International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 21s, 2025
https://theaspd.com/index.php

Development Of Optimized Formulation, Evaluation And Pharmacokinetics Of Budesonide For Colon By Using Design Of Experiment

Sanjay J. Kshirsagar[1], Rupanjali S. Gaikwad[1]
[1]Department of Pharmaceutics, MET's Institute of Pharmacy, Adgaon, Nashik, (Savitribai Phule Pune University, Pune, Maharashtra, India) , grupanjali@yahoo.in

Abstract
The aim of this research work is to develop optimized colon specific formulation of Budesonide by using design of experiment and evaluate colon specific drug delivery system to treat inflammatory bowel diseases. Budesonide matrix tablets were prepared by wet granulation method using time dependent polymer Eudragit RL100 and coated to prevent initial drug release in gastric region. The formulation was systematically optimized using design of experiment software. Central composite design was employed to study the effect of each independent variable on dependent variables Thickness (mm), Hardness (kg), Drug release (%). (control) and Drug release (%) (test). The Matrix tablets of Budesonide were optimized by using Central composite Experimental Design (2 Factor, 2 Level, and DesignExpert Version 13). The independent variables selected were PVP-30(mg) (X1) MCC PH101 (mg) (X2), and Eudragit RL100 (%) (X3) with their low and high levels for preparing 13 runs of formulations and dependent variable selected were Thickness (mm), Hardness (kg), Drug release (%). (control) and Drug release (%) (test) Finally optimized was selected for further characterization.
In vitro drug release study was performed with simulated colonic contents using New Zealand White rabbit. The drug release study in absence of rabbit cecal content medium were carried out using USP II dissolution rate test apparatus (100 rpm, 37±0.5°C) in 900 ml 0.1N HCl for 2 h, Then it is replaced with pH 7.4 phosphate buffer solution, dissolution was continued for 3 h, the dissolution study in pH 6.8 phosphate buffer solution for control was performed without rabbit cecal content. As the usual colonic transit time is 20-30 h, so the dissolution study was continued further for another 24 h. The absorbance was measured using UV/Visible spectrophotometer (UV-730, Jasco) at 246 nm. The graph of cumulative percentage drug release versus time
In order to find out best release pattern, the in vitro release drug release data for optimized batches were fitted to Zero order, First order and Higuchi kinetic equations models. As per ICH guidelines, stability study of formulation was performed.
TF9's exceptional friability, combined with its minimal weight variation (0.32%), consistent thickness (0.47±0.03 mm), and precise hardness (4±0.01 kg), underscores its overall superiority in quality and consistency. TF9 is identified as the optimized batch based on its drug content of 99.75±0.01%, hardness measurement of 4±0.01 kg, friability measurement of 0.29%. The kinetic equations were used i.e., Zero, First-order and Higuchi model. Both the kinetic rate constant (k) and the determination coefficient (R^2) were calculated and presented in graphs. The best fit model with the highest determination coefficient (R^2 is 0.9823) value for optimized batch was Zero order.
Keywords: *Budesonide, Eudragit RL100, Experimental Design, ICH guidelines, Higuchi model.*

INTRODUCTION

For local treatment of a variety of bowel diseases targeted drug delivery into the colon is highly desirable. The colon is believed to be a suitable absorption site for peptides and protein drugs, because of reasons such as, less diversity and intensity of digestive enzymes, comparative proteolytic activity of colon mucosa. [1-3]

An ideal controlled drug delivery system delivers the drug at a predetermined rate, locally or systemically for a specified period of time and to its site of action. [4] To optimize the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug and maximize utilization by using smallest quantity by minimizing side effects in shortest possible time of drug administered is the main aim of a controlled drug delivery system is. The oral controlled release systems based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as continuous release system for a prolonged period of time with normal transit of the dosage form; delayed transit with continuous release systems to prolong their residence in the gastrointestinal tract along with their release and delayed release systems involves release

of drug only at specific site in the GIT. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. [5-6] Colon specific drug delivery system is considered to be beneficial in the local and systemic treatment of ileocecal and colon related diseases and disorders. [7]

Inflammatory bowel disease (IBD) is an idiopathic inflammatory disorder occur in humans are Crohn's disease and ulcerative colitis. These two forms of the diseases are clinically related and they have histologically distinct chronic inflammation in the bowel, characterized by intermittent courses of acute attacks. [8]

pH varies throughout the GIT and it depends upon factors like diet, food intake, intestinal motility and disease states. The colonic delivery uses this variation in pH along the GIT to target the drug. GIT pH shows increases with range 1.2, 6.6 and 7 in stomach, proximal small intestine and distal small intestine respectively. [9-10]

Localizing orally administered drugs into the colon is particularly complicated because it is difficult to predict the exact residence time of dosage forms in the stomach and small intestine. The residence time of drug depends on parameters such as fasted or fed state, meal composition and intensity of peristalsis. As a result, a solid dosage form may stay in the stomach from few minutes to 8 h and in the small intestine from 3 to 5 h. Intestinal transit time is important for nearly all orally targeting delivery systems. Colonic transit times (estimated from the difference in mouth to cecum and whole gut transit times) ranged from 50 to 70 hrs. Men had slightly shorter transit times than women and this was most apparent in more proximal colon. [11]

For targeting of drug to colon, time dependent delivery has been proposed. Time dependent systems release their drug load after a preprogrammed time delay until the drug reaches the colon. The lag time in this case is the time required to transit the drug from mouth to colon. For synchronous delivery of a drug at a pre-selected time so that patient receives the drug when needed at a pre-selected site of the gastrointestinal tract time controlled systems are helpful. [12] To achieve successful colonic delivery through oral route, the formulation must prevent drug release in the upper GIT, pH, Transit time, pressure differences and gastrointestinal microflora and enzymes approaches used.[13] Budesonide is a glucocorticoid used to treat Crohn's disease, asthma, COPD, hay fever and allergies, and ulcerative colitis. Lower doses of corticosteroids provide an anti-inflammatory effect, while higher doses are immunosuppressive. [14]

MATERIAL AND METHODS

Material

Budesonide was obtained as gift sample from Emcure pharma, Pune and Eudragit RL 100, Micro crystalline Cellulose, PVPK-30, magnesium stearate and talc of pharmaceutical grade were procured from Colorcon Asia Ltd, Goa

Methods

Preparation of the matrix tablets of Budesonide (Time dependent)

Matrix tablets blend containing Budesonide were dry blended with granulated using 5% w/v ethanolic solution of Talc as a binder and prepared by wet granulation method using MCC PH101 grade. The granules prepared using wet a sieve No. 22, then were dried at 50°C for 15 min. The dried granules then sieved again with No. 22 sieve. The oversized granules retained on sieve No. 22 were kept aside. This granule mixture was blended with magnesium stearate (5% w/w) and compressed using single punch tablet machine, equipped with flat-faced punches of 12 mm diameter. All the materials were accurately weighed, mixed and passed through a mesh (250µm/sieve no. 60) to ensure complete mixing. The tablets were prepared by compressing the through mixed materials using 6mm round, flat and plain faced punches. The composition of the core tablets is given in Table 1.

