RESEARCH ARTICLE

Development of an Optimized Budesonide Delivery System: A Controlled-Release Approach for Targeting the Colon

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Received: 30th Sep, 2024; Revised: 23rd Oct, 2024; Accepted: 11th Nov, 2024; Available Online: 25th Dec, 2024

ABSTRACT

This study focused on the development and optimization of a colon-targeted Budesonide tablet formulation designed for controlled release and targeted delivery to the colon. A combination of controlled-release polymers (Xanthan Gum and Hypromellose K4M) and coating polymers (Eudragit S100 and Eudragit L100) was utilized to achieve the desired drug release profile. A systematic approach using fractional and full factorial designs was employed to identify the key variables influencing drug release at specific time points. The formulation was optimized to ensure minimal premature release in the upper GIT and maximum release in the colon. In vitro dissolution studies revealed that the optimized formulation closely matched the reference-listed drug (RLD), with 18.07% release at 2 h, 42.63% at 4 h, 84.78% at 8h and 91.32% at 12 h. The similarity factor (f2) of 83 and difference factor (f1) of 3 confirmed the high level of similarity between the two formulations. The optimized formulation successfully delivered Budesonide in a controlled manner, providing a cost-effective and scalable solution for treating inflammatory bowel diseases.

Keywords: Colon-Targeted; Controlled Release; Polymers; Inflammatory Bowel Diseases; Enteric Coating,

How to cite this article: Prajapati B, Atara S. Development of an Optimized Budesonide Delivery System: A Controlled-Release Approach for Targeting the Colon. International Journal of Drug Delivery Technology. 2024;14(4):1971-80. doi: 10.25258/ijddt.14.4.5

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Inflammatory bowel diseases, which include ulcerative colitis, Crohn's disease, and irritable bowel syndrome (IBS), are chronic, progressive disorders that severely impact the eminence of life for millions of people worldwide.[1] The global prevalence of IBD has been rising steadily over the past few eras, particularly in industrialized nations. Recent estimates suggest that over 10 million people are currently affected by IBD globally, with approximately 3 million cases in Europe and 1.6 million in the United States alone.[2] In countries like India and China, where IBD was once rare, the incidence is also rapidly increasing, likely due to changes in diet, urbanization, and lifestyle.[3] The chronic nature of these diseases often leads to long-term complications, including an increased risk of colorectal cancer, with IBD patients being 2 to 5 times more likely to develop colon cancer than the general population.[4] In the Indian subcontinent alone, over 66,000 new cases of colon cancer are reported annually, making it one of the leading causes of cancer-related deaths in the region.[5] Therapeutic management of IBD typically involves the use of anti-inflammatory agents to control symptoms, reduce inflammation, and prevent disease progression.[6] Budesonide, a potent glucocorticoid, is one of the most commonly used drugs for managing moderate to severe cases of IBD, particularly ulcerative colitis and Crohn's disease. Its ability to suppress inflammation and modulate immune response makes it a valuable therapeutic agent.[7] However, like many IBD drugs, its efficacy is highly dependent on targeted delivery to the site of inflammation in the colon. Current commercial formulations of Budesonide often rely on extended-release or delayed-release systems to ensure the drug reaches the colon intact, avoiding premature absorption in the upper gastrointestinal tract. Despite their effectiveness, these formulations come with significant limitations. Most extended-release systems are based on complex multi-matrix technologies, which involve a combination of hydrophilic, lipophilic, and amphiphilic components. These formulations require specialized equipment and manufacturing processes, resulting in high production costs and variable batch-to-batch performance. Additionally, the complex nature of these systems makes scaling up for large-scale manufacturing challenging, limiting the availability of cost-effective treatments for patients, especially in low- and middle-income countries.[8] With IBD becoming more prevalent in regions with limited healthcare resources, the need for affordable and scalable treatment options has never been more critical. Budesonide, a potent anti-inflammatory corticosteroid, is highly effective in treating IBD, particularly ulcerative colitis and Crohn's disease. However, its therapeutic success largely depends on delivering the drug directly to the site of inflammation—namely, the colon. When Budesonide is released prematurely in the upper parts of GIT, such as the stomach or small intestine, several critical issues arise. First, systemic side effects increase due to greater systemic exposure, leading to complications such as adrenal suppression, osteoporosis, increased susceptibility to infections, and metabolic disturbances.[9-10]These systemic effects, which are minimized with localized colonic release, are undesirable and compromise

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Table 1: Composition of Budesonide Controlled-Release Tablet Formulations with Different Polymers

Raw material	A	B	C	D	E
Budesonide (mg)	9	9	9	9	9
Soya lecithin (mg)	10	10	10	10	10
Microcrystalline Cellulose (mg)	45	45	45	45	45
Lactose Monohydrate (mg)	135	135	135	135	135
Hydroxypropyl cellulose (mg)	….	….	90	….	….
Xanthan Gum (mg)	90	….	….	….	45
Carbopol (mg)	….	90	….	….	….
Hypromellose K4M (mg)	….	….	….	90	45
Aerosil (mg)	6	6	6	6	6
Mg. stearate (mg)	5	5	5	5	5
Core Weight (mg)	300	300	300	300	300

