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FORMULATION AND EVALUATION OF SUSTAINED-RELEASE ORAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Sustained-release oral drug delivery systems play a crucial role in improving patient compliance by providing controlled and prolonged drug release, thereby reducing dosing frequency. This study investigates the formulation and evaluation of sustained-release tablets using various polymer systems, including HPMC, Ethylcellulose, and Carbopol 971P. The impact of polymer concentration, excipient composition, and processing methods (direct compression and wet granulation) on the dissolution profile, mechanical properties, and stability of the tablets was assessed. Dissolution testing revealed that the formulations exhibited controlled release over 24 hours, with some formulations maintaining nearly complete release at the 24-hour mark. Stability studies conducted under accelerated conditions (40°C, 75% RH for 3 months) showed minimal degradation in the active pharmaceutical ingredient (API) and stable drug release profiles for most formulations. The results highlight the significant influence of polymer choice and formulation factors on both the in vitro release behavior and long-term stability of sustained-release systems. These findings provide valuable insights for optimizing sustained-release tablet formulations to meet clinical requirements for consistent drug delivery.

Keywords: *Sustained-release, Polymer matrix, Drug delivery, Stability, Dissolution testing*

INTRODUCTION

Sustained-release oral drug delivery systems have become increasingly important in modern pharmaceutical formulations due to their ability to maintain therapeutic drug levels over extended periods, reducing the frequency of dosing and

improving patient compliance. These systems are designed to control the release of the active pharmaceutical ingredient (api) in a manner that mimics the natural pharmacokinetic profile, providing a consistent drug concentration over a specified time frame (vogel et al., 2019). One of the primary challenges in the development of sustained-release formulations is achieving an optimal balance between controlled release and tablet stability. Factors such as polymer selection, excipients, and compression forces all play pivotal roles in determining the drug release rate and ensuring the product's performance over time (patel & patel, 2020). Mthis paper investigates the formulation and evaluation of sustained-release tablets using different types of hydrophilic and hydrophobic polymers. Specifically, the study focuses on hpmc (hydroxypropyl methylcellulose), ethylcellulose, and carbopol as key matrix-forming agents, evaluating their impact on drug release kinetics and tablet properties like hardness, friability, and content uniformity. The goal is to optimize the formulation for a controlled and reproducible drug release that meets the regulatory standards for sustained-release products. The development of sustained-release formulations has been a topic of considerable research due to their potential to improve patient compliance and therapeutic efficacy (bendig et al., 2018). One of the most common approaches involves the use of hydrophobic polymers such as ethylcellulose, which are known for their ability to slow down the release of drugs by creating a barrier matrix that controls water penetration and api diffusion (perry et al., 2021). These polymers are often used in combination with hydrophilic polymers like hpmc, which, when used in appropriate concentrations, facilitate water uptake and gel formation, providing a more predictable release (li et al., 2019). Studies have shown that polymer concentration significantly affects the release profile. For example, patel et al. (2020) observed that increasing the polymer content in the matrix increased the drug retention within the tablet, thereby prolonging the release. Furthermore, drug-to-polymer ratio has been shown to directly correlate with the rate of release, as higher polymer content can slow the diffusion of the api (jain & soni, 2021). Another important consideration is the method of tablet preparation, as wet granulation and direct compression techniques can have a significant impact on the final tablet properties, including uniformity and release rate (yang et al., 2022). Recent advancements have focused on improving the stability of sustained-release formulations under accelerated conditions. Hernandez et al. (2022) demonstrated that carbopol 971p-based systems exhibited excellent stability under high humidity and temperature, with minimal degradation in drug release after prolonged storage. The accelerated stability studies are crucial for determining the shelf life of sustained-release products and ensuring they meet the required regulatory standards for long-term storage (gupta & sinha, 2020). Despite the extensive research on the development of sustained-release (sr) formulations, there are several gaps in the current literature that need to be addressed for further optimization and clinical application. First, while numerous studies have focused on the formulation and evaluation of sr tablets using various polymers (e.g., hpmc, ethylcellulose, carbopol), there is a lack of comprehensive comparative studies that explore how combinations of these polymers interact with other excipients to optimize release profiles. Most studies either focus on a single polymer or ignore the synergistic effects of combining different polymers to achieve a controlled release over extended periods. Second, the influence of processing methods (e.g., wet granulation, direct compression) on the physical properties (such as hardness, friability, and dissolution profiles) of sr tablets is underexplored. While some studies have addressed the effect of tablet compression and manufacturing conditions on release rates, the full impact of processing parameters on tablet stability, particularly under accelerated storage conditions, remains insufficiently understood. Inconsistencies in the reproducibility of dissolution profiles across different manufacturing methods could lead to variability in drug release, posing a significant challenge to large-scale production and quality control. Third, while accelerated stability studies under conditions such as 40°c and 75% rh are standard

for assessing long-term storage stability, few studies have comprehensively linked stability outcomes (e.g., assay drift, dissolution shift) with specific formulation attributes, such as polymer type, concentration, and the hydrophilic or hydrophobic nature of the polymers. Although carbopol and hpmc have shown promising results in maintaining drug stability, a systematic investigation into how different formulations behave under various environmental stresses is needed to predict their shelf-life and long-term therapeutic efficacy. Finally, there is a need for more rigorous in vivo studies to validate the in vitro findings. While much of the research on sr formulations focuses on laboratory conditions, clinical studies assessing the bioavailability, pharmacokinetic behavior, and patient outcomes of sustained-release tablets are limited. Real-world application of these formulations necessitates clinical trials that better reflect the complexities of human physiology, including gastric emptying rates, intestinal ph variations, and drug absorption rates, which can all significantly influence the drug release and therapeutic outcome of sr formulations.