Characterization of Granules

The granules for budesonide matrix tablets were prepared by wet granulation method according to the formula. The granules were characterized by angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio to analyze rheological parameters.

Enteric coating of the matrix tablets of Budesonide

The Budesonide matrix tablets were further coated with Eudragit RL-100 solution. A different concentration (5, 10 and 15 % w/v) of coating solution of Eudragit RL-100 was prepared in a mixture of

Isopropyl alcohol: acetone (1:1). The matrix tablets were coated by immersion in the coating solution followed by dip coating technique. The wet tablets are dried in in coating pan. Alternative dipping and drying steps may be repeated several times to obtain the desired coating. The coated tablets prepared by hand-dipped into the dipping solutions of Eudragit RL-100 solution for a dwell time of 1 second, removed from the dipping solution, then dried under ambient conditions. This procedure was repeated. The coatings were smooth, hard, and shiny, and had no bubbles or cracking. Upon exposure to ambient conditions, no cracks were seen in the coatings.

Name of Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Budesonide (mg)	9	9	9	9	9	9	9	9	9
PVPK-30(mg)	5	5	5	5	5	5	5	5	5
MCC PH101(mg)	325	300	275	325	300	275	325	300	275
Magnesium Stearate (mg)	8	8	8	8	8	8	8	8	8
Talc(mg)	8	8	8	8	8	8	8	8	8
Eudragit RL100 (%)	5	5	5	10	10	10	15	15	15
Total Weight (Mg)	360	335	310	365	340	315	370	345	320

Table 1. Formulation composition of matrix tablets of Budesonide (Time dependent)

Experimental design [15]

Central composite design was employed to studythe effect of each independent variable on dependent variables Thickness (mm), Hardness (kg), Drug release (%). (control) and Drug release (%) (test). Matrix tablets of Budesonide were prepared by wet granulation method. The Matrix tablets of Budesonide were optimized by using Central composite Experimental Design (2 Factor, 2 Level, and Design Expert Version 13). The independent variables selected were PVP-30(mg) (X1) MCC PH101 (mg) (X2), and Eudragit RL100 (%) (X3) with their low and high levels for preparing 13 runs of formulations and dependent variable selected were Thickness (mm), Hardness (kg), Drug release (%). (control) and Drug release (%) (test) Finally optimized was selected for further characterization.

Independent variable Level	Low level (-1)	High level (+1)
PVPK-30(mg)	2	5
MCC PH101(mg)	250	320
Eudragit RL100 (%)	5	15

Table 2: Variables and intervals selected to perform Central composite design.

Formulation code	PVPK-30(mg)	MCC PH101(mg)	Eudragit RL100 (%)
TF1	5	320	5
TF2	3.5	285	18.409
TF3	2	250	5
TF4	2	250	15
TF5	2	320	5
TF6	5	250	5
TF7	3.5	226.137	10
TF8	2	320	15
TF9	5	320	15
TF10	3.5	285	10
TF11	3.5	285	1.59104
TF12	3.5	343.863	10
TF13	5	250	15

Table 3: DOE Suggested batches

Post Formulation evaluation of tablets of Budesonide (Time dependent)

1. General appearance:

The formulated tablets were assessed for its general appearance and observations were made for shape, colour and texture.

2. Weight variation [16]

The 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official weight variation test.

$$\% \text{ Weight variation} = \frac{\text{Average waight - Weight of each tablet}}{\text{Average weight}} \text{ x } 100$$

3. Thickness [17]

The Digital Vernier Calliper used to determine thickness of the tablet.

4. Hardness [18]

The Monsanto tablet hardness tester used to determine crushing strength of ten tablets. A tablet hardness of about 4-7 kg/cm^2 is considered adequate for mechanical stability.

5. Friability [16]

The friability testing of the tablets was carried out by using Roche Friabilator (Model 902, India). Accurately weighed six tablets from each batch of tablets and placed in the tumbling chamber and rotated at 25 rpm for a period of 4 min. Tablets were taken and again weighed. The percentage loss was determined by using the formula:

$\%\textbf{Friability} = [(W_1\text{-}W_2)/W_1] \times 100$

Where,

W_1= weight of tablets before test, W_2 = weight of tablets after test

6. Drug content [19]

Accurately weighed the fine powder of tablets equivalent to 9 mg was dissolved in 50 ml of phosphate buffer, pH 7.4. and the volume was made up to 100 ml with phosphate buffer 7.4. The solution was filtered through a membrane filter (0.22 µm) and analyzed for drug content using UV/Visible spectrophotometer (UV-730, Jasco) at 246 nm.

7. In vitro drug release studies [20]

Preparation of simulated colonic fluids

All experiments were conducted according to the institutional animal ethics committee (VIVO/PR/2022/P03802) and they were maintained at proper animal housing facility following standard ethical measures. New Zealand White rabbit weighing (2-3 Months, weighing NLT 2 kg) was maintained on a normal diet. The rat cecal content medium at 4% w/v level is obtained after 7 days of enzymatic induction with 1 ml of 2% w/w Eudragit RL 100 dispersion gives the supreme environment for assessing the susceptibility of Eudragit RL 100 to colonic bacterial degradation. Hence, the rabbits were treated with Eudragit RL 100 dispersion for inducing the enzymes specifically acting on Eudragit RL 100. The procedure involved oral treatment of rabbits with 1 ml of 2% w/v Eudragit RL 100 dispersion for 7 days. Before the commencement of drug release study, six rabbits were euthanized using Methanol. The abdomen was opened, the caecai were traced, ligated at the both ends with thread, dissected and immediately transferred into pH 6.8 phosphate buffer solution (previously bubbled with carbon dioxide). The cecal contents were individually weighed, pooled and suspended in the phosphate buffer solution to give 4% w/v dilution. As the caecum is naturally anaerobic, all the operations were carried out under carbon dioxide. The experimental animal, rats were handled in accordance with institutional guidelines.

In vitro drug release study in the absence of rabbit cecal contents

The drug release study of matrix tablets of Budesonide was assessed by continuing the drug release study in absence of rabbit cecal content medium using USP II dissolution rate test apparatus (100 rpm, 37±0.5°C) in 900 ml 0.1N HCl for 2 h. Then the dissolution medium was replaced with phosphate buffer solution pH 7.4 (900 ml) and dissolution was continued for 3 h without rabbit cecal content in phosphate buffer solution pH 6.8 (control study) and the experiment was continued for 24 h as the usual colonic

transit time is 20-30 h. At different time intervals, 5.0 ml of sample was withdrawn and replaced with 5.0 ml of fresh phosphate buffer solution.

The absorbance was measured using UV/Visible spectrophotometer (UV-730, Jasco) at 246 nm. The graph was plotted against cumulative percentage drug release versus time. The experiment was done in triplicate and data were expressed in mean ± SD.