patient safety. Second, premature release leads to reduced efficacy, as the drug concentration in the colon may become insufficient to manage inflammation effectively, and the duration of action is shortened, undermining long-term therapeutic goals. Third, Budesonide's therapeutic effect is intended for the inflamed mucosa of the colon, and premature action in non-target areas results in wasted drug potential and under-treatment of colonic inflammation. Fourth, early absorption subjects Budesonide to significant first-pass metabolism, reducing the amount of active drug available at the target site, thereby diminishing its therapeutic impact.[11] To overcome these challenges, colon-targeted drug delivery systems ensure that Budesonide remains stable in the upper GIT and releases only in the colon, reducing systemic absorption, avoiding premature degradation, and maintaining high therapeutic efficacy.[12] By using specialized polymers like Xanthan gum and Hypromellose K4M, such formulations provide sustained release where it is most needed, minimizing side effects and optimizing treatment outcomes for patients with IBD. This targeted delivery approach not only enhances the drug's effectiveness but also offers a safer therapeutic option, particularly for long-term management of chronic inflammation in the colon. This study seeks to address these challenges by developing a novel, simplified CDDS for Budesonide using a combination of natural and synthetic polymers. The primary objective of this research is to create a formulation that achieves consistent, prolonged drug release in the colon while simplifying the manufacturing process to make it scalable and cost-effective. By employing systematic experimental designs, including screening and fractional factorial design, this study seeks to optimize the formulation to meet these goals. The present work outlines the development and optimization of a colon-targeted Budesonide tablet formulation, highlighting the benefits of using natural and synthetic polymers to create a stable, cost-effective, and scalable drug delivery system. The results will have significant implications for the treatment of IBD, providing a practical solution to the rising global burden of this disease.

MATERIALS AND METHODS

Materials

The active ingredient, Budesonide, was procured from M/s Aarti Industries Ltd. Polymers such as Xanthan gum and Hydroxypropyl cellulose were sourced from M/s CP Kelco and M/s Ashland Aqualon, respectively. Stearic acid was supplied by M/s Stearinerie Dubois FilsSA, and Lecithin (soya) was obtained from M/s Lipoid GmbH. Additionally, Microcrystalline cellulose and Lactose Monohydrate were procured from M/s Ming-Tai Chemical Co. Ltd. and M/s DMV-Fonterra Excipients, respectively. M/s Peter Greven supplied magnesium stearate, while Silica colloidal hydrated came from M/s Grace GmbH. For coating purposes, Methacrylic acid-methyl methacrylate copolymer (1:1 and 1:2) was sourced from M/s Evonic Rohm GmbH, and M/s Jungbunzlauer Ladenburg GmbH provided Triethyl citrate.

Methods

Screening of controlled-release polymer

The screening of controlled-release polymers involved the preparation of multiple tablet formulations containing

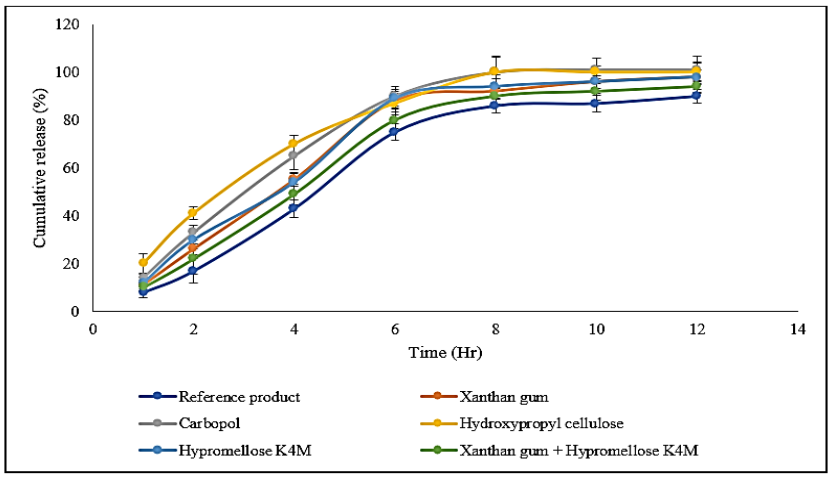

Figure 1: Dissolution Profiles of Budesonide Tablets Using Different Controlled-Release Polymers

Table 2: Details of trials as per fractional factorial design for the selection of independent variables

Std	Run	Block	Factor 1 A: Soya lecithin mg	Factor 2 B: Xanthan gum mg	Factor 3 C: Mg stearate mg	Factor 4 D: Hypromellose K4M mg
5	1	Block 1	-1.00	-1.00	1.00	1.00
1	2	Block 1	-1.00	-1.00	-1.00	-1.00
4	3	Block 1	1.00	1.00	-1.00	-1.00
8	4	Block 1	1.00	1.00	1.00	1.00
2	5	Block 1	1.00	-1.00	-1.00	1.00
3	6	Block 1	-1.00	1.00	-1.00	1.00
7	7	Block 1	-1.00	1.00	1.00	-1.00
6	8	Block 1	1.00	-1.00	1.00	-1.00

Budesonide as the active ingredient. Each formulation included various excipients, such as soya lecithin as a surfactant, microcrystalline cellulose and lactose monohydrate as diluents, Aerosil as a glidant, and magnesium stearate as a lubricant. A range of controlled-release polymers was tested, including Xanthan Gum, Carbopol, Hydroxypropyl Cellulose, Hypromellose K4M, and a combination of Xanthan Gum and Hypromellose K4M. The formulations were prepared by thoroughly mixing the active ingredient with the excipients, followed by compression into tablets with a uniform core weight. The details of the materials used in each formulation are presented in Table 1. Each tablet formulation was evaluated for its ability to control the release of Budesonide over a specified period.

Quality Target Product Profile (QTPP) identification

The initial step in the formulation development was to define the Quality Target Product Profile (QTPP) to ensure that the final product would match the dissolution profile of the innovator product. The QTPP elements were carefully outlined, considering the critical attributes required for pharmaceutical equivalence, such as the dosage form, dosage design, and route of administration.

Screening of independent variables

A fractional factorial design was conduted to screen for the independent variables that could significantly impact the in-vitro dissolution profile of the Budesonide prolonged-release tablets. A 2-level, 4-factor fractional factorial design (2^{4-1})was chosen to minimize the number of experiments while providing adequate information on factor interactions. The factors selected for evaluation included Soya Lecithin (surfactant), Xanthan Gum (controlled-release polymer), Magnesium Stearate (hydrophobic lubricant), and Hypromellose K4M (controlled-release polymer). Each factor was evaluated at two levels, denoted as low level (-1) and high level (+1), with the objective of identifying how variations in their concentrations influenced the drug release profile over time. The key response variables measured were the drug release % at three critical time points: 2, 4, and 12. This design allowed for the simultaneous investigation of main effects and possible interactions between the selected factors, providing insights into which excipients had the most significant impact on achieving the target dissolution profile.

