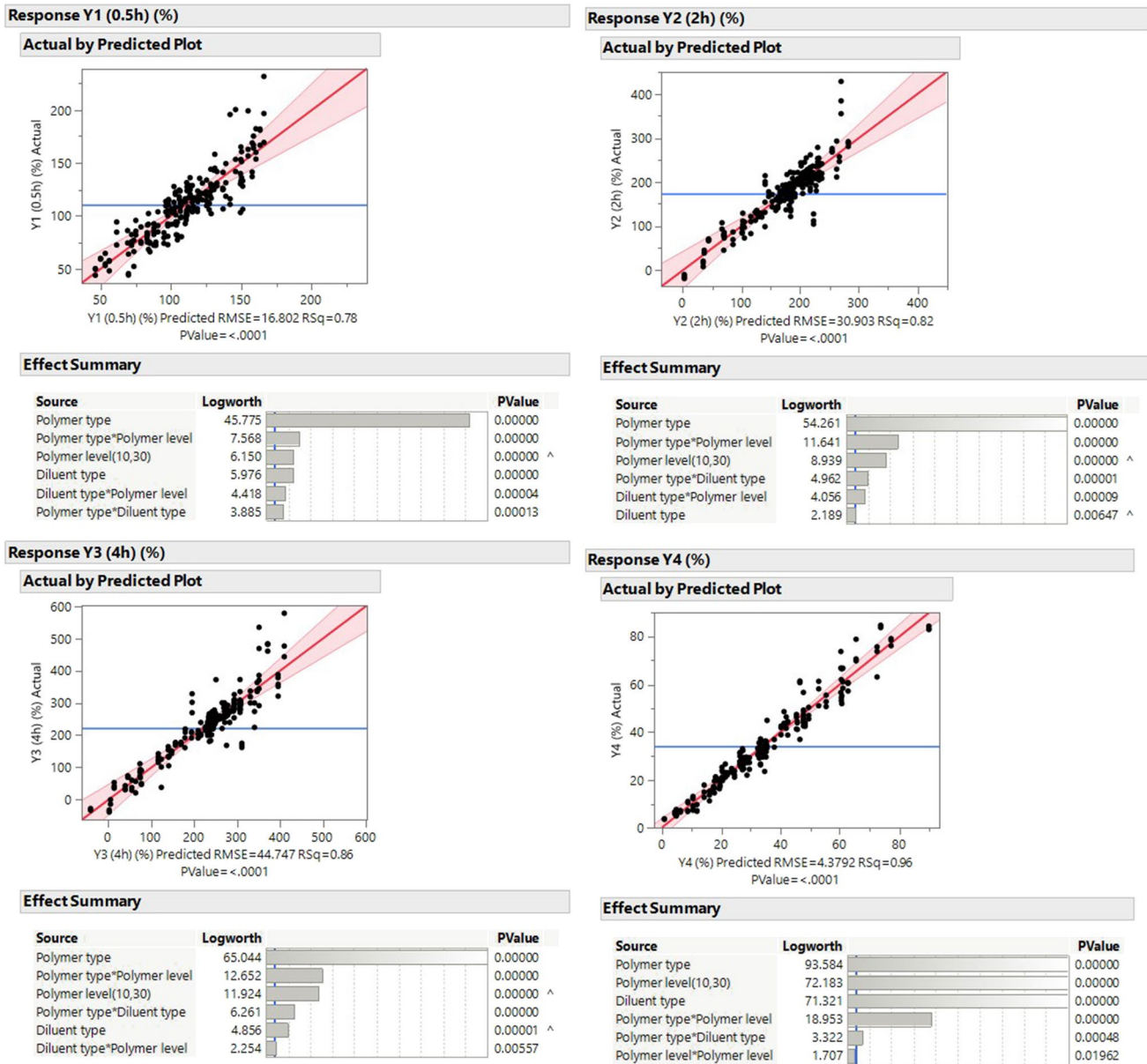


Fig. 2 Scatter plot of the observed *versus* the predicted values for the swelling percentage at 0.5 h (Y1), 2 h (Y2), 4 h (Y3), and erosion percentage (Y4), accompanied by an effect summary report. The

black dots are showing the response values obtained after performing the 72 experiments

addition, ANOVA (Table S3 in the supplementary material) was used to evaluate the suitability of the selected mathematical model for predicting responses ($p < 0.05$). Outliers in the data were measured by studentized residuals, revealing a normal distribution of the data and enhancing the robustness of the model.