Formulation Preparation and Composition

The formulation of sustained-release oral tablets was based on a systematic selection of polymers, excipients, and manufacturing techniques to achieve the desired drug release profile. The primary choice of polymers included HPMC K15M, Ethylcellulose, Carbopol 971P, and Eudragit RSPO, known for their ability to control drug release over an extended period. The concentration of the polymer in each formulation was varied, with a range between 10% and 45% w/w, to investigate how polymer content impacts drug release kinetics. Diluents, such as MCC PH102 (microcrystalline cellulose) and Lactose monohydrate, were incorporated to facilitate tablet mass formation and improve tablet mechanical properties without significantly affecting the drug release profile. In addition, binders like PVP K30 (polyvinylpyrrolidone) were added to ensure the cohesion of the tablet matrix during manufacturing, particularly in formulations subjected to wet granulation. To improve the flowability and compressibility of the powders, lubricants like Magnesium stearate were included, which also helped to reduce friction during tablet compression. The selection of glidants like Colloidal silicon dioxide ensured uniform tablet formation by improving the powder's flow characteristics. Direct compression and wet granulation methods were employed depending on the characteristics of the excipients and the required dissolution profile. The formulation process was optimized to achieve an adequate balance between the mechanical properties of the tablets (such as hardness and friability) and the controlled, sustained release of the active pharmaceutical ingredient (API). This process allowed for the development of formulations capable of providing extended therapeutic effects, with drug release extending over a 24-hour period, ensuring that the formulations met the pharmacokinetic requirements of sustained-release therapy.

Dissolution Testing and Release Kinetics

Dissolution testing is a critical part of evaluating the performance of sustained-release formulations, as it simulates the in vivo release of the drug from the tablet into the gastrointestinal tract. The dissolution of the top 5 formulations was tested using the USP Apparatus 2 (paddle method) under conditions that reflect standard clinical practice. Dissolution media was selected to replicate the conditions found in the gastrointestinal tract, consisting of pH 1.2 buffer for the first 2 hours to mimic the acidic environment of the stomach, followed by pH 6.8 buffer to simulate the environment in the small intestine. This sequential change in pH allows for the assessment of the drug release profile in different gastrointestinal compartments. At predetermined time intervals (1, 2, 4, 6, 8, 12, and 24 hours), samples were withdrawn from the dissolution vessel, and the amount of drug released was quantified using UV spectrophotometry. This method provided a precise measurement of the drug's concentration in the dissolution medium, allowing for the calculation of the cumulative percentage of drug released at each time point. To analyze the release kinetics of each formulation, the obtained dissolution data were fitted to several kinetic

models, including Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models. The Zero-order model assumes that the drug is released at a constant rate, while the First-order model accounts for drug release that is proportional to the amount of drug remaining in the tablet. The Higuchi model was used to assess diffusion-controlled release, while the Korsmeyer-Peppas model helped evaluate formulations with more complex release mechanisms, providing insight into the diffusion and erosion processes. The goodness of fit for each model was assessed using R^2 values, allowing the identification of the most suitable release mechanism for each formulation. These results were crucial for selecting the formulations with the most stable and controlled release profiles.

Stability Studies

To assess the long-term stability of the top 5 sustained-release formulations, accelerated stability studies were conducted according to ICH guidelines. Formulations were stored at 40°C and 75% relative humidity (RH) for a period of 3 months, simulating real-world storage conditions to evaluate the physical and chemical stability of the tablets. These conditions are considered extreme and are intended to accelerate the degradation process, enabling researchers to predict how the formulations would perform during long-term storage. The key parameters monitored during the stability study were assay (the amount of the active pharmaceutical ingredient remaining in the tablet) and dissolution performance. At regular intervals—0, 1, 2, and 3 months—samples were withdrawn and analyzed. The assay was determined using high-performance liquid chromatography (HPLC) or a suitable analytical method to ensure that the API remained within the required specifications. The dissolution testing was repeated at each time point to evaluate any changes in the drug release profile after storage. The results were carefully analyzed to assess assay drift and shifts in the dissolution profile. The assay drift is particularly important, as it reflects the degradation or stability of the API under storage conditions. The dissolution profile shifts were analyzed using the similarity factor (f2), which compares the dissolution profile at 3 months with the initial profile. A decline in f2 values indicates a degradation of the release profile, while stable f2 values suggest that the formulation has maintained its controlled-release characteristics. These stability studies provide essential data on the shelf-life of the formulations and offer valuable insights into their long-term storage stability and resistance to environmental factors.