Optimisation of controlled-release colon-targeted tablet of Budesonide

The methodology for the full factorial design study involved using a three-level factorial design (3^3), where three key factors—control release polymer ratio (Xanthan Gum to Hypromellose K4M), coating polymer ratio (Eudragit L100 to Eudragit S100), and plasticizer percentage—were evaluated at three levels (-1, 0, +1). These levels corresponded to different ratios and percentages, with the control release polymer ratio ranging from 30:70 to 70:30, the coating polymer ratio ranging from 30:70 to 70:30, and the plasticizer concentration ranging from 10% to 20%. The design aimed to optimize

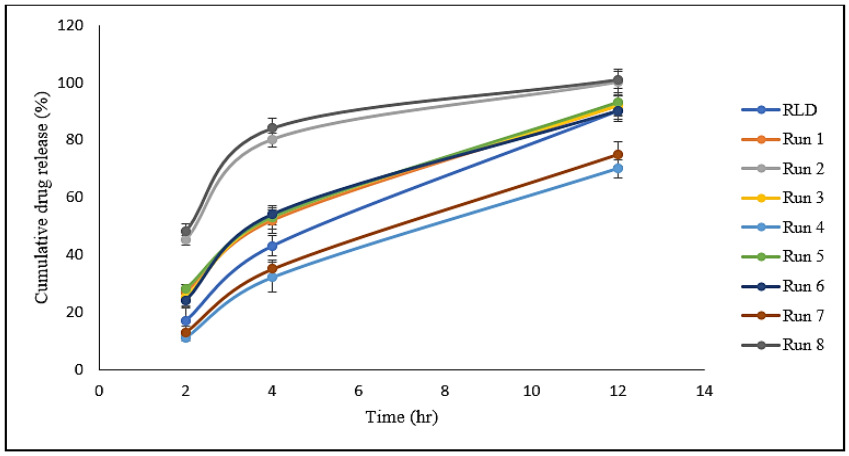

Figure 2: Comparative Dissolution Profiles of Different Formulations at 2, 4, and 12 H

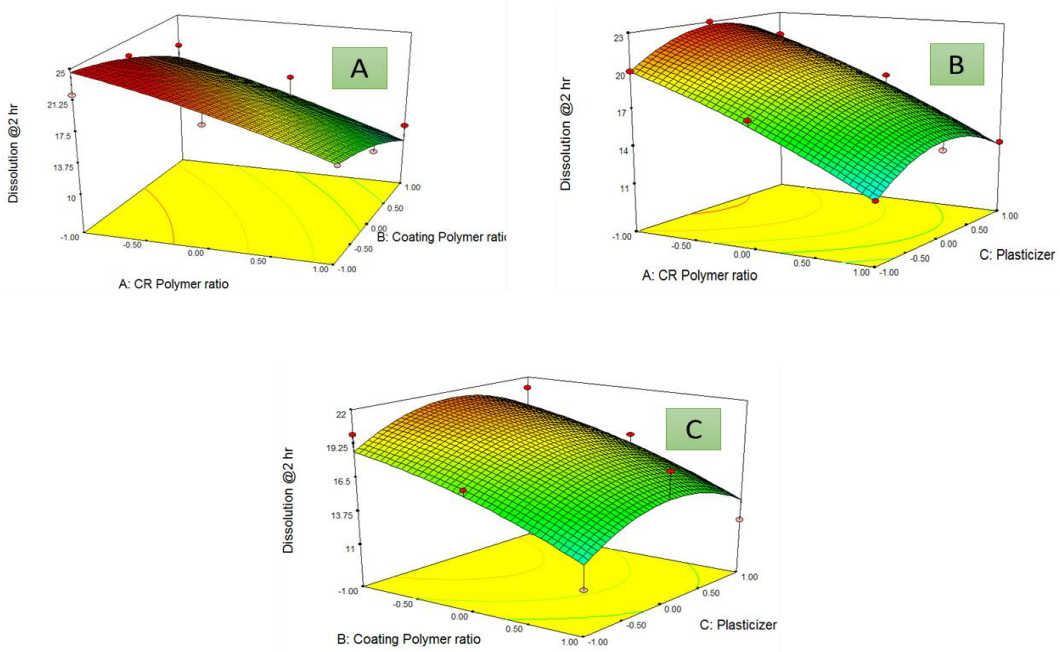

Figure 3: 3D Surface Response Plots for Dissolution at 2 Hours(Plot A illustrates the interaction between CR polymer ratio and coating polymer ratio, Plot B shows the effect of CR polymer ratio and plasticizer, and Plot C highlights the interaction between coating polymer ratio and plasticizer)