Effect of Factors on Swelling and Erosion

The predictive models for Y1, Y2, Y3, and Y4 had adjusted R^2 values of 0.7378, 0.8189, 0.8340, and 0.9483,

respectively, and were close to 1. The similarity of these values was suggestive of the goodness of fit. The root-mean-square-error (RMSE) for Y1, Y2, Y3, and Y4 were 16.80, 30.90, 44.75, and 4.38, respectively. An overall analysis of the models indicated that a better fit was obtained for Y4 (erosion), followed by Y3 (swelling at 4 h). Erosion had a higher R^2 and a lower RMSE, which indicated its superior ability to account for unexplained variations. As shown in Fig. 2, the swelling percentage at different time points is mainly affected by the polymer type. On the other hand, the three main factors strongly affected erosion.

Swelling and Erosion Performance

The swelling capacity of hydrogels is a crucial factor influencing drug release kinetics by controlling not only the rate at which water diffuses into the matrix but also drug dissolution and diffusion throughout the gel layer of the hydrophilic matrix [16–20]. This reflects the ability of hydrophilic polymers to develop a network structure when they come in contact with water [22]. Despite the availability of various analytical techniques, such as X-ray tomography techniques [60], nuclear magnetic resonance [61–63], texture analysis [50, 64], and various imaging techniques [65–67], the gravimetric method stands out for its simplicity and straightforwardness when investigating the swelling behavior of tablets [48, 68–70]. In our work, while the amount of mirabegron in the formulation and the surface area/volume ratio [71] were kept constant, there are some effects that cannot be overlooked. First, the drug-to-polymer ratio changes with varying polymer amounts, which can significantly influence the release kinetics (water uptake and erosion). The significance of this phenomenon may vary based on drug solubility. For the particular case of a soluble drug substance such as mirabegron, as the drug dissolves and is released from the matrix, the hydrated gel layer tends to weaken, particularly at higher drug-to-polymer ratios. This weakening influences erosion kinetics, with the rate of erosion becoming more relevant in the later stages of drug release [14, 43]. Notably, a higher drug-to-polymer ratio can even lead to an initial burst release due to the rapid dissolution of the soluble drug, compromising therapeutic efficacy. Second, the ratio between the polymer and the diluent may also affect the properties of the gel layer and the rate of release since the diffusivity and the diffusional path length are altered. Generally, in the presence of an insoluble or hydrophobic diluent, dissolution fluid penetration into the matrix is significantly retarded, leading to a decrease in water ingress and subsequent drug release [72]. Otherwise, water-soluble diluents, such as lactose, facilitate gel formation and decrease the time for the dissolution medium to permeate the tablet core. Soluble substances act as channeling agents by quickly dissolving and diffusing outward, thereby decreasing tortuosity and/or increasing matrix porosity. Increasing the polymer-to-diluent ratio enhances the release rate as the diffusivity of the drug in the gel layer is improved [73]. Figure 3 presents the swelling profiles (a) and erosion (Y4) (b) of all formulations (F1 to F72). The vertical bars represent the standard deviation between the three experimental trials. A direct relationship was observed between the degree of swelling and the polymer amount (Fig. 3a). As expected, for larger quantities of polymer, the water uptake rate was greater [74]. Most likely because of their chemical nature, the PEO- and HPMC-based matrix tablets showed the highest swelling rates, with PEO 303 and HPMC K100M formulations achieving 384.55% (F33)