8. Swelling studies [19]

The swelling studies were carried for all formulations. These tablets were glued to a piece of glass slide. The glass slide and tablets were weighed initially (W_1). The tablets were placed in different dissolution media (pH 1.2, 6.8, and 7.4) using USP type II dissolution apparatus (Electrolab, India) in 900 ml dissolution medium at 100 rpm, 37°C ± 0.5°C. The swollen tablets were taken out at predetermined time intervals, and using tissue paper, excess of water on their surface was carefully removed and tablets were reweighed (W_2). The study was carried out over a period of 24 h and the tablets were observed for rupturing. The % swelling index was calculated using the following formula:

Swelling index = W_2-W_1/W_2 x 100

W_1- Initial weight of tablet; W_2- Weight of hydrated tablet

9. Stability Study [21]

The stability study was conducted according to International Conference on Harmonisation (ICH) guidelines. All the formulations were stored in aluminum packaging laminated with polyethylene (cellophane packets) and kept in humidity chamber (Oswal Scientific, Chandigarh, India) at 30°C ± 2°C/65% ±5% RH (room temperature studies) and 40°C ± 2°C/75% ±5% RH (accelerated temperature studies) for 6 months. The tablets were analyzed after 0 day, 1 month, 2 months, 3 months, and 6 months. At the end of the study period, the tablets were observed for the change in physical appearance, color, and drug content.

RESULTS AND DISCUSSION

Characterization of Granules

The granules for budesonide matrix tablets were prepared by wet granulation method according to the formula. The granules were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio. The parameters for evaluation of granules are depicted in Table 4.

Formulation Batches	Angle of Repose (θ)	Bulk density Db	Tapped density Dt	Carr's Index 100 x (Dt)-(Db)/ (Dt)	Hausner Ratio
TF1	27.14±0.5	0.41±0.12	0.42±0.005	2.38	1.02
TF2	28.56±0.4	0.40±0.6	0.42±0.005	2.38	1.02
TF3	27.15±0.7	0.41±0.5	0.42±0.005	2.38	1.02
TF4	27.56±0.8	0.41±0.12	0.42±0.005	2.38	1.02
TF5	28.10±0.9	0.41±0.6	0.43±0.005	4.65	1.04
TF6	27.15±0.5	0.41±0.20	0.42±0.005	2.38	1.02
TF7	28.26±0.8	0.41±1.05	0.42±0.005	2.38	1.02
TF8	29.01±0.5	0.41±1.85	0.42±0.005	2.38	1.02
TF9	27.58±1.02	0.40±0.6	0.43±0.005	4.65	1.04
TF10	27.10±0.02	0.41±0.2	0.42±0.03	2.38	1.02
TF11	28.16±0.01	0.40±0.3	0.42±0.02	4.76	1.05
TF12	27.99±0.2	0.42±0.01	0.43±0.01	2.32	1.02
TF13	26.5±0.5	0.41±0.02	0.43±0.01	4.65	1.04

±S.D. n=3

Table 4: Characterization of Granules

1. Weight Variation test

Formulation Batches	Weight Variation test
TF1	0.56
TF2	0.63
TF3	0.45

TF4	0.36
TF5	0.55
TF6	0.78
TF7	0.73
TF8	0.49
TF9	0.32
TF10	0.46
TF11	0.54
TF12	0.63
TF13	0.74

±S.D. n=3

Table 5: Weight variation test of TF1-TF13

2. Thickness

Formulation Batches	Thickness(mm)
TF1	0.47±0.365
TF2	0.5±0.946
TF3	0.49±0.364
TF4	0.49±0.145
TF5	0.49±0.03
TF6	0.47±0.135
TF7	0.48±0.541
TF8	0.49±0.532
TF9	0.47±0.01
TF10	0.49±0.558
TF11	0.49±0.647
TF12	0.48±0.387
TF13	0.47±0.347

Table 5: Thickness (mm) of TF1-TF13

ANOVA for Quadratic model

Response 1: Thickness

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0012	9	0.0001	14.20	0.0257	significant
A-PVPK-30	0.0008	1	0.0008	81.94	0.0028	
B-MCC PH101	0.0000	1	0.0000	0.0000	1.0000	
C-Eudragit RL100	0.0000	1	0.0000	2.12	0.2413	
AB	0.0000	1	0.0000	0.0000	1.0000	
AC	0.0000	1	0.0000	0.0000	1.0000	
BC	0.0000	1	0.0000	0.0000	1.0000	
A^2	0.0002	1	0.0002	20.67	0.0199	
B^2	0.0001	1	0.0001	6.83	0.0795	
C^2	0.0000	1	0.0000	1.71	0.2825	
Residual	0.0000	3	9.763E-06			
Cor Total	0.0013	12				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 14.20 implies the model is significant. There is only a 2.57% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	0.0031		R^2	0.9771
Mean	0.4831		Adjusted R^2	0.9083
C.V. %	0.6468		Predicted R^2	NA[1]
			Adeq Precision	10.3277

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 10.328 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors

Thickness	=
+0.4900	
-0.0100	A
+0.0000	B
+0.0012	C
+0.0000	AB
+0.0000	AC
+0.0000	BC
-0.0082	A^2
-0.0035	B^2
+0.0018	C^2

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors

Thickness	=
+0.238694	
+0.018945	PVPK-30
+0.001645	MCC PH101
-0.001168	Eudragit RL100
+3.43593E-19	PVPK-30 * MCC PH101
+5.79790E-18	PVPK-30 * Eudragit RL100
+1.76233E-19	MCC PH101 * Eudragit RL100
-0.003659	$PVPK\text{-}30^2$
-2.88615E-06	$MCC\ PH101^2$
+0.000071	Eudragit $RL100^2$

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

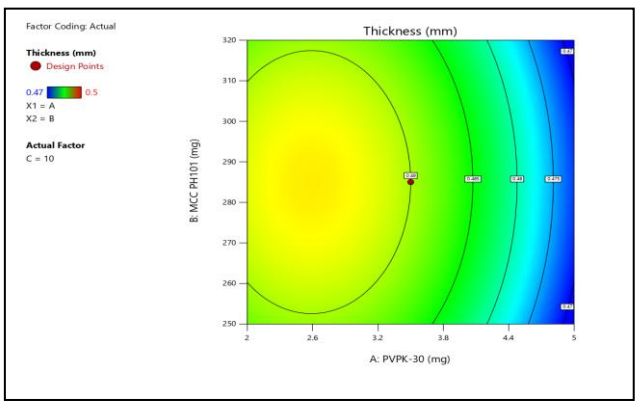


Figure 1: Counter Plot

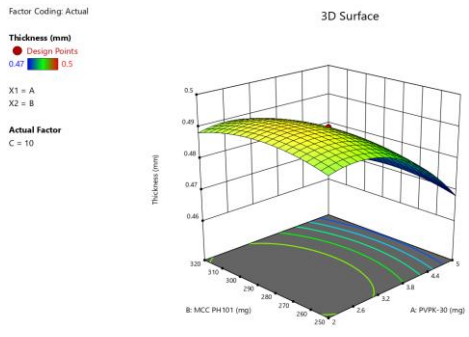


Figure 2: 3D Surface Plot

3. Hardness

Batch TF9 is identified as the optimized batch based on its hardness measurement of 4±0.01 kg. This low standard deviation indicates exceptional consistency in tablet hardness, which is crucial for ensuring uniform mechanical strength and handling characteristics. Among all batches, TF9's precise hardness, combined with its minimal weight variation (0.32%) and consistent thickness (0.47±0.03 mm), underscores its suitability for reliable manufacturing and high-quality tablet production.