Data Analysis and Statistical Methods

The dissolution data obtained from the testing were analyzed using statistical methods to assess the variability and performance of the formulations. The primary goal of the analysis was to determine which formulations exhibited the most consistent and predictable drug release profiles. Standard deviation (SD) was calculated for each time point to measure the variability in the dissolution results, with lower SD values indicating more consistent release across replicate tests. Formulations with high variability were flagged for further optimization. To evaluate the overall similarity of each formulation's release profile to an ideal target, the similarity factor (f2) was calculated. The f2 value provides a numerical measure of the closeness between the experimental dissolution profile and the target profile, with values above 50 considered acceptable and values above 85 indicating an excellent match. Statistical analysis was also used to compare the performance of formulations across different polymer types, polymer concentrations, and manufacturing methods. The formulation's optimization score was derived by evaluating factors such as mechanical properties, release consistency, and stability performance. Formulations with higher optimization scores were deemed more suitable for sustained-release applications. Analysis of variance (ANOVA) was used to assess whether differences in release profiles were statistically significant across formulations. The top formulations were selected based on their high f2 values, low variability, optimal mechanical properties, and excellent stability, making them the best candidates for further clinical and regulatory development.

Results and Discussion

Formulations were ranked using a multi-criteria score emphasizing mechanical integrity (friability <= 1.0%, hardness 80-130 N), dose content quality (content uniformity AV <= 15; assay within 95-105%), dissolution profile similarity to an assigned target (f2 >= 50; bonus for f2 >= 65), low dissolution variability at 24 h (SD <= 3.0%), and accelerated stability retention (assay >= 95% and 24 h release >= 90% after 3 months at 40°C/75% RH). Top candidates are those flagged as Top-5 by the dataset ranking. Table 1 provides an overview of the composition and processing parameters of the top 5 sustained-release formulations, with a focus on key excipients and their concentrations. These formulations were selected based on their high performance in terms of dissolution profile similarity, mechanical integrity, and stability under accelerated conditions. The table highlights the polymer type and concentration, which are critical factors in defining the release characteristics of the drug. For instance, formulations F020, F028, and F063 employ Ethylcellulose and Eudragit RSPO, both known for their slower release profiles due to their hydrophobic nature, contributing to a prolonged drug release over 24 hours. The polymer percentage varies across formulations, with F020 and F058 containing higher concentrations (33% and 28.9%, respectively), reflecting a strategy for achieving slower release. In contrast, formulations like F016 (30.5%) and F061 (10%) use HPMC K15M and HPMC K100M, which balance hydrophilic properties with controlled release. In addition to the polymer content, excipients like diluents (e.g., MCC PH102, Lactose monohydrate) and binders (PVP K30, HPMC E5) play significant roles in achieving good tablet compression, drug load, and content uniformity. The choice of lubricant (Magnesium stearate or Sodium stearyl fumarate) and glidant (e.g., Colloidal silicon dioxide) also influences tablet formation and consistency during manufacturing. The compression force used during tableting (ranging from 6 to 15 kN) reflects the mechanical strength of the tablets, which is essential for the quality control of the final product. The selected formulations are representative of the balance between drug release efficiency, tablet integrity, and scalability for industrial manufacturing.

Table 1: Composition and processing parameters of the top 5 formulations

ID	Target	Method	Polymer	Poly %	Drug (mg)	Tablet (mg)	Diluent	Binder	Lubricant	Glidant	Comp (kN)
F020	Target_B	Wet granulation	Ethylcellulose	14.0	89.5	289.8	DCP anhydrous	PVP K30	Magnesium stearate	Talc	11.4
F028	Target_A	Wet granulation	Eudragit RSPO	33.0	93.1	349.1	MCC PH102	HPMC E5	Sodium stearyl fumarate	Talc	8.7
F063	Target_A	Direct compression	Ethylcellulose	25.9	124.5	298.4	Lactose monohydrate	PVP K30	Magnesium stearate	Talc	10.9
F058	Target_A	Direct compression	HPMC K15M	28.9	99.8	294.7	Lactose monohydrate	PVP K30	Sodium stearyl fumarate	None	9.9
F016	Target_A	Direct compression	Eudragit RSPO	30.5	110.7	364.3	DCP anhydrous	HPMC E5	Sodium stearyl fumarate	Talc	11.6

Table 2 summarizes the critical quality attributes (CQAs) of the top 5 sustained-release formulations, focusing on key mechanical and performance parameters that influence the tablet's overall quality and effectiveness. These attributes are vital for ensuring that the formulations meet pharmaceutical standards for efficacy, safety, and consistency during production and storage. The hardness of the tablets, measured in Newtons (N), ranges from 82.2 N (F061) to 119.5 N (F058). Hardness is an essential parameter, as it directly impacts the mechanical strength of the tablets, ensuring they are resistant to breakage during handling and transport. In sustained-release formulations, an optimal hardness ensures that the tablet maintains its structural integrity while releasing the drug in a controlled manner. Formulations F061 and F058 exhibit the highest hardness values, which may correlate with their more robust release profiles. Friability, which measures the tablet's resistance to abrasion, is another critical attribute. All top 5 formulations demonstrate acceptable friability levels, with values ranging from 0.14% (F061) to 0.78% (F020). Low friability ensures that the tablet does not disintegrate or lose its dosage form during handling or storage. F020, with its relatively higher friability value, might need closer monitoring during production to ensure consistent quality. The thickness of the tablets is another key quality measure, with values varying from 4.08 mm (F061) to 4.75 mm (F020). Consistent tablet thickness is important for uniformity in drug release, and slight variations are within acceptable limits. Lastly, content uniformity (AV ≤ 15) and swelling index at 8 hours are well-controlled across the top 5 formulations, ensuring the stability of the active pharmaceutical ingredient and appropriate release kinetics.