and 431.17% (F50) swelling within 4 h, respectively. During swelling and drug release, water gradually penetrates into the matrix tablet, decreasing the polymer's glass transition temperature (T_g) and forming a rubbery region next to the glassy region [7]. Turner *et al.* reported that PEO tends to swell and erode at a much faster rate than HPMC [75]. In the PEO-based matrix, swelling is relatively rapid, up to 4 h; however, as time progresses, significant erosion occurs. In contrast, HPMC-based matrices exhibited continuous swelling increases, indicating greater gel strength and minimal erosion. The higher the molecular weight of the polymer is, the greater the degree of swelling observed across different grades of the same polymer. In the case of Polyox, the sequence was as follows: PEO N-750 < PEO 1105 < PEO N-60 K < PEO 303. This difference was not as large for HPMC, although HPMC K100M showed greater swelling than HPMC K4M, as observed previously [76]. Higher-molecular-weight polymers typically have longer polymer chains and a more complex structure. These longer chains are more entangled within the matrix, leading to a denser and more interconnected network and stronger gel layer, decreasing susceptibility to erosion [42, 47, 77, 78]. Interestingly, from the swelling experiments (Fig. 3a), differences in polymer percolation thresholds for the ER matrices can be identified. A controlled release over a prolonged period of time can only be obtained if the percolation threshold of the polymer is exceeded. It can be seen that lower percolation concentrations could be obtained when the matrix tablets were formulated with higher molecular weight PEO or HPMC polymers [78, 79]. In the case of matrices composed of PVA-80, it may be reasonably assumed that the threshold limit was not exceeded, given that the slope of the swelling curve tends towards zero. Below the percolation threshold, matrix tablets would erode, and there would be no capacity for the formation of a mechanically robust matrix, resulting in fast drug release.

In fact, the PVA-80- and CAR-71G-based formulations stand out from the other polymers due to their distinct behavior. After achieving maximum water uptake, a slight decrease in swelling was observed for the PVA-80 matrices, which was attributed to matrix erosion. CAR-71G is a type A carbomer homopolymer of high molecular weight that is ideal for direct compression processes. The hydrophilic nature and crosslinked structure of acrylic acid make it a potential candidate for ER formulations since it readily hydrates, absorbs water, and swells. The ability of CAR to swell is dependent on the polymer amount, the degree of chemical crosslinking, and the medium pH [80]. The acrylic acid backbone of the polymer provided pH-dependent properties. At higher pH values, ionization of the carboxylic acid groups in CAR occurs, leading to ionic repulsion between charges within the same group. This phenomenon manifests as the expansion of the polymer network or swelling.