Formulation Batches	**Hardness(kg)**
TF1	4±0.1
TF2	5±0.2
TF3	6±0.03
TF4	6±0.5
TF5	5±0.01
TF6	4±0.6
TF7	4±0.03
TF8	6±1.2
TF9	4±0.01
TF10	6±0.05
TF11	4±0.04
TF12	5±0.06
TF13	4±0.02

Table 6: Hardness of TF1-TF13

ANOVA for Linear model

Response 2: Hardness

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	6.69	3	2.23	6.67	0.0115	Significant
A-PVPK-30	6.13	1	6.13	18.33	0.0020	
B-MCC PH101	0.0340	1	0.0340	0.1019	0.7569	
C-Eudragit RL100	0.5266	1	0.5266	1.58	0.2409	
Residual	3.01	9	0.3341			
Cor Total	9.69	12				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 6.67 implies the model is significant. There is only a 1.15% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	0.5780		**R^2**	0.6898
Mean	4.85		**Adjusted R^2**	0.5864
C.V. %	11.93		**Predicted R^2**	0.4686
			Adeq Precision	6.9947

The **Predicted R^2** of 0.4686 is in reasonable agreement with the **Adjusted R^2** of 0.5864; i.e. the difference is less than 0.2.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 6.995 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors

Hardness	=
+4.85	
-0.8750	A

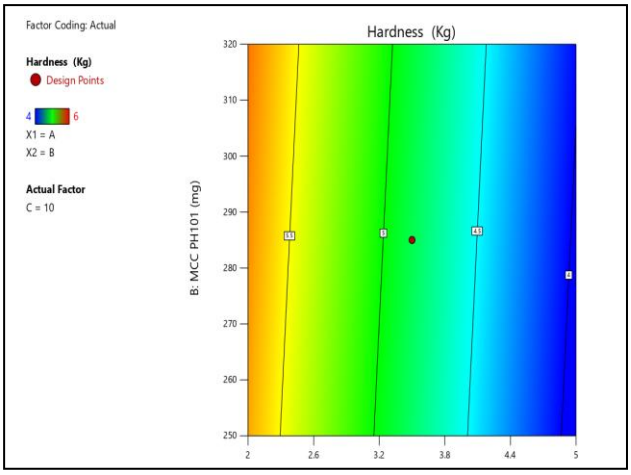
+0.0499	B
+0.1964	C

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors

Hardness	=
+6.08856	
-0.583333	PVPK-30
+0.001426	MCC PH101
+0.039274	Eudragit RL100

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.



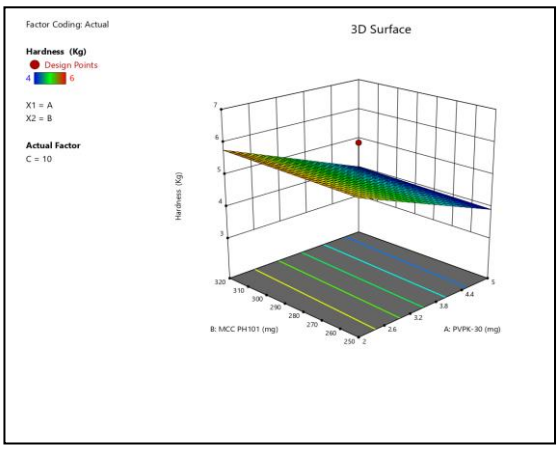


Figure 4: 3D Surface Plot

4. Friability

Batch TF9 is identified as the optimized batch based on its friability measurement of 0.29%. This low friability percentage indicates superior resistance to mechanical stress and less propensity for the tablets to chip, crumble, or break, which is crucial for maintaining tablet integrity during handling and transportation. TF9's exceptional friability, combined with its minimal weight variation (0.32%), consistent thickness (0.47±0.03 mm), and precise hardness (4±0.01 kg), underscores its overall superiority in quality and consistency. These attributes collectively make TF9 the preferred choice for reliable and durable tablet production.

Figure 3: Counter Plot

Formulation Batches	Friability (%)
TF1	0.35
TF2	0.36
TF3	0.47
TF4	0.43
TF5	0.47
TF6	0.35

TF7	0.38
TF8	0.35
TF9	0.29
TF10	0.30
TF11	0.33
TF12	0.45
TF13	0.39

Table 7: Friability (%) of TF1-TF13

5. Drug content

Batch TF9 is identified as the optimized batch based on its drug content of 99.75±0.01%. This extremely high drug content, coupled with the lowest standard deviation among the batches, indicates exceptional uniformity and accuracy in the formulation, ensuring each tablet delivers a precise and consistent dose.

Formulation Batches	**TF1**	**TF2**	**TF3**	**TF4**	**TF5**	**TF6**	**TF7**	**TF8**	**TF9**	**TF10**	**TF11**	**TF12**	**TF13**
Drug content (%)	99.69±0.9	98.12±0.3	99.02±1.5	99.15±1.2	99.60±0.6	99.60±0.6	99.07±0.8	97.89±0.1	99.75±0.01	97.86±0.326	94.56±0.45	96.63±0.654	95.63±0.498

±S.D. n=3

Table 8: Drug content for Formulation (TF1- TF13)

6. Swelling index

Batch TF9 exhibits a swelling index of 62.30%, indicating its ability to absorb moisture and expand under controlled conditions. This moderate swelling index suggests TF9 can maintain structural integrity while facilitating controlled release characteristics, which is advantageous for certain drug formulations requiring specific dissolution profiles. Despite not having the highest swelling index among all batches tested, TF9's overall balance of key parameters such as minimal weight variation (0.32%), consistent thickness (0.47±0.03 mm), excellent hardness (4±0.01 kg), low friability (0.29%), and high drug content (99.75±0.01%) positions it as the optimized batch for ensuring reliable and consistent tablet manufacturing processes.

Formulation Batches	**TF1**	**TF2**	**TF3**	**TF4**	**TF5**	**TF6**	**TF7**	**TF8**	**TF9**	**TF10**	**TF11**	**TF12**	**TF13**
Swelling index (%)	66.52	64.21	65.24	63.54	64.41	63.25	63.25	61.15	62.30	64.20	64.20	69.35	75.16

Table 9: Swelling Index (TF1-TF13)

7. In vitro drug release study:

Dissolution data of matrix tablets are reported in below respective tables. Dissolution study for each formulation was carried out in triplicate, in acid and buffer stage.