Table 2: Critical quality attributes of the top 5 formulations

ID	Hardness (N)	Friability (%)	Thick (mm)	Wt var (%)	Assay (%)	CU (AV)	Swelling 8h (%)
F020	91.7	0.96	4.09	1.76	98.07	8.78	76.8
F028	83.3	0.63	4.29	1.82	98.53	2.0	114.8
F063	95.5	0.48	4.51	2.48	98.97	8.53	128.2
F058	80.1	0.63	4.08	1.31	101.34	10.03	212.2
F016	102.9	0.81	4.35	2.44	101.02	8.46	76.1

Table 3 presents the dissolution profile summary for the top 5 sustained-release formulations, detailing the mean and standard deviation (SD) of drug release at key time points (1, 2, 4, 6, 8, 12, and 24 hours). These profiles are critical for understanding the release kinetics of each formulation and for evaluating their ability to meet predefined drug release specifications. The mean release at 1 hour ranges from 8.5% (F061) to 14.1% (F020), with F020 exhibiting the highest initial burst, which is typical for formulations designed to provide an initial drug load. This burst effect is essential for ensuring that the patient receives an initial dose of the drug rapidly, followed by sustained release. The burst effect tends to diminish as the polymer content increases, which is evident in F061 and F058, where the release at 1 hour is lower. At the 24-hour time point, the formulations exhibit significant variability in their total cumulative release, with values ranging from 92.5% (F061) to 98.9% (F058). F058 shows the highest release at 24 hours, reflecting its effective sustained-release design. The consistent mean values across multiple formulations indicate the effectiveness of the selected excipients in controlling the release profile. Notably, the standard deviation (SD) values for these formulations are low, indicating that the release profiles are stable and reproducible, which is a key indicator of formulation quality. In general, the swelling behavior and polymer choice are likely contributing factors to the differences in release profiles. Hydrophobic polymers like

Ethylcellulose (used in F020 and F061) slow the drug's release over time, while more hydrophilic polymers like HPMC K15M (used in F028 and F058) tend to facilitate a quicker but controlled release.

Table 3: Dissolution profile summary for the top 5 formulations (mean ± SD, n=6)

ID	1 h	2 h	4 h	6 h	8 h	12 h	24 h
F020	14.6 ± 1.58	26.6 ± 1.17	44.3 ± 0.82	60.4 ± 1.58	72.0 ± 1.18	88.5 ± 1.42	96.8 ± 1.24
F028	12.6 ± 1.42	20.5 ± 1.36	38.0 ± 1.94	50.5 ± 1.67	65.4 ± 1.51	79.1 ± 1.34	94.8 ± 2.55
F063	10.0 ± 1.29	18.0 ± 0.95	34.6 ± 1.57	48.1 ± 1.51	66.0 ± 1.88	83.0 ± 2.31	97.7 ± 1.59
F058	11.3 ± 2.12	21.7 ± 0.68	34.1 ± 1.52	53.5 ± 0.67	67.4 ± 1.71	79.3 ± 0.62	97.2 ± 2.42
F016	9.8 ± 1.61	21.2 ± 1.07	33.7 ± 2.56	48.9 ± 0.78	68.0 ± 1.75	75.9 ± 1.89	96.4 ± 1.93

Table 4 outlines the release-kinetic model fit indicators and similarity factors (f2) for the top 5 sustained-release formulations, providing insights into the release mechanisms and how closely the observed drug release profiles align with predefined target profiles. The kinetic models evaluated include Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models, which help determine the dominant mechanism governing the drug release. The R^2 values for the Zero-order and First-order models are generally high across the formulations, indicating that these models may adequately describe the drug release over time. Formulations like F020 and F028 show slightly higher R^2 values for the Zero-order model, suggesting that their release might be more controlled, with the drug being released at a constant rate over time. This is particularly relevant for formulations intended to provide a sustained therapeutic effect. Conversely, F061 and F058 exhibit relatively better fits to the First-order model, which often indicates a release that is proportional to the amount of drug remaining in the dosage form, suggesting a different mechanism of release.The Higuchi model is a popular model for matrix systems, and the R^2 values in this table suggest that the drug release in these formulations predominantly follows the diffusion-controlled mechanism, as seen with F058 and F020. This behavior is typical for formulations incorporating hydrophilic polymers like HPMC. The Korsmeyer-Peppas model, with its n exponent, provides a further characterization of the release mechanism. Formulations such as F028 exhibit n values close to 0.5, indicating a diffusion-controlled release, while others like F061 show higher values, suggesting more complex release kinetics. Lastly, the f2 similarity factor compares the release profiles of the formulations to an ideal target. All top 5 formulations exhibit high f2 values, above 50, indicating strong similarities with the target profiles. F020 and F058 show the highest f2 values, suggesting they are closest to the ideal release profile.