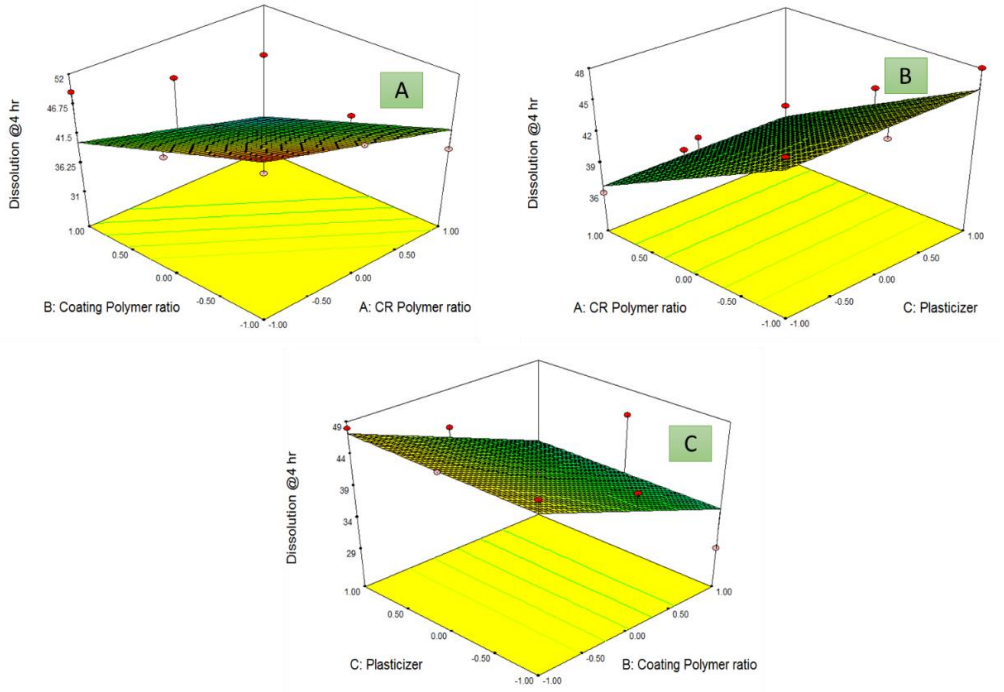

Figure 4: 3D Surface Response Plots for Dissolution at 4 Hours (Plot A illustrates the interaction between CR polymer ratio and coating polymer ratio, Plot B shows the effect of CR polymer ratio and plasticizer, and Plot C highlights the interaction between coating polymer ratio and plasticizer)

the formulation for controlled-release and targeted release in the colon, evaluating the impact of these factors on drug dissolution at four key time points—2, 4, 8, and 12 h. A total of 27 experimental runs were performed as suggested by the factorial design. Dissolution studies were conducted for each formulation using a standard dissolution apparatus, and the % of drug released at 2, 4, 8, and 12 h was measured as the primary response. The data from these experiments were analyzed using response surface methodology (RSM) to model the effect of the independent variables on the dissolution profile, and analysis of variance (ANOVA) was performed to identify significant factors and interactions. The goal was to optimize the formulation for sustained drug release over 12 h, ensuring minimal premature release in the upper part of GIT and targeted delivery particular to the colon.

Preparation of controlled-release colon-targeted tablet of Budesonide

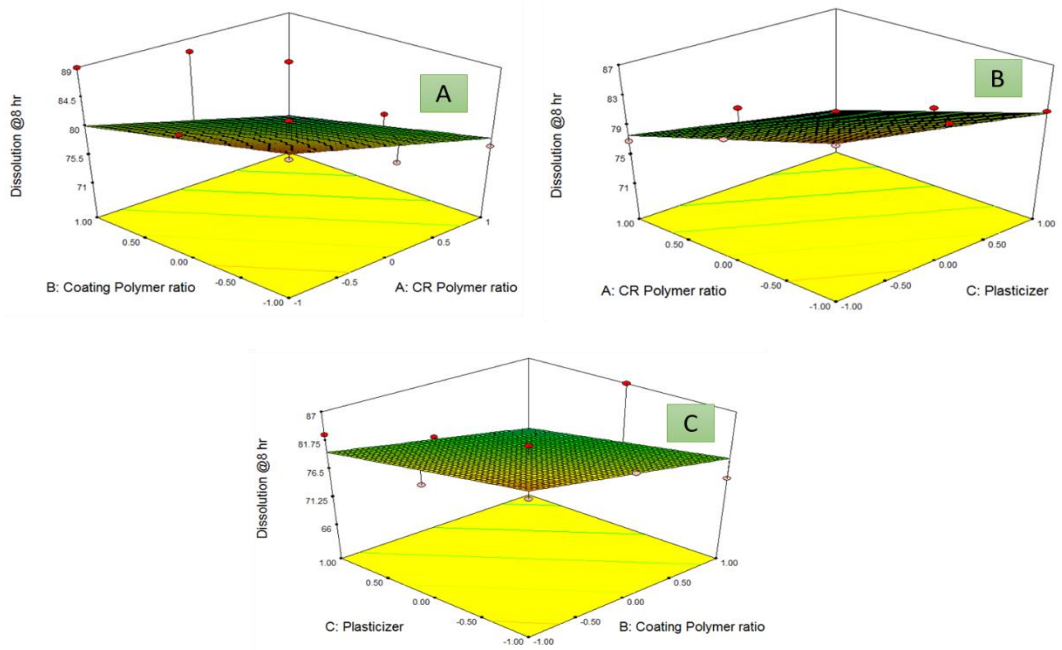

Figure 5: 3D Surface Response Plots for Dissolution at 8 Hours (Plot A illustrates the interaction between CR polymer ratio and coating polymer ratio, Plot B shows the effect of CR polymer ratio and plasticizer, and Plot C highlights the interaction between coating polymer ratio and plasticizer)