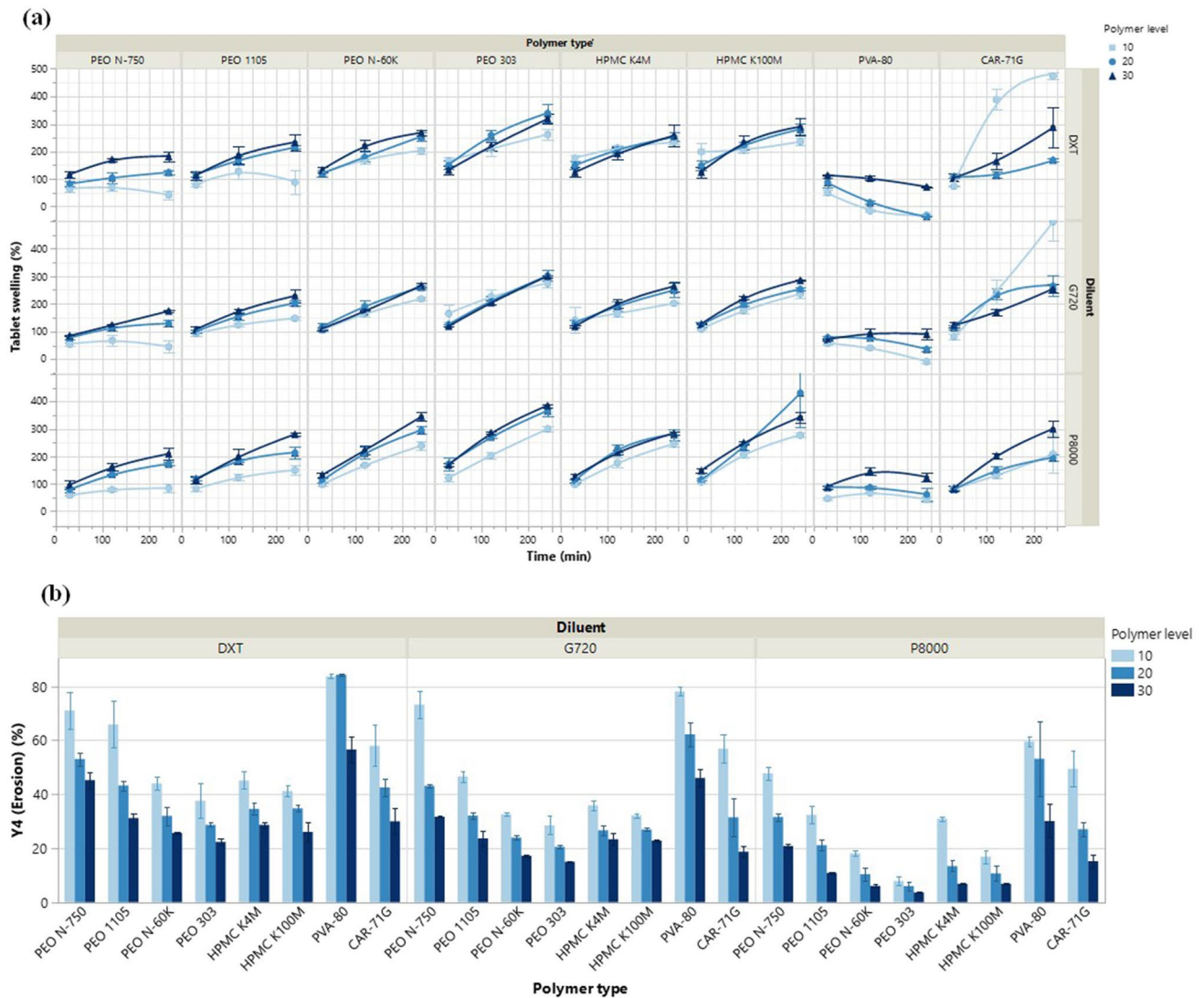


Fig. 3 Tablets swelling profiles (a) and erosion (Y4) (b) by different polymers and diluents for the studied formulations. The blue gradient represents polymer amounts ranging from 30% (dark triangle) to 20%

(mid-circle) to 10% (light square). Results represent the mean of three independent experiments. Standard deviation is indicated by the error bars

Moreover, the hydration of the polymer results in a rapid decrease in the T_g ($T_g = 105^\circ\text{C}$), and a relaxation response of the polymer chains is likely to occur due to stresses introduced by the presence of the dissolution solvent [80–82]. Although CAR has many advantages as a candidate for ER matrix tablets, there are only a few reports on its application. The potential of CAR-71G for *in vitro* drug release was evaluated by Fayed *et al.* [82]. Increasing the amount of CAR in the formulation resulted in sustained drug release, particularly at concentrations higher than 10%. No swelling studies were found for ER formulations containing only CAR-71G as a polymer. Similar to our results, the percentage of swelling at 4 h for matrices that contained mixtures of HPMC and CAR-71G (for a total of 20%) was approximately 300% [83]. The exceptional behavior of CAR-71G

at 10% observed in the swelling profiles (Fig. 3a) is likely attributed to its inherent crosslinked network. At lower CAR-71G concentrations, there might be fewer polymer chains and crosslinks. The greater the porosity is, the greater the amount of water penetration, allowing for greater expansion and swelling [84]. The rapid incorporation of a water mass induces increased swelling; however, this leads to an unstable nongel-based matrix structure. In contrast, higher concentrations may result in a more closely packed network, restricting water absorption and, consequently, the ability of the polymer to swell. Additionally, the combination of CAR with other polymers, such as HPMC, at different proportions has synergistic effects on delaying drug release [82, 83].

Within the context of hydrophilic polymeric matrices containing water-soluble drugs, excipients other than matrix