Formulation Batches	**% Release without rat cecal content medium**	
	0.1 N HCl for 2 hrs.	**PH 7.4 Phosphate buffer for 3 hrs.**
TF1	1.12±0.7	7.22±0.9
TF2	1.45±0.5	7.11±1.58
TF3	1.15±0.4	7.15±0.8
TF4	0.98±0.7	5.42±0.9
TF5	0.87±0.8	5.20±0.3
TF6	0.74±1.02	5.59±1.07
TF7	0.63±0.8	3.12±0.9

TF8	0.64±0.9	3.45±0.8
TF9	0.60±0.6	3.20±0.7
TF10	0.65±0.2	3.15±0.02
TF11	0.63±0.3	4.89±0.01
TF12	0.62±0.01	5.21±0.03
TF13	0.64±0.05	5.16±0.04

±S.D. n=3

Table 10: % of Budesonide release from matrix formulation in 0.1 N HCl for 2 hrs. and pH 7.4 Phosphate buffer for 3 hrs. Without rat cecal content medium

Batch	% Release with rat cecal content medium	
	0.1 N HCl for 2 hrs.	pH 7.4 Phosphate buffer for 3 hrs.
TF1	1.02±1.02	7.02±0.8
TF2	1.12±0.8	6.98±0.5
TF3	1.08±0.9	6.25±1.05
TF4	0.88±0.8	4.02±0.5
TF5	0.77±0.2	4.78±0.9
TF6	0.70±1.6	4.59±1.5
TF7	0.53±0.7	2.98±0.8
TF8	0.54±0.9	2.96±0.3
TF9	0.51±0.8	2.74±0.4
TF10	0.50±0.02	2.15±0.03
TF11	0.61±0.03	4.03±0.05
TF12	0.62±0.1	4.12±0.01
TF13	0.64±0.4	6.21±0.02

±S.D. n=3

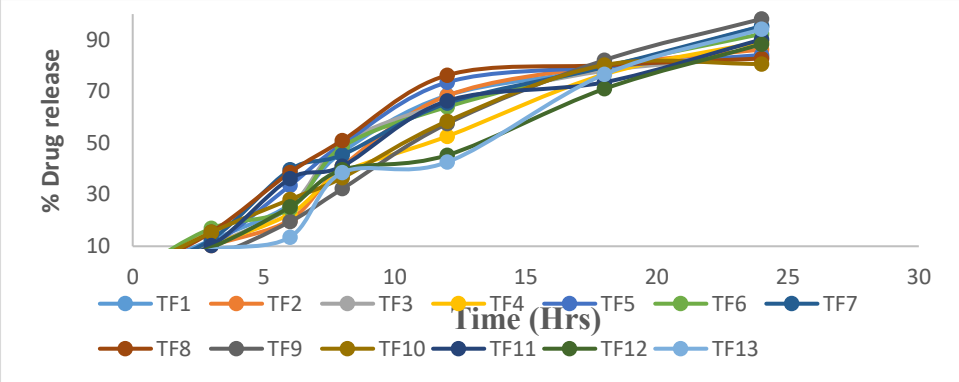
Table 11: % of Budesonide release from matrix formulation in 0.1 N HCl for 2 h and pH 7.4 Phosphate buffer for 3 h with rat cecal content medium

Time (Hrs.) / Batch	% Budesonide release												
	TF1	**TF2**	**TF3**	**TF4**	**TF5**	**TF6**	**TF7**	**TF8**	**TF9**	**TF10**	**TF11**	**TF12**	**TF13**
3	12.40±0.25	10.23±0.32	10.51±0.5	10.52±0.7	10.45±1.07	16.95±0.8	12.59±0.5	15.45±1.02	6.05±0.9	15.40±0.25	10.23±0.32	9.51±0.5	8.52±0.7
6	26.14±0.12	20.21±1.06	25.26±0.6	22.54±0.5	33.56±1.11	24.55±0.2	39.65±0.4	38.56±0.78	19.52±1.05	28.14±0.12	36.21±1.06	25.26±0.6	13.54±0.5
8	46.56±0.89	41.04±0.6	49.63±0.4	38.52±0.5	49.52±0.8	48.56±0.9	45.45±0.8	51.02±0.45	32.30±0.8	36.56±0.89	41.04±0.6	39.63±0.4	38.52±0.5
12	68.45±0.25	68.35±0.4	65.32±0.7	52.62±0.6	73.56±0.9	64.03±1.04	65.45±0.6	76.30±0.48	57.52±0.3	58.45±0.25	66.35±0.4	45.32±0.7	42.62±0.6
18	79.25±0.26	80.0±1.15	78.02±1.57	76.63±0.7	79.56±0.4	79.65±1.3	79.48±0.4	80.18±0.5	82.15±0.4	80.25±0.26	73.58±1.15	71.02±1.57	76.63±0.7
24	95.24±0.14	86.24±0.9	83.21±0.1	89.32±0.4	84.17±0.7	92.31±1.2	95.31±0.7	82.78±0.4	98.12±0.8	80.68±0.14	90.19±0.9	88.31±0.1	94.15±0.4

±S.D. n=3

Table 12: % of Budesonide release from matrix formulation in pH 6.8 Phosphate buffer for 24 h without rat cecal content medium (Control)

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 21s, 2025
https://theaspd.com/index.php

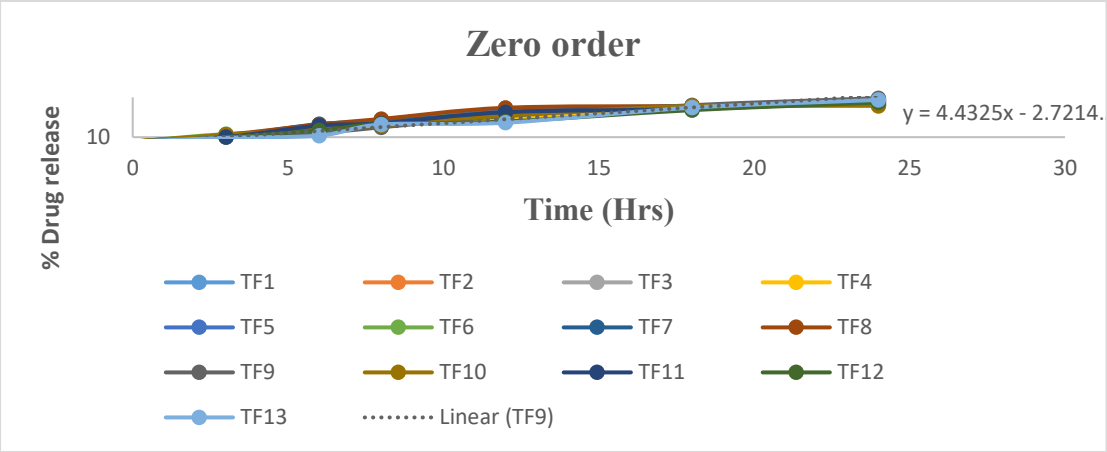


Graph 1- % of Budesonide release from matrix formulation in pH 6.8 Phosphate buffer for 24 h without rat cecal content medium (Control)