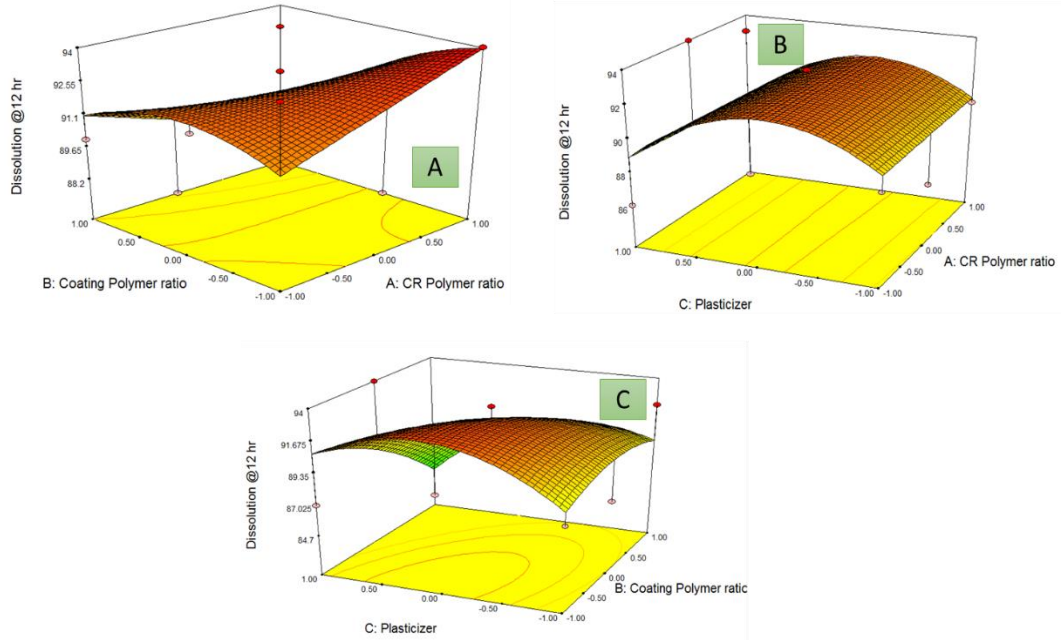

Figure 6: 3D Surface Response Plots for Dissolution at 12 Hours (Plot A illustrates the interaction between CR polymer ratio and coating polymer ratio, Plot B shows the effect of CR polymer ratio and plasticizer, and Plot C highlights the interaction between coating polymer ratio and plasticizer)

The preparation of Budesonide tablets began with the sifting of the active ingredient, Budesonide (9 mg), along with the excipients including Soya Lecithin (10 mg), Microcrystalline Cellulose (45 mg), and Lactose Monohydrate (135 mg) using a 20# sifter. These sifted materials were then subjected to dry mixing for 10 minutes. A binder solution was prepared using purified water, and the dry mix was wet granulated in a rapid mixer granulator. These were dried using a fluidized bed dryer. After drying, the granules were sifted again using a 20# sifter and milled with a multimill (1.5 mm/1.0 mm screens). In the pre-lubrication and lubrication phase, the control release polymers—Xanthan Gum (45 mg) and Hypromellose K4M (45 mg)—along with Colloidal Silicon Dioxide (6 mg, Aerosil), Magnesium Stearate (5 mg), and other lubricants were sifted using a 40# sifter and then blended with the dried granules. This mixture of thesewas then compressed into tablets consuming a "D" tooling, with a 9 mm round shape, concave design, and beveled edges. The compression parameters included an average tablet weight of 300 mg, hardness between 90 N to 120 N, a thickness of 4.5 mm to 4.8 mm, and friability

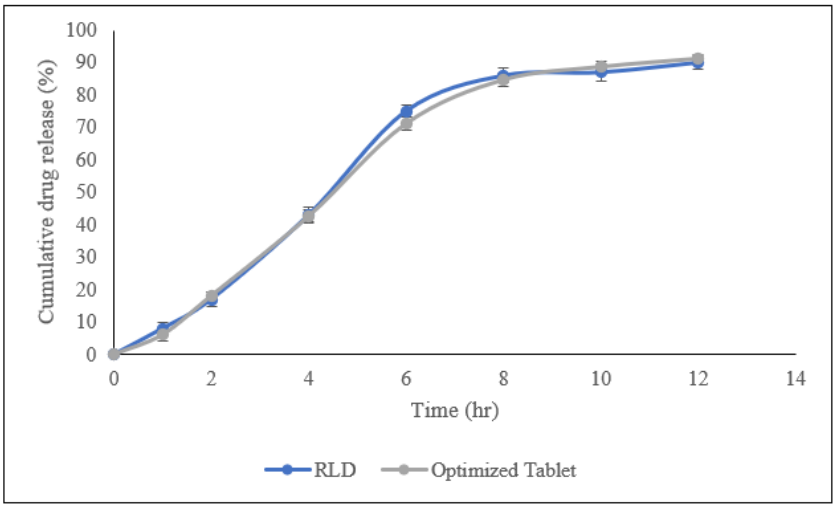

Figure 7: In Vitro Release Profile Comparison of Optimized Budesonide Tablet and RLD

at nil. The tablets were subsequently coated using a pan coated utilizing a combination of Eudragit L100 (10 mg) and Eudragit S100 (10 mg) as the coating polymers, with Purified Talc (5 mg) as the anti-tacking agent, Titanium Dioxide (2 mg) as an opacifier, and TEC (3 mg) as the plasticizer, ensuring a final coated tablet weight of 330 mg.

Comparison of in vitro release profile of the optimized tablet with the RLD

The in vitro drug release study was conducted using USP Apparatus-II (Paddle) under controlled circumstances. The dissolution medium consisted of 0.1 M HClholding 0.5% MacrogolCetostearyl Ether (MCE) for the acid stage, followed by a pH 7.2 phosphate buffer encompassing 0.5% MCE for the buffer stage. The medium volume was 500 mL for the acid stage and 1000 mL for the buffer stage, with the paddle rotating at 100 RPM. The temperature was sustained at 37 ± 0.5 ℃ throughout the test. Drug release was monitored at predefined time points: after 1 and 2 h in the acid stage, followed by 2, 4, 6, 8, 10, and 12 h in the buffer stage. At each time point, aliquots were withdrawn from the medium, filtered to remove any particulate matter, and appropriately diluted. The absorbance was unrushed using a UV spectrophotometer at a wavelength of 246 nm to quantify the amount of drug released.[13]After each withdrawal, an equal volume of fresh medium was added to preserve sink conditions throughout the dissolution test.