formers (e.g., type of diluent) should not be regarded as neutral. Diluents can significantly influence water penetration, erosion, and hence the mechanism of drug release. The swelling behavior of the prepared tablets was similar among the different diluents tested, although a greater water uptake capacity was observed for formulations with P8000. After observing swelling at 4 h (Y3) for the P8000-based formulations containing 30% polymer, it was possible to verify that they consistently showed higher percentages of swelling than DXT and G720. For example, swelling at 4 h was observed for PEO N-60 K-based formulations containing P8000 (F8) at 345.22%, while DXT and G720 formulations exhibited swelling of 266.81% and 267.72%, respectively. Although P8000 was used as a diluent in this work, it is noteworthy that PEG itself is a hydrophilic polymer with crosslinks that swells significantly in aqueous environments. The swelling mechanism of PEG is rooted in its versatile nature, which is driven by its hydrophilic properties and the crucial role of hydrogen bonding enabled by the presence of hydroxyl (-OH) groups in its molecular chain [85]. PEG has been commonly formulated with polymers of higher molecular weight (e.g., PEO), leveraging their increased swelling capacity in combination with the hydrophilic attributes of PEG [41, 86, 87]. When combined with HPMC, lactose, microcrystalline cellulose, partially pregelatinized maize, and PEG 6000 (P6000), had a modifying effect on the drug release profile. This contribution is imparted through potential interactions between the filler and HPMC, which can affect the degree of polymer hydration, i.e., the properties of the gel layer around the tablet and its diffusivity [88–90]. There are also reports in the literature describing the effect of NaCMC on the dissolution of three model drugs with different ionic natures and aqueous solubilities from gel-forming PEO matrices [91]. Similar results were previously reported for NaCMC and HPMC combinations, where the drug release rate varied based on the drug characteristics and matrix composition [92].

Matrix erosion was measured as the weight loss from the matrix tablets immersed in water (Fig. 3b). Typically, the erosion phase follows initial swelling and drug diffusion. During erosion, the polymer matrix undergoes dissolution, gradually enabling drug release into the surrounding medium. The observed erosion behavior was opposite to that obtained for swelling. Figure 4 depicts the relationship between the mean swelling and erosion at 4 h, presented as a scatterplot. The polymers are distinguished by different colors, with each point representing a single formulation. A linear regression model was fitted with R^2 to approximately 0.756. Formulations with 10% CAR-71G were excluded due to atypical behavior. P8000-based formulations showed a slow rate of polymer erosion, enhancing water absorption and reducing erosion. As expected, lower molecular weight polymers resulted in weaker gel layers, shorter diffusion paths, and higher erosion rates.

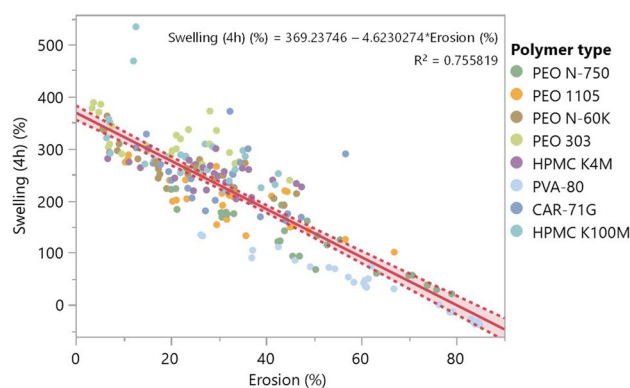


Fig. 4 Linear fitting of the percentage of mean swelling at 4 h versus the percentage of erosion

Conversely, the PVA-80-based formulations exhibited the highest erosion, correlating with their lowest swelling rates. PVA-80, prepared by hydrolysis of polyvinyl acetate, contains numerous -OH groups, and its water solubility is influenced by its degree of hydrolysis [93]. The high solubility polymers like PVA demonstrated a linear drug release profile, which can be attributed to the synchronization between the swelling and erosion fronts, implying a predominant erosion-controlled mechanism [25, 94].

Table IV Swelling Kinetic Parameters According to the Vergnaud Model

Formulation	Swelling Kinetic Parameters			
	k	n	R^2	R^2 Adj
F3	42.35	0.19	1.000	0.999
F7	27.34	0.44	1.000	0.984
F13	33.90	0.25	1.000	0.997
F14	32.03	0.37	0.999	0.971
F17	31.12	0.34	1.000	0.999
F19	22.63	0.37	1.000	1.000
F22	41.61	0.30	1.000	0.996
F23	30.23	0.39	1.000	0.995
F25	47.81	0.28	1.000	0.992
F29	47.94	0.37	0.999	0.984
F30	40.04	0.39	1.000	1.000
F36	23.04	0.47	1.000	1.000
F41	35.62	0.37	0.999	0.894
F46	62.50	0.25	1.000	0.998
F50	8.68	0.71	0.999	0.864
F51	28.36	0.42	1.000	0.955
F54	38.84	0.34	1.000	1.000
F61	47.51	0.22	1.000	0.917
F64	19.89	0.42	1.000	0.998
F70	44.71	0.31	1.000	0.992
F71	52.37	0.31	1.000	0.999