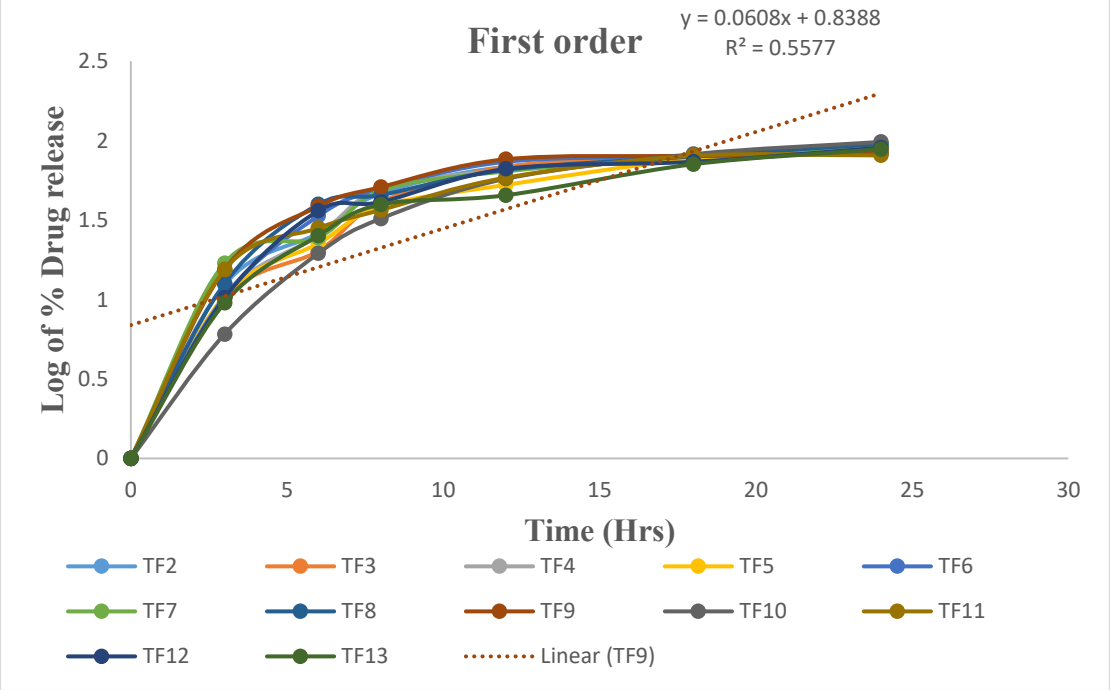
Kinetic analysis

In order to define the release mechanism that gives the best description of the release pattern; the in vitro release data for all optimized batches were fitted to kinetic equations models.

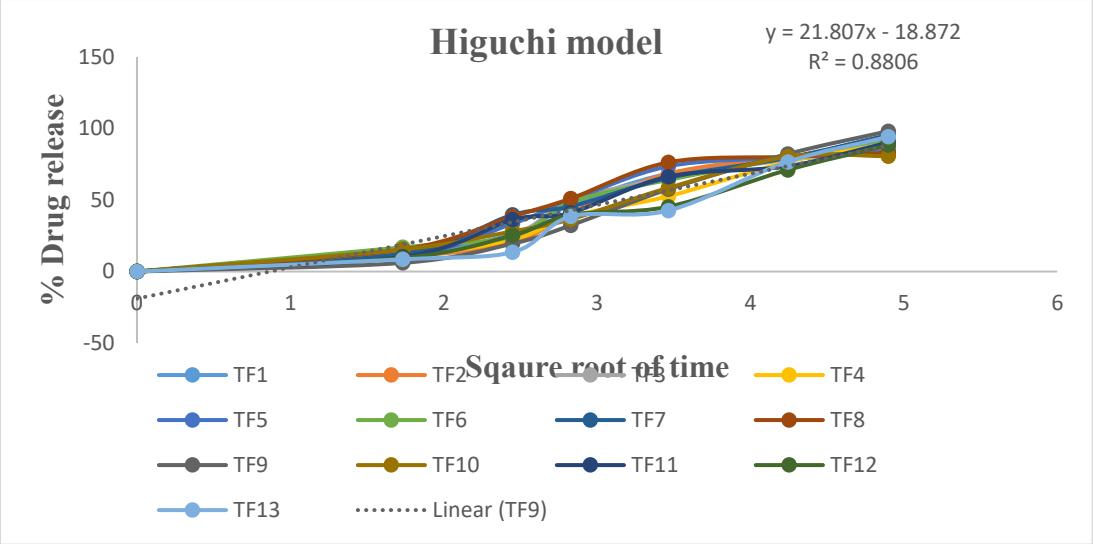
The kinetic equations were used i.e., Zero order, First-order and Higuchi model. Both the kinetic rate constant (k) and the determination coefficient (R^2) were calculated and presented in below graphs. The best fit model with the highest determination coefficient (R^2) value for optimized batch was Zero order.



Graph 2: Zero order Kinetics (Control)



Graph 3: First order Kinetics (Control)



Graph 4: Higuchi model (Control)

ANOVA for Linear model

Response 3: Drug Release (Control)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	211.99	3	70.66	3.95	0.0473	significant
A-PVPK-30	203.41	1	203.41	11.38	0.0082	
B-MCC PH101	8.00	1	8.00	0.4474	0.5203	
C-Eudragit RL100	0.5728	1	0.5728	0.0320	0.8619	
Residual	160.92	9	17.88			
Cor Total	372.91	12				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 3.95 implies the model is significant. There is only a 4.73% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	4.23		**R^2**	0.5685
Mean	89.23		**Adjusted R^2**	0.4246
C.V. %	4.74		**Predicted R^2**	0.2539
			Adeq Precision	5.1269

The **Predicted R^2** of 0.2539 is in reasonable agreement with the **Adjusted R^2** of 0.4246; i.e. the difference is less than 0.2.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 5.127 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors

Drug Release	=
+89.23	
+5.04	A
-0.7654	B
+0.2048	C

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors

Drug Release	=
+83.29071	
+3.36167	PVPK-30
-0.021868	MCC PH101
+0.040960	Eudragit RL100