RESULTS AND DISCUSSION

Screening of controlled-release polymer

The dissolution profiles of the tablets, as shown in Figure 1, showed significant variations depending on the polymer used. Xanthan Gum exhibited a gradual release, with 11% of Budesonide released at the 1-hour mark and 98% released by the 12th hour. This profile was somewhat comparable to the reference product but showed slightly faster release in the earlier stages.[14] Carbopol, on the other hand, exhibited a much faster release, reaching 100% drug release by the 8th hour, indicating that it was less effective at providing sustained drug release over the desired 12-hour period.[15]Hydroxypropyl Cellulose also demonstrated rapid drug release, achieving complete release within 10 h, which was faster than the target profile.[16] Hypromellose K4M displayed a more controlled release pattern, with 12% of Budesonide released at 1 hour and 98% by 12 h, closely matching the innovator product. However, the best performance was observed with the combination of Xanthan Gum and Hypromellose K4M, which provided a release profile that closely mirrored the reference product. This formulation exhibited 10% release at 1 hour, 22% release at 2 h, and achieved 94% release by the 12th hour, indicating a well-controlled and sustained drug release.[17] The combination of Xanthan Gum and Hypromellose K4M offered the most desirable balance between initial drug release and extended control over time, making it the most suitable choice for further optimization. The results suggest that the synergistic effect of these two polymers provided a more gradual and controlled release compared to the individual polymers, which either released the drug too quickly or needed to maintain a consistent release pattern over the extended period.[18]

Quality Target Product Profile (QTPP) identification

The QTPP was carefully defined to warrant that the final Budesonide tablet formulation encounters pharmaceutical equivalence as well as bioequivalence requirements with the reference listed drug (RLD). Several key elements were established as targets to guide the formulation development, ensuring both therapeutic efficacy and patient acceptability. The dosage form was determined to be a tablet, which aligned with the pharmaceutical equivalence requirement that mandates the same dosage form as the RLD. This ensures consistency in drug delivery and patient experience. The dosage design was set as prolonged-release tablets to match the innovator's label claims and ensure sustained drug release over an extended period, which is crucial for maintaining therapeutic drug levels in the colon and managing inflammatory bowel diseases effectively. The oral route of administration was also specified as it is a common and acceptable method for such formulations, further adhering to equivalence requirements. The dosage strength of 9 mg was selected to

match that of the RLD, ensuring appropriate therapeutic dosing and compliance with regulatory standards.[19]One of the most critical aspects of the QTPP was the pharmacokinetics, which targeted maximum plasma concentrations of Budesonide at 13-14 h post-administration. This was crucial to ensuring the bioequivalence of the developed formulation with the RLD, guaranteeing rapid onset of action and sustained efficacy. Additionally, the formulation's bioequivalence to the RLD ensures the new product would meet therapeutic goals, providing reliable treatment for patients. Stability was another key element, with a target of at least a 24-month shelf-life at room temperature. This target was chosen to meet or exceed the shelf-life of the RLD, ensuring the product's long-term efficacy and safety under normal storage conditions. The development of a stable formulation is critical to maintaining drug potency and preventing degradation over time. In terms of physical attributes, while color, shape, and appearance were not considered directly linked to the drug's safety and efficacy, they were designed to ensure patient acceptability. Patient compliance can be influenced by the appearance and size of the tablets, which is why the size of the tablet was targeted to be similar to the RLD for ease of swallowing and overall treatment adherence. Although the RLD is a scored tablet, the QTPP set the target for the generic tablet to be unscored, as score configuration was not deemed critical to the drug's therapeutic performance.

Screening of independent variables

The screening of independent variables was conducted using a fractional factorial design (2^4-1), which involved four key factors: Soya Lecithin (surfactant), Xanthan Gum (controlled-release polymer), Magnesium Stearate (hydrophobic lubricant), and Hypromellose K4M (controlled-release polymer). The objective of this design was to identify which factors had a significant impact on the dissolution profile of the Budesonide prolonged-release tablets and to determine the optimal concentrations of these excipients to match the reference product's drug release profile. A total of eight runs were suggested by StatEase® DesignExpert software. The trials conducted were as per the details mentioned in Table 2.

Impact of Individual Factors on Drug Release

The equations (in coded terms) for all three responses are as follows:

Drug release at 2 hr = +27.63 + 0.37A – 9.38B – 0.13C - 7.88D

Drug release at 4 hr = +55.38 + 0.12A – 11.88B – 12.38D

Drug release at 12 hr = +89.13 – 0.13A – 7.38B – 0.88C – 6.63D

The three equations generated from this work provide valuable insights into the effects of the key excipients—Soya Lecithin (A), Xanthan Gum (B), Magnesium Stearate (C), and Hypromellose K4M (D)—on the drug release profile of Budesonide at different time points (2, 4, and 12 h). In the equation for drug release at 2 h, the most significant factors are Xanthan Gum (B) and Hypromellose K4M (D), both having strong negative coefficients (-9.38 and -7.88, respectively), indicating that higher concentrations of these controlled-release polymers effectively slow down early drug release, preventing premature absorption in the upper gastrointestinal tract. Soya Lecithin (A) has a minor positive influence (+0.37), while Magnesium Stearate (C) shows a negligible effect (-0.13), suggesting their limited role in early drug release. By the 4-hour mark, the equation shows that Xanthan Gum and Hypromellose K4M remain the dominant factors, with even more pronounced effects (coefficients of -11.88 and -12.38, respectively), ensuring a gradual and controlled drug release. Soya Lecithin continues to have a minimal positive impact (+0.12), and Magnesium Stearate is not a significant contributor at this stage. At 12 h, Xanthan Gum (B) and Hypromellose K4M (D) again play crucial roles, with coefficients of -7.38 and -6.63, respectively, demonstrating their ability to sustain drug release over the entire period. Soya Lecithin and Magnesium Stearate show small negative coefficients (-0.13 and -0.88), indicating their limited influence on long-term drug release. Overall, the equations confirm that Xanthan Gum and Hypromellose K4M are the most critical variables controlling the prolonged drug release, with Soya Lecithin and Magnesium Stearate having minimal impact. These findings highlight the importance of optimizing the concentrations of Xanthan Gum and Hypromellose K4M to achieve the anticipated controlled-release profile, while the limited role of Soya Lecithin and Magnesium Stearate suggests that their levels can remain constant without significantly affecting the dissolution behavior.This behavior aligns with the expected performance of these polymers, as both Xanthan Gum and Hypromellose K4M are known for their ability to form a gel matrix in the existence of aqueous media, slowing down the release of the drug by creating a barrier for diffusion.[20-21]