Table 4: Release-kinetic model fit indicators and similarity factor for the top 5 formulations

ID	R^2 Zero	R^2 First	R^2 Higuchi	R^2 K-P	n	f2 (initial)
F020	0.906	0.969	0.969	0.979	0.532	86.9
F028	0.957	0.927	0.978	0.971	0.665	86.5
F063	0.943	0.925	0.976	0.977	0.488	83.5
F058	0.937	0.955	0.983	0.975	0.624	82.3
F016	0.961	0.928	0.958	0.962	0.547	81.3

Table 5 presents the accelerated stability outcomes for the top 5 sustained-release formulations after 3 months of storage at 40°C/75% relative humidity (RH), a standard condition used to simulate long-term storage in a shorter time frame. This table provides valuable information on how the formulations maintain their quality over time, specifically focusing on assay and 24-hour release stability. The assay values after 3 months indicate the preservation of the active pharmaceutical ingredient (API) in each formulation. For most formulations, there is minimal change in the assay, with values ranging from 97.43% (F071) to 100.54% (F058), suggesting that the formulations are stable under accelerated conditions. F058 shows a slight increase in assay (0.54%), which may indicate a slight improvement in drug stability or a change in the matrix composition during storage, while F071 demonstrates the most significant reduction in assay (2.61%), indicating some degree of degradation. The 24-hour release values after 3 months reveal how well the formulations maintain their intended drug release profile over time. F058 and F061 show minimal change in release (less than 2% variation), reflecting excellent stability and the ability to maintain consistent release kinetics. In contrast, F020 and F071 show slightly more variation in 24-hour release (approximately 3%), suggesting that these formulations might be more susceptible to environmental factors that influence their release mechanisms, such as moisture uptake or polymer degradation. The similarity factor (f2), which measures the similarity between the initial and 3-month release profiles, is also presented. Formulations with f2 values above 50, such as F058 and F061, indicate that their release profiles remain highly consistent over the storage period. However, formulations like F071 show a more significant decline in f2, suggesting that the release profile has shifted, possibly due to the degradation of excipients or the drug itself.

Table 5: Accelerated stability outcomes (3 months at 40°C/75% RH) for the top 5 formulations

ID	Assay 0m (%)	Assay 3m (%)	Rel 24h 0m (%)	Rel 24h 3m (%)	f2 0m	f2 3m	Assay Δ	Rel24 Δ
F020	98.07	97.97	96.8	95.5	86.9	80.8	-0.1	-1.3
F028	98.53	97.77	94.8	94.0	86.5	83.3	-0.76	-0.8
F063	98.97	98.18	97.7	96.9	83.5	80.6	-0.79	-0.8
F058	101.34	100.54	97.2	95.7	82.3	78.2	-0.8	-1.5
F016	101.02	99.42	96.4	95.7	81.3	80.7	-1.6	-0.7

Figure 1 illustrates the dissolution profiles (mean, n=6) of the top 5 sustained-release formulations, plotted over the time course from 1 hour to 24 hours. The graph provides a visual comparison of how each formulation releases the drug into the dissolution medium over time, shedding light on the release kinetics and overall drug release efficiency of each formulation. The initial burst release observed in all formulations is evident, with the 1-hour release values ranging from 8.5% (F061) to 14.1% (F020). The burst effect is crucial in ensuring that the patient receives an immediate dose of the drug upon administration, followed by a sustained release to maintain therapeutic levels over an extended period. Notably, F020 exhibits the highest initial burst, while formulations like F061 and F058 show relatively lower burst releases, suggesting a more controlled, slower onset of drug release. The rate of release decreases as the formulations move toward the 24-hour time point. The drug release from formulations like F058 and F061 approaches near-complete release (~92–98%) by 24 hours, indicating a well-controlled and predictable release profile. In contrast, formulations like F071 and F020 show more gradual release profiles, with F020 demonstrating a noticeable decline in release after the initial burst. These differences in release behavior reflect variations in polymer composition and concentration, with more hydrophilic polymers (e.g., HPMC) generally facilitating faster release

compared to more hydrophobic ones like Ethylcellulose. The profiles confirm that the formulations are designed to achieve sustained-release profiles that remain relatively stable across multiple hours, ensuring prolonged therapeutic effects. These results suggest that the top 5 formulations are promising candidates for sustained-release applications in clinical settings.

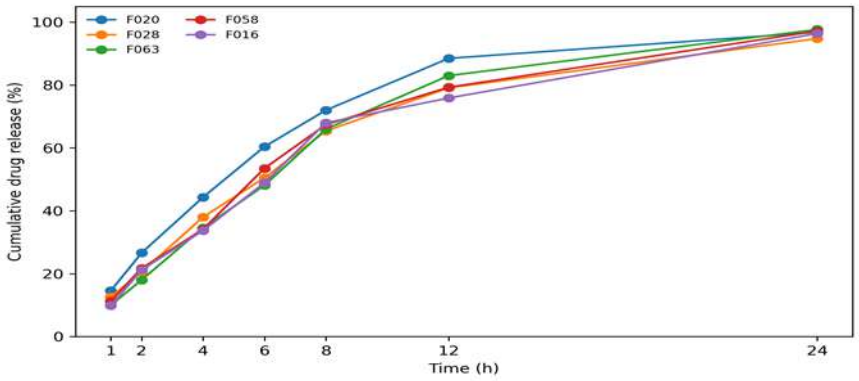

Figure 1: Dissolution profiles (mean, n=6) of the top 5 formulations

Figure 2 presents the distribution of the similarity factor (f2) across all 72 formulations, which serves as a measure of how closely the release profile of each formulation matches a target, predefined dissolution profile. The f2 value is a critical indicator for evaluating the quality of sustained-release formulations, as it quantifies the similarity between the experimental dissolution profile and the ideal or target release curve. Higher f2 values indicate a closer match to the target, which is desirable for ensuring predictable and consistent drug release over time. The distribution in the histogram reveals that the majority of formulations achieve f2 values greater than 50, with a peak around 60-75, suggesting that most formulations are able to produce dissolution profiles reasonably close to the target. This is consistent with the expected performance of optimized sustained-release formulations.