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

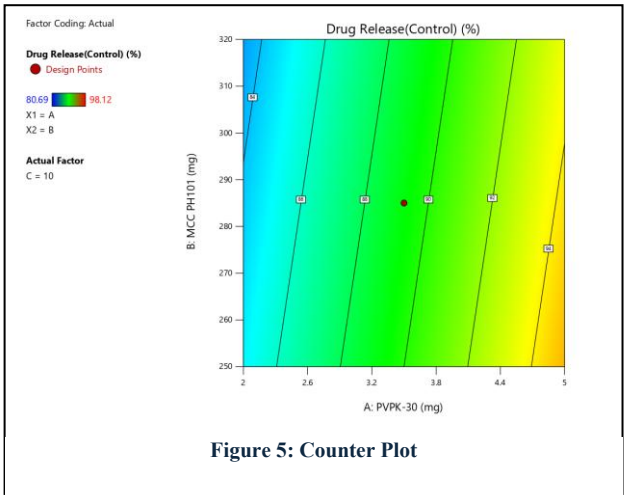


Figure 5: Counter Plot

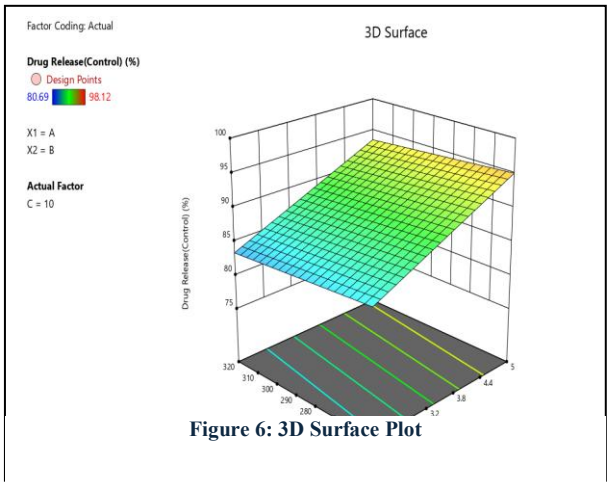
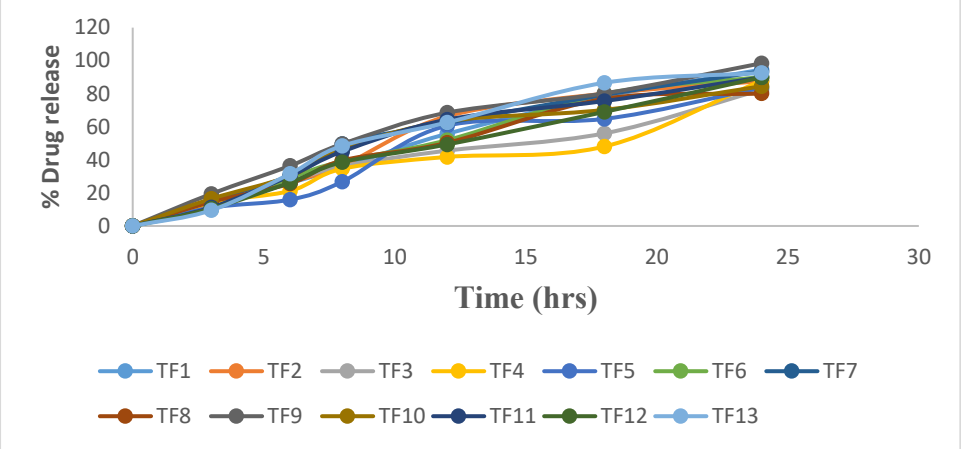


Figure 6: 3D Surface Plot

Time (Hrs.)/ Batch	% Budesonide release												
	TF1	TF2	TF3	TF4	TF5	TF6	TF7	TF8	TF9	TF10	TF11	TF12	TF13
3	12.94±0.09	13.27±0.04	11.19±0.17	14.10±0.18	11.05±0.15	10.09±0.12	15.38±0.12	14.56±0.05	19.44±0.15	16.45±0.25	11.24±0.32	10.51±0.5	9.52±0.7
6	25.94±0.15	26.51±0.09	26.63±0.16	21.19±0.17	15.93±0.06	28.98±0.17	30.43±0.12	25.63±0.04	36.38±0.16	30.14±0.12	30.2±1.06	26.26±0.6	31.54±0.5
8	35.51±0.18	36.45±0.07	36.12±0.17	34.63±0.16	26.83±0.19	39.18±0.15	49.63 ±0.12	39.63±0.11	49.63±0.18	46.55±0.89	45.04±0.6	38.63±0.4	48.52±0.5
12	55.78±0.16	66.40±0.17	45.60±0.23	41.78±0.03	60.71±0.16	51.92±0.11	62.36±0.17	50.32±0.21	68.56±0.05	63.45±0.25	64.35±0.4	49.32±0.7	62.62±0.6
18	78.29±0.16	80.02±0.20	56.03±0.10	48.07±0.07	64.81±0.16	79.96±0.18	79.32±0.16	76.92±0.11	80.25±0.14	70.25±0.26	75.58±1.15	69.02±1.57	86.63±0.7
24	94.56±0.15	87.63±0.19	82.36±0.12	87.86±0.10	83.66±0.16	90.15±0.17	93.55±0.16	80.14±0.18	98.45±0.25	84.55±0.14	89.96±0.9	89.93±0.1	92.56±0.4

Table 13: % of Budesonide released from matrix formulation in pH 6.8 Phosphate buffer for 24 h with rat cecal content medium (Test)

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 21s, 2025
https://theaspd.com/index.php

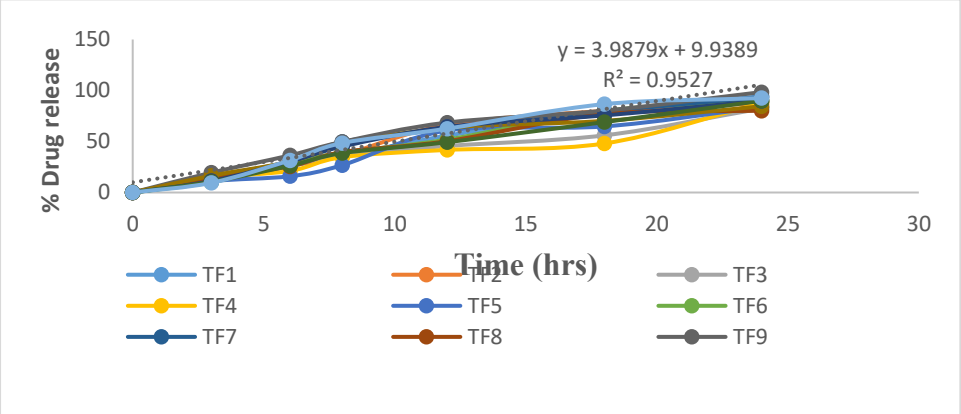


Graph 5: % of Budesonide released from matrix formulation in pH 6.8 Phosphate buffer for 24 h with rat cecal content medium (Test)

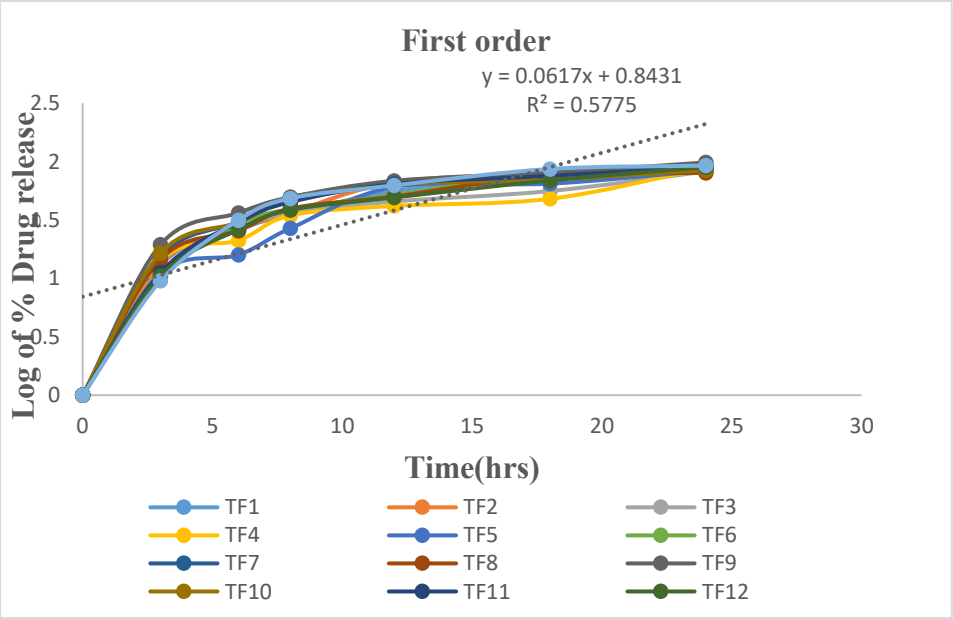
Kinetic analysis

In order to define the release mechanism that gives the best description of the release pattern; the in vitro release data for all optimized batches were fitted to kinetic equations models.

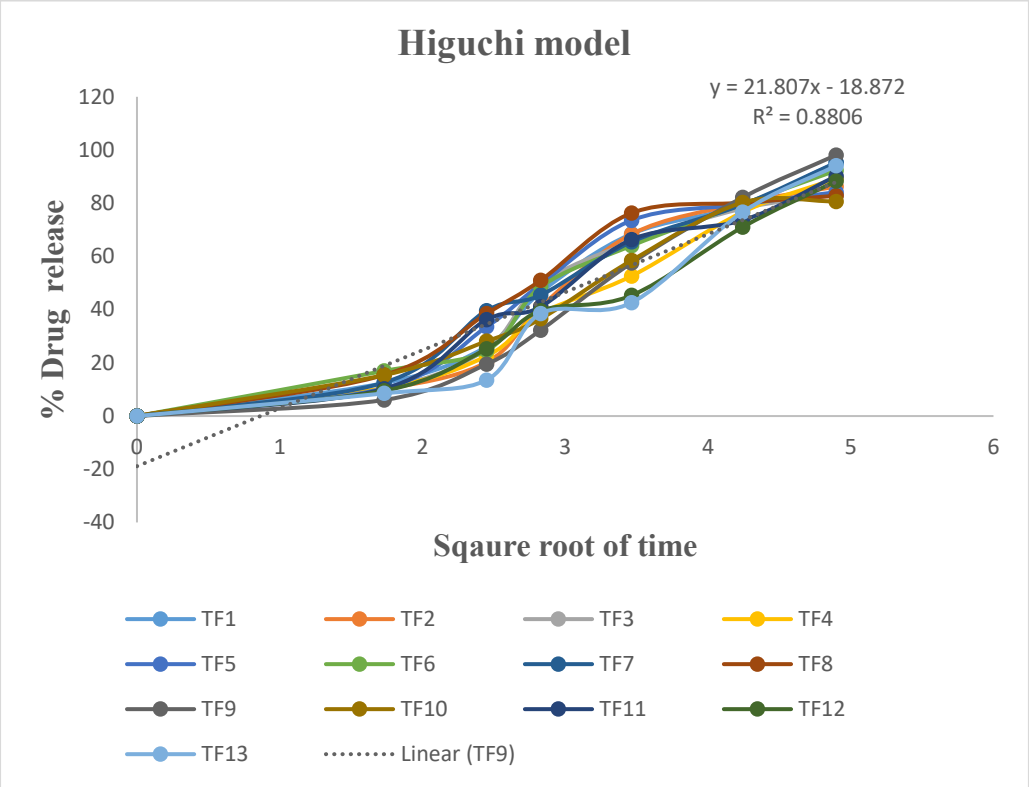
The kinetic equations were used i.e., zero, first-order and Higuchi model. Both the kinetic rate constant (k) and the determination coefficient (R^2) were calculated and presented in below graphs. The best fit model with the highest determination coefficient (R^2) value for optimized batch was Zero order.



Graph 6: Zero order Kinetics (Test)



Graph 7: First order Kinetics (Test)



Graph 8: Higuchi model Kinetics (Test)

ANOVA for Linear model

Response 4: Drug release (test)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	219.11	3	73.04	5.90	0.0165	significant
A-PVPK-30	217.36	1	217.36	17.55	0.0023	
B-MCC PH101	0.3570	1	0.3570	0.0288	0.8689	
C-Eudragit RL100	1.39	1	1.39	0.1125	0.7450	
Residual	111.47	9	12.39			
Cor Total	330.58	12				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 5.90 implies the model is significant. There is only a 1.65% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	3.52		**R^2**	0.6628
Mean	88.87		**Adjusted R^2**	0.5504
C.V. %	3.96		**Predicted R^2**	0.3057
			Adeq Precision	5.8331

The **Predicted R^2** of 0.3057 is not as close to the **Adjusted R^2** of 0.5504 as one might normally expect; i.e. the difference is more than 0.2. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doing confirmation runs.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 5.833 indicates an adequate signal. This model can be used to navigate the design space.

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 21s, 2025
https://theaspd.com/index.php

Final Equation in Terms of Coded Factors

Drug release	=
+88.87	
+5.21	A
-0.1617	B
+0.3194	C

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors

Drug release	=
+77.38920	
+3.47500	PVPK-30
-0.004620	MCC PH101
+0.063872	Eudragit RL100

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

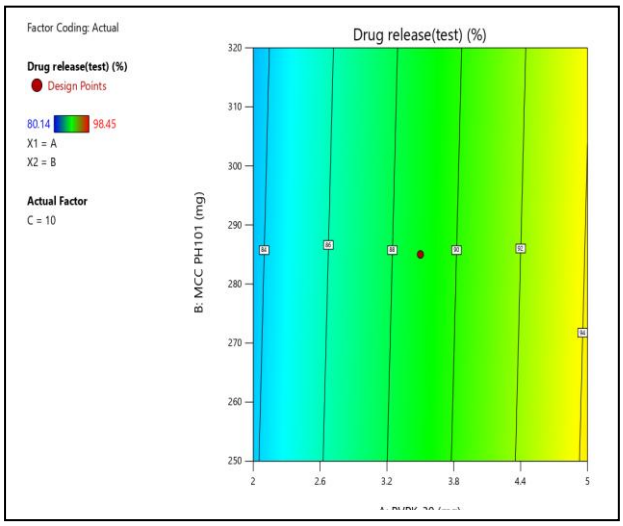


Figure 7: Counter Plot

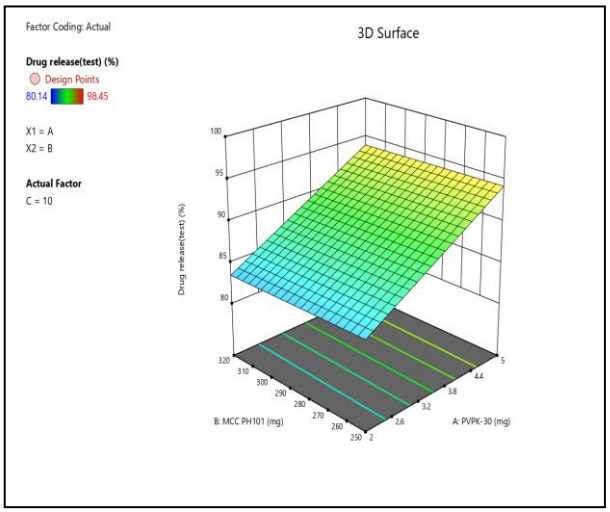


Figure 8: 3D Surface Plot

CONCLUSION

The colon-specific Budesonide formulation with Eudragit RL100 has shown low drug release provide significant therapeutic benefits to the patients in terms of safety, efficacy, and patient compliance. The dissolution rate studies were performed to evaluate the dissolution