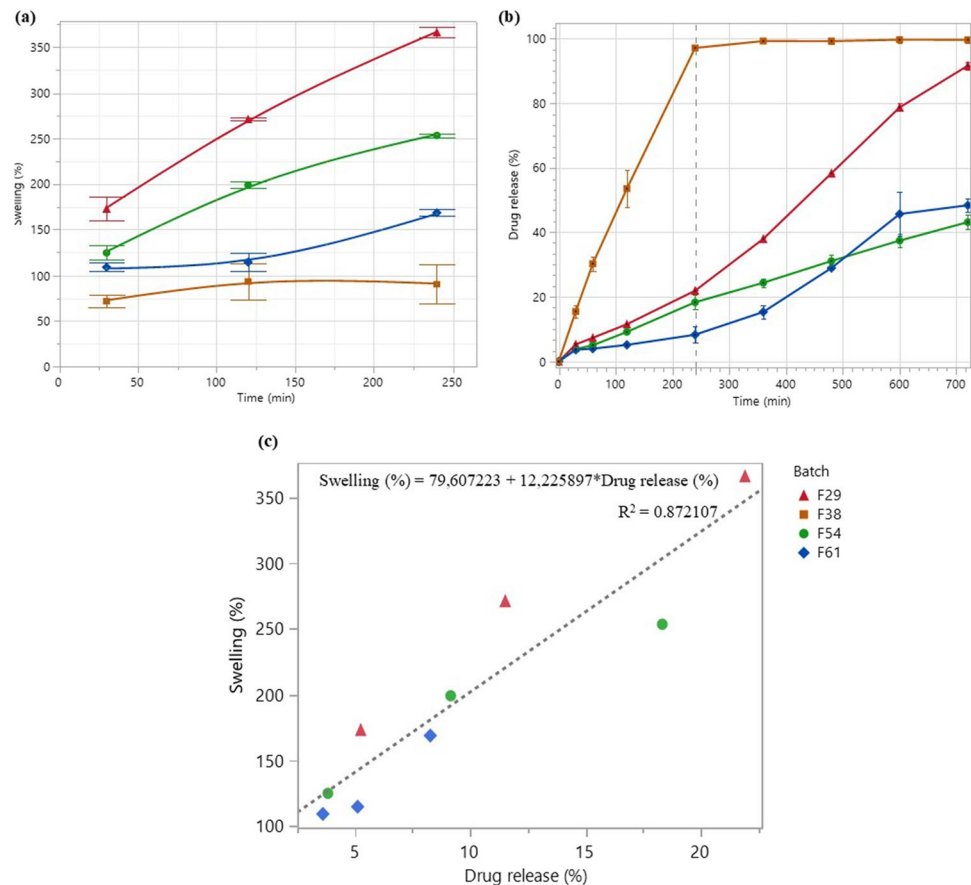
In previous works by Won *et al.* [95], there were distinct results where PVA-80 demonstrated greater water uptake than CAR-71G and high-viscosity PEO (MW = 5,000,000). The erosion behavior was not assessed.

Finally, the swelling data of the tablet formulations containing 20% polymer were analyzed using the Vergnaud model. Since erosion is the predominant mechanism and the formulations start to erode almost immediately, the model was not applied to PVA-80-based formulations. The kinetic results are presented in Table IV. In general, the swelling data exhibited a strong model fit, with R^2 values exceeding 0.99 for all the samples. The exponent, n , from the Vergnaud equation revealed that most ER matrix tablets exhibited diffusion-controlled mechanisms, as the exponent was less than 0.5. The rate of polymer relaxation surpasses the rate of water penetration into the matrix. The high value of n ($n=0.71$) for F50 (HPMC K100M and P8000 combination) suggested anomalous or complex behavior. Although the mechanism of water uptake in matrices composed of HPMC has been widely described [42, 96], the addition of P8000 as an adjuvant clearly resulted in a change in the properties of the matrix and its behavior when interacting with water. Upon contact with water, the percentage of nongelated residual cores in the HPMC tablets decreased with time, and the use of P6000 as a soluble filler increased the percentage [88].