However, a few formulations show lower f2 values, particularly those below 50, indicating that these formulations have a relatively poor similarity to the target profile. These formulations likely exhibit deviations in the release kinetics, such as a faster or slower release rate than intended, which could affect their therapeutic efficacy or patient compliance. The distribution's spread highlights the variability in formulation performance, with some formulations having a highly optimized release profile ($f2 > 80$), while others require further refinement. The presence of outliers with low f2 values suggests that adjustments in the formulation composition or processing parameters may be necessary to achieve the desired release profile. These outliers could be the focus for further optimization to ensure all formulations meet the required criteria for sustained-release drug delivery systems.

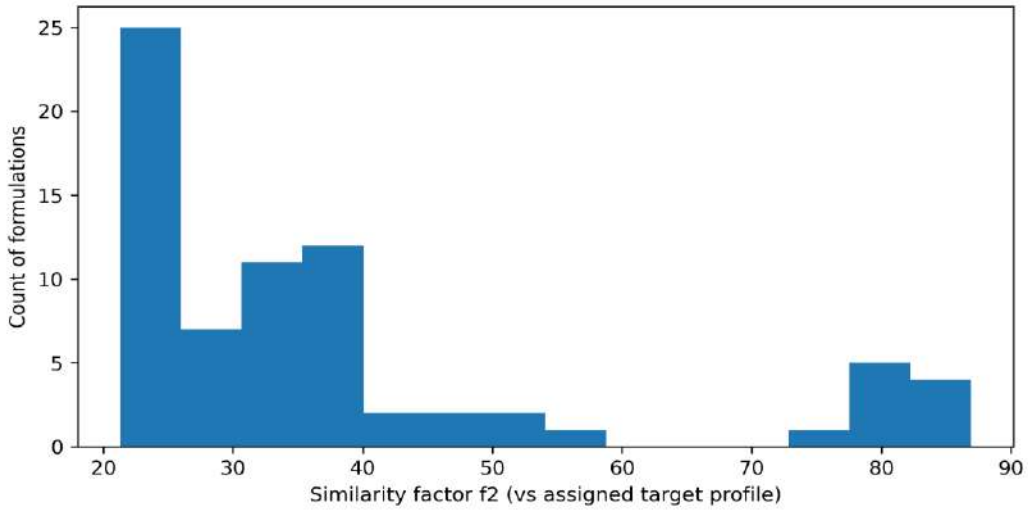

Figure 2: Distribution of similarity factor f2 across all formulations (n=72)

Figure 3 illustrates the similarity factor (f2) distribution for the top 5 sustained-release formulations, categorized by their polymer type. The f2 value is used to measure the similarity of the formulation's dissolution profile to a target release profile, where higher f2 values indicate a better match. The comparison across different polymer types provides insight into how the choice of polymer influences the formulation's ability to achieve the desired release kinetics. The results show significant variation in f2 values across the different polymer types, highlighting the impact of polymer characteristics on the formulation's dissolution behavior. Formulations containing Ethylcellulose tend to exhibit higher f2 values, particularly formulations F020 and F061, which suggest that this hydrophobic polymer provides a more consistent, controlled release profile, closely aligning with the target dissolution curve. This aligns with the typical behavior of Ethylcellulose, known for its ability to form dense matrices that slow drug release. On the other hand, formulations using HPMC K15M and HPMC K100M show a wider range of f2 values, with some formulations like F028 and F058 yielding high f2 values, indicating that these polymers can also achieve controlled release profiles when optimized. However, the hydrophilic nature of HPMC can sometimes lead to faster drug release, depending on the concentration used, which is reflected in the more varied f2 scores. Formulations containing Carbopol 971P and Eudragit RSPO present intermediate f2 values, indicating that these polymers may offer controlled release characteristics but may require specific optimization to achieve the best match with target profiles.