Comparison of *in vitro* release profiles

The drug release profiles across the various runs as depicted in Figure 2 show distinct differences based on the composition of excipients used, particularly Xanthan Gum and Hypromellose K4M, which were critical in controlling the release of Budesonide over time. The reference listed drug (RLD) displayed a gradual release with 17% of the drug released at 2 h, 43% at 4 h, 86% at 8 h and 90% at 12 h. At the 2-hour mark, formulations with higher levels of Xanthan Gum and Hypromellose K4M released around 10-15% of the drug, whereas formulations with lower levels of these polymers exhibited a more rapid release, with up to 40-50% of the drug being released within the same period. This indicates that the presence of these controlled-release polymers effectively reduced the rate of early drug release, preventing premature drug absorption in the upper GIT. At 4-hour mark, the optimized formulations released between 40-60% of the drug, which is in line with the target profile, ensuring that a sufficient amount of the drug reaches the colon for therapeutic action. By 12 h, the best-performing formulations with higher concentrations of Xanthan Gum and Hypromellose K4M released around 90-98% of the drug, closely matching the reference product's dissolution behavior.

In comparison, Run 1 closely matched the RLD with 27% released at 2 h, 52% at 4 h, and 92% at 12 h, indicating

that this formulation successfully mimicked the reference product's profile. Run 2 showed much faster release, with 45% at 2 h, 80% at 4 h, and 100% at 12 h, suggesting insufficient control over drug release, likely due to lower concentrations of controlled-release polymers. Conversely, Run 4 had a much slower release, with only 11% at 2 h, 32% at 4 h, and 70% at 12 h, indicating excessive retardation of drug release. Runs 3, 5, and 6 demonstrated relatively balanced release profiles, with results close to the RLD, particularly at the 12-hour mark, showing 92%, 93%, and 90% drug release, respectively. Run 8 exhibited the fastest release of all, with 48% drug release at 2 h and 101% at 12 h, representing significant early release that could lead to premature drug absorption in the upper GIT. These variations underscore the critical role of optimizing the concentrations of Xanthan Gum and Hypromellose K4M, as their levels directly influence the dissolution rate, with a balanced combination required to achieve the desired prolonged release matching the RLD.

Interaction Between Xanthan Gum and Hypromellose K4M

The interaction between Xanthan Gum and Hypromellose K4M was a critical finding in this study. The combination of these two polymers demonstrated a synergistic effect, resulting in a more controlled and sustained release profile than when either polymer was used alone. In formulations where both polymers were present at higher concentrations (+1 levels), the dissolution profile was more consistent with the target release, with drug release occurring gradually over the 12-hour period. The synergistic action of these two polymers likely results from their ability to form a more robust gel matrix, further enhancing the controlled-release mechanism.[22]This observation is particularly important, as it indicates that the combination of Xanthan Gum and Hypromellose K4M is crucial for achieving the desired extended-release profile. Based on the fractional factorial design results, it was concluded that the levels of Xanthan Gum and Hypromellose K4M are the primary factors that need to be further optimized to ensure a consistent and predictable release profile. The results demonstrated that these two polymers are responsible for controlling the drug release rate over the entire 12-hour period, whereas Soya Lecithin and Magnesium Stearate do not significantly contribute to the dissolution profile. These findings will guide the subsequent optimization efforts, focusing on fine-tuning the polymer concentrations to achieve the desired prolonged-release characteristics. Additionally, the minimal impact of Soya Lecithin and Magnesium Stearate simplifies the formulation process, allowing for a more streamlined focus on the key controlled-release polymers.

Optimisation of controlled-release colon-targeted tablet of Budesonide

The full factorial design (3^3) was used to optimize the formulation of the Budesonide controlled-release tablets, assessing the effects of three independent variables—Control Release (CR) Polymer Ratio, Coating Polymer Ratio, and Plasticizer Percentage—on the drug release profiles at 2, 4, 8, and 12 hours. The responses at these time points were analyzed using response surface methodology (RSM), and the models were fitted using ANOVA to determine the significance of each factor.

Drug Release at 2 H

The dissolution at 2 hours is crucial for evaluating early drug release and preventing premature absorption. The final equation for drug release at 2 hours in terms of coded factors is:

$$\text{Dissolution at 2 h} = 19.30 - 4.00A - 2.83B + 0.39C - 0.25AB - 0.56A^2 - 0.72B^2 - 2.39C^2$$

where A is the CR polymer ratio, B is the coating polymer ratio, and C is the plasticizer. The ANOVA for this model showed that the CR polymer ratio and the coating polymer ratio had the most significant impact on dissolution at 2 hours, with p-values < 0.0001. The quadratic term for the plasticizer (C^2) was also significant ($p = 0.0011$), suggesting a non-linear relationship. The R-squared value of 0.9256 and Adjusted R-squared of 0.8862 indicate a strong fit to the model. A 3D surface plot (Figure 3) shows how the CR polymer and coating polymer ratios influence the dissolution profile at 2 hours.