Swelling and Erosion Through *In Vitro* Drug Release and Microscopic Studies

To demonstrate the robustness of the screening experimental design, four different formulations (F29, F38, F54, and F61) with significantly different swelling profiles were selected for *in vitro* dissolution profiling. To visually assess swelling/erosion behavior, the tablets were immersed in 10 mL of blue solution, and images were captured and processed over time with a digital microscope (DVM6, Leica Microsystems, Wetzlar, Germany). Figure 5 shows the swelling profiles (Fig. 5a), the respective dissolution profiles (Fig. 5b), and a plot of swelling *versus* dissolution up to 240 min (Fig. 5c). The captured images for four of the formulations under investigation are depicted in Fig. 6. It should be noted that these data correspond to independent tests, each of which (dissolution, swelling, and microscopy) was carried out individually. The PVA-80 formulation (F38) exhibited the lowest swelling rate and the fastest drug release. As illustrated in Fig. 6, the erosion front is clearly visible in the PVA-80-based formulation, showing a rapid reduction in tablet size. This phenomenon may be attributed to the suboptimal percolation threshold of PVA-80, as previously hypothesized (see [Swelling and erosion performance](#) section). A low amount (up to 30%) of polymer in the matrix favored surface erosion and, therefore, water penetration and drug

Fig. 5 Swelling profile (a), drug release profile (b) and plot of swelling *versus* drug release for up to 240 min (c) for F29, F38, F54 and F61