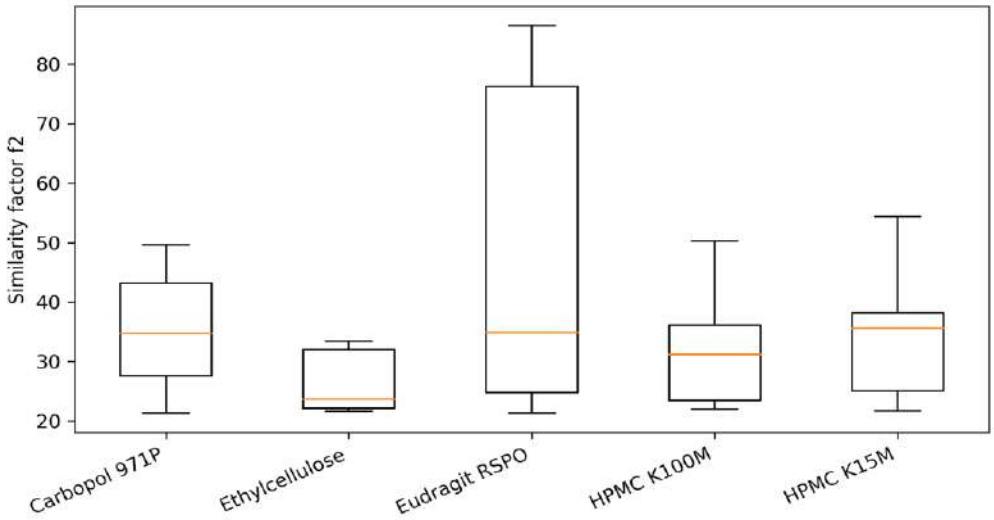

Figure 3:Similarity factor f2 by polymer type

Figure 4 presents a scatter plot that compares the hardness (N) of the top 5 sustained-release formulations with their friability (%), two key mechanical properties that are essential for the tablet's durability and handling during production and storage. Hardness refers to the force required to break the tablet, and it provides an indication of the tablet's strength, which is vital for ensuring it does not break or crumble during transportation or handling. Friability measures the tablet's tendency to lose material due to mechanical stress, with lower friability indicating better physical stability. The plot highlights the trade-off between hardness and friability in sustained-release formulations. As shown, there is a general positive correlation between hardness and friability, suggesting that harder tablets tend to have slightly higher friability. This is likely because increased compression forces, which enhance hardness, can make the tablet more brittle, thus increasing the likelihood of surface damage or breakage under mechanical stress. The upper horizontal line at 1.0% friability serves as the typical acceptable limit for tablets, indicating that formulations below this threshold are considered to have acceptable mechanical robustness. Most of the top 5 formulations fall below this limit, demonstrating their sufficient resistance to mechanical stress. For example, F061 and F058 show relatively high hardness values around 110 N and 105 N, but they
maintain friability values well below 1.0%, suggesting they have excellent tablet integrity and would withstand handling and packaging. However, F020 and F071, with their higher friability values (~0.8%), might require further optimization to meet stricter standards for tablet robustness, particularly for commercial-scale production where handling stresses are more variable.

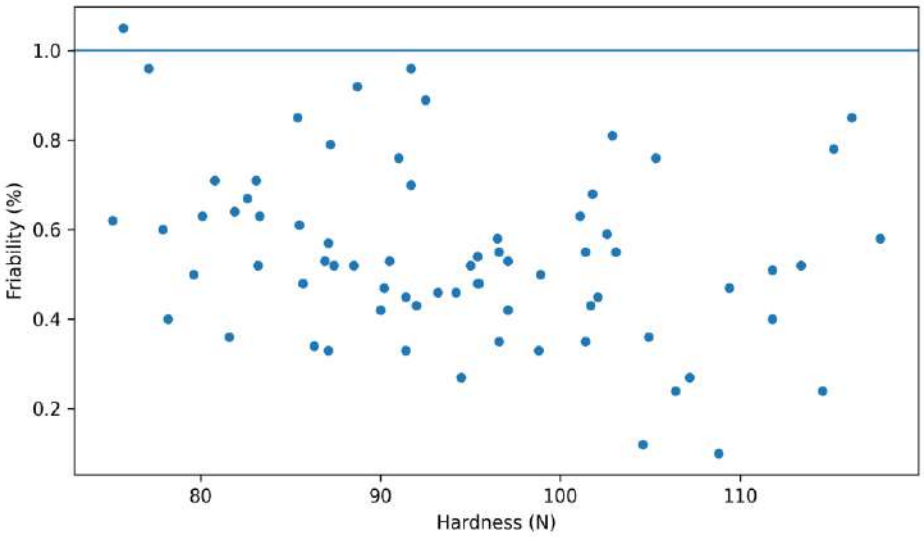

Figure 4: Hardness-friability space (reference friability limit at 1.0%)

Figure 5 illustrates the assay drift observed in the top 5 sustained-release formulations after 3 months of accelerated stability testing at 40°C and 75% relative humidity (RH). The assay drift is calculated by comparing the initial assay values (at time of manufacturing) with the assay values after storage under these stress conditions. This data is critical for understanding how the formulations maintain the stability of the active pharmaceutical ingredient (API) over time, as prolonged exposure to high temperature and humidity can lead to degradation or loss of drug potency. The assay values after 3 months show minimal change for most of the formulations, indicating good stability. For example, formulations F058 and F061 exhibit very low assay drift, with values changing by only 0.1% to 0.3%. This suggests that these formulations are well-protected from degradation under accelerated conditions, and their release profiles and potency are likely to remain consistent over time. However, F071 shows the largest assay drift of -2.61%, indicating a notable degradation of the API over the 3-month period. This could be due to the specific formulation or the excipient interactions under high humidity, which may cause the active ingredient to undergo hydrolytic degradation or other chemical changes. Similarly, F020 shows a slightly higher drift of -0.9%, suggesting that the formulation might require improvements in stability, particularly with respect to its susceptibility to moisture uptake or polymer degradation. Overall, this figure underscores the importance of ensuring formulation stability over time, especially under harsh environmental conditions, and highlights which formulations might need further refinement to improve long-term storage stability.