Drug Release at 4 H

For sustained drug release, the dissolution at 4 hours needs to remain steady. The final equation for drug release at 4 hours is:

$$\text{Dissolution at 4 h} = 41.41 - 4.61A - 5.78B + 0.056C$$

The ANOVA analysis revealed that both the CR polymer ratio and coating polymer ratio were significant at the 4-hour mark ($p = 0.0006$ and $p < 0.0001$, respectively), while the plasticizer had no significant effect ($p = 0.9620$). The R-squared value for this model was 0.6410, with an Adjusted R-squared of 0.5942. The response surface plot (Figure 4) illustrates the influence of CR and coating polymers on the drug release at 4 hours, showing that higher CR and coating polymer ratios reduced the release rate.

Drug Release at 8H

The dissolution at 8 hours is critical for assessing prolonged drug release. The equation for drug release at 8 hours is:

$$\text{Dissolution at 8 h} = 79.30 - 4.22A - 3.28B - 2.72C$$

ANOVA results showed that all three factors—CR polymer ratio, coating polymer ratio, and plasticizer—significantly impacted the dissolution at 8 hours, with p-values of 0.0010, 0.0074, and 0.0229, respectively. The R-squared for this model was 0.5566, and the Adjusted R-squared was 0.4988, indicating a moderate fit. The surface plot (Figure 5) demonstrates that a balanced polymer ratio is essential for achieving the desired drug release at 8 hours.

Drug Release at 12 H

By 12 hours, the goal is to achieve a near-complete drug release (≥90%). The final equation for drug release at 12 hours is:

$$\text{Dissolution at 8 h} = 92.11 - 1.44B - 0.67C - 1.42AB - 2.67C^2$$

The ANOVA indicated that no single factor had a significant effect on drug release at 12 hours, with p-values > 0.05 for all variables. The model's R-squared value was 0.3853, and the Adjusted R-squared was only 0.0599, indicating that the model did not fit the data well.

Despite this, the drug release at 12 hours consistently approached 90%, as shown in the surface plot (Figure 6).

Optimization and Overlay Plot

The goal of the optimization study was to ensure that the drug is released gradually over time, minimizing early release while maximizing the amount of drug delivered at the 12-hour mark. The constraints and solutions presented in the optimization process are focused on achieving a balanced drug release profile at key time points (2, 4, 8 and 12 h) by adjusting the controlled-release polymer ratio, coating polymer ratio, and plasticizer percentage. The target ranges for dissolution at 2 h (14-18%), 4 h (40-44%), 8 h (84-86%), and 12 h (≥90%) were set to ensure sustained and controlled drug release, with the goal of maximizing therapeutic efficacy while preventing premature drug absorption. The desirability function, which considers the importance and weight of each parameter, was used to rank solutions based on how well they met the desired drug release profile. The five solutions identified in this process demonstrate slight variations in the controlled-release polymer ratio, coating polymer ratio, and plasticizer percentage, with each formulation achieving a desirability score close to 1.0, indicating strong alignment with the target dissolution goals. The first solution, selected as the optimal formulation, features a controlled-release polymer ratio of -0.90, a coating polymer ratio of 0.56, and a plasticizer value of -1.00. This formulation yielded drug release values of 17.9977% at 2 h, 42.292% at 4 h, and 90.4402% at 12 h, with a desirability score of 0.956, indicating near-perfect satisfaction of the target constraints. This optimized formulation is ideal for delivering Budesonide in a controlled and sustained manner, ensuring that the drug reaches the colon for effective treatment while minimizing systemic side effects.These findings support the development of a robust formulation for Budesonide, enabling prolonged drug action and minimizing premature absorption in the upper gastrointestinal tract.

Comparison of in vitro release profile of the optimized tablet with the RLD

The evaluation of the in vitro release between the optimized Budesonide tablet and the reference listed drug (RLD) shows a strong alignment, confirming the success of the formulation as shown in Figure 7. At the 2-hour mark, the optimized tablet released 18.07%, closely matching the RLD's 17%, indicating effective control over the initial release. By 4 h, both formulations showed nearly identical release rates (42.63% for the optimized tablet and 43% for the RLD), highlighting the optimized tablet's ability to sustain release. At the end of 8 h, the drug release from theRLD was 86% and that from the optimized tablet was 84.78% indicating that there was an insignificant difference in the release patterns. At 12 h, the optimized tablet released 91.32%, closely mirroring the RLD's 90%, indicating complete and consistent drug release. The calculated similarity factor (f2) of 83 and difference factor (f1) of 3 confirm that the release profiles are highly similar. Overall, the optimized formulation successfully replicates the RLD's release pattern, ensuring targeted and controlled drug delivery over 12 h.

CONCLUSION

The present study successfully developed and optimized a colon-targeted Budesonide tablet formulation using a combination of controlled-release and coating polymers. The use of Xanthan Gum and Hypromellose K4M as controlled-release polymers, along with Eudragit L100 and Eudragit S100 as coating polymers, allowed for a precise drug release profile that closely matched the reference listed drug (RLD). Through systematic experimentation using fractional factorial and full factorial designs, the study identified the critical variables influencing drug release at key time points and optimized the formulation to ensure controlled release in the gastrointestinal tract, with targeted delivery to the colon.

The optimized formulation achieved drug release rates of 18.07% at 2 h, 42.63% at 4 h, 84.78% at 8 h, and 91.32% at 12 h, which closely mirrored the RLD's release profile. The similarity factor (f2) of 83 and difference factor (f1) of 3 confirmed that the optimized formulation and the RLD exhibited highly similar release behaviors. These results demonstrate the formulation's ability to ensure targeted drug delivery, minimizing premature release in the upper GIT and providing prolonged release in the colon, where therapeutic action is needed. The optimized formulation also presents a scalable and cost-effective solution, addressing both the therapeutic needs of patients and the limitations of existing commercial Budesonide formulations. Overall, the study provides a robust foundation for further development and commercial application of colon-targeted Budesonide tablets, offering enhanced treatment options for patients with IBD.

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