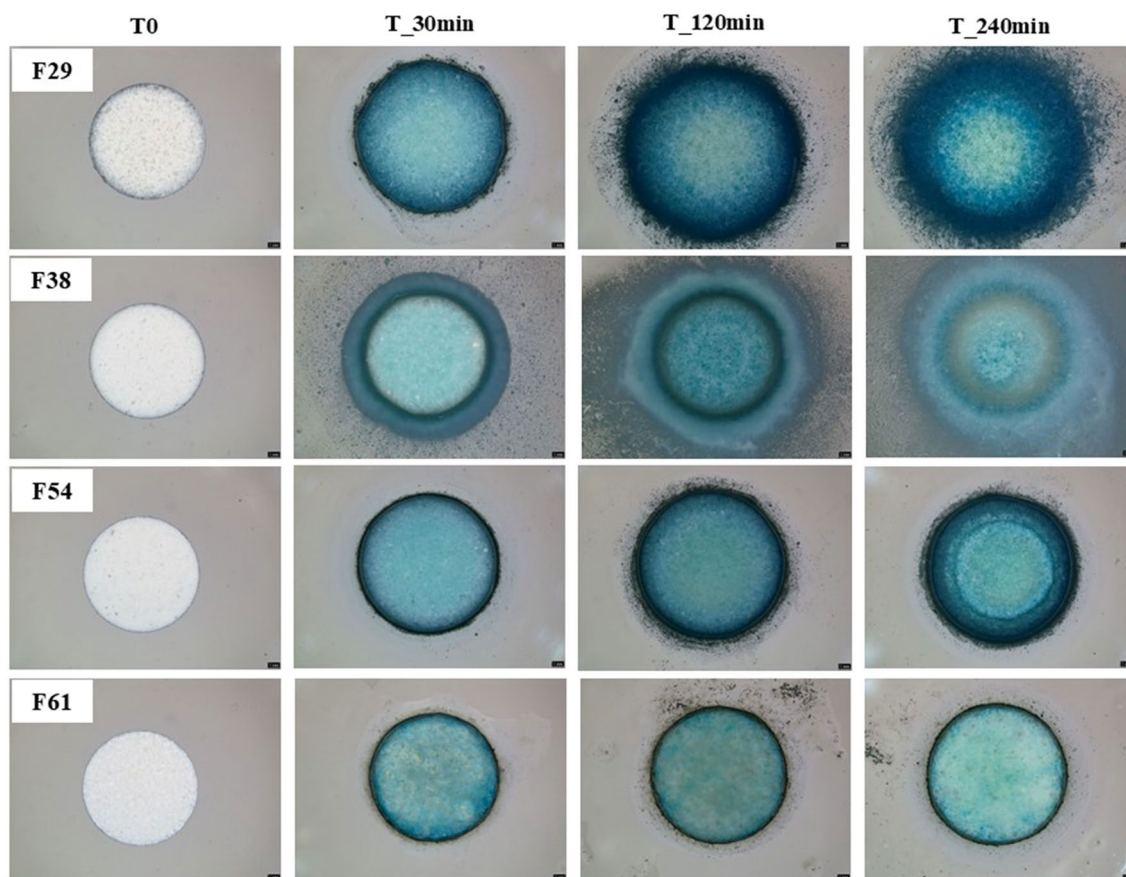


Fig. 6 Microscope image sequence of swollen tablets after 30, 120 and 240 min in water for F29, F38, F54 and F61

diffusion. The drug release rate from the PEO (F29) matrix tablet was faster than that from the HPMC (F54) and CAR-71G (F61) tablets. The *in vitro* dissolution plot and microscopy images provide further corroboration of these findings, indicating that the drug release rate is similar for both the PEO and HPMC matrices for up to 4 h (dashed gray line). Following this period, F29 was observed to be remarkably faster. The mechanical stress applied during the dissolution method enhanced water penetration into the PEO matrix, decreasing the gel strength [78]. Moreover, the HPMC gel layer is more resistant than PEO, as the HPMC matrix system contains more hydrophobic substituents, reducing water penetration and leading to a slower hydration rate and constant drug release [97]. A plot was constructed for the hydrophilic matrices whose main release mechanism was diffusion and swelling (PEO, HPMC, and CAR-71G), comprising the percentage of swelling *versus* dissolution for up to 240 min. A degree of correlation was observed ($R^2=0.872$). While the research article does not primarily address drug release and the correlation analysis was conducted with only three time points, which should be interpreted with caution, the preliminary findings are promising and highlight the potential for future research. The results presented here are specific to mirabegron; however,

future work should be developed to transpose this screening tool to support the early development of other molecules with different properties.

Conclusion

This study highlights the effectiveness of a screening methodology for developing mirabegron ER matrix tablet formulations. By employing a QbD approach, we investigated the impact of polymer type, diluent type, and polymer amount on tablet swelling and erosion using a full factorial design with 72 runs. Hydration and erosion studies by gravimetric analysis were used as exploratory but reliable methods to quickly assess matrix tablet behavior early in drug product development. With a reduced amount of drug substance, it was possible to test a large number of variables. Results showed that swelling increased with higher molecular weight and polymer amount, with HPMC- and PEO-based formulations exhibiting notable swelling rates and gel layer formation. Notably, the present study revealed that PVA-80 had the highest degree of erosion, followed by immediate tablet surface erosion, revealing the synchronization of the movement of swelling and erosion fronts.

Highly crosslinked CAR-71G differs structurally from formulations whose predominant mechanism is swelling. It is important to acknowledge that CPPs were not the focus of this research. A solid knowledge of the physicochemical properties of polymers, as well as a study of the formulation as a whole rather than simply the polymer, are elements that must be considered. The swelling and erosion studies could benefit from additional time points or the combination of multiple analytical methodologies to obtain further insights into the dynamics of the matrix tablet. This study supports a QbD approach in early pharmaceutical formulation development, advancing our understanding of mirabegron release mechanisms and emphasizing the value of exploring swelling and erosion behaviors. By utilizing mirabegron as a model drug, we streamlined the investigation of interactions between the drug substance and excipients typically presented in ER formulations (diluent and matrix formers). This strategy paves the way for the importance of screening exploratory designs as reliable, cost-effective, time-saving, and resource-efficient approaches. The findings herein provide an initial framework for understanding polymer-diluent interactions in ER matrices. This study thus establishes a foundation for future research exploring diverse API-polymer dynamics, with the objective of further supporting ER formulation development. Future research should be conducted not only to extend and validate these insights by exploring a broader range of drug substances and polymers, but also to transpose and apply this knowledge to later stages of formulation development.

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Data Availability Data will be made available on request.

Declarations

Conflict of Interest The authors declare no conflicts of interest.

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