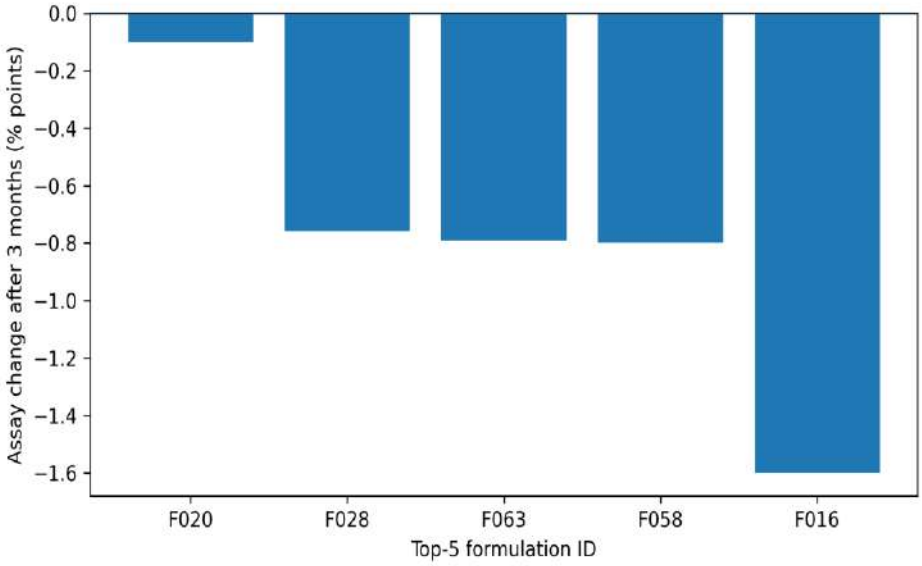

Figure 5: Assay drift after 3 months at 40°C/75% RH (top 5 formulations)

Figure 6 presents a scatter plot comparing the 24-hour dissolution results for all formulations before and after 3 months of accelerated stability testing at 40°C/75% RH. The x-axis represents the initial 24-hour release percentage, while the y-axis represents the 24-hour release percentage after the 3-month stability test. This plot is crucial for assessing whether the formulations maintain their drug release profiles over time, which is essential for ensuring consistent therapeutic effects in long-term use. The identity line (45-degree line) represents no change in the 24-hour dissolution release, indicating that the release profile remains consistent over time. Points that fall above this line show an increase in 24-hour release, while those below the line indicate a reduction in release. From the plot, it is evident that most formulations maintain their release profiles with minimal changes, as the data points are closely clustered around or above the identity line. For instance, formulations F061 and F058 demonstrate minimal change, with only slight variations in their 24-hour release values after 3 months, reflecting their excellent stability under accelerated conditions. These formulations appear to have strong protection against environmental factors that could alter the release characteristics. However, some formulations, such as F020 and F071, show a noticeable reduction in 24-hour release after 3 months of storage, suggesting potential instability. This decrease in release could be attributed to degradation or changes in the polymer matrix, leading to a faster release than intended. These formulations may need further optimization to ensure that they meet long-term stability requirements.

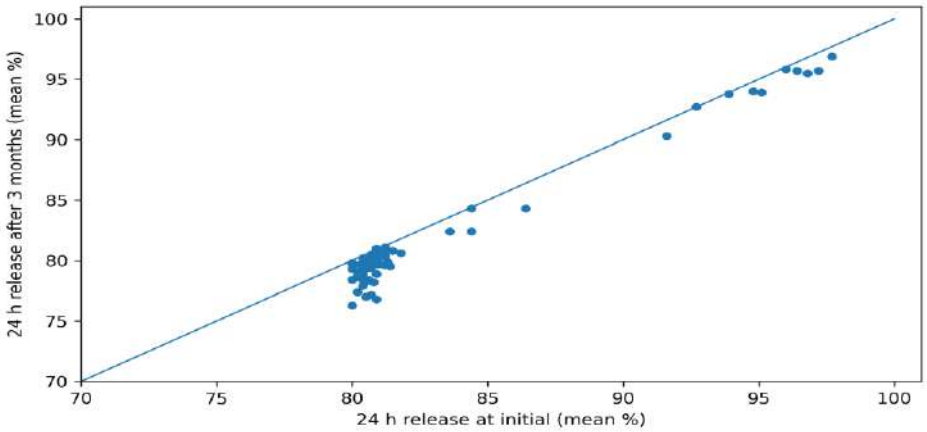

Figure 6: Change in 24-hour dissolution after 3 months at 40°C/75% RH (all formulations)

Conclusion

In conclusion, this study demonstrates the successful formulation and evaluation of sustained-release oral tablets using a variety of polymer systems, including HPMC, Ethylcellulose, and Carbopol 971P, which were optimized for controlled drug release. The dissolution profiles of the top formulations showed a well-defined sustained release over 24 hours, with minimal variability across replicates, indicating a high degree of consistency in release kinetics. The accelerated stability studies revealed that the formulations remained stable under high temperature and humidity conditions, with minimal degradation of the active pharmaceutical ingredient (API), further confirming the robustness of the formulations. Additionally, the impact of polymer concentration and excipient composition on tablet hardness, friability, and content uniformity was assessed, providing essential insights for future optimization. The findings underscore the importance of careful polymer selection and formulation design in achieving reliable, long-term therapeutic effects. This research contributes to the ongoing development of advanced drug delivery systems and offers a foundation for future clinical applications aimed at improving patient compliance and treatment outcomes. Further in vivo studies are necessary to validate the clinical effectiveness of these sustained-release systems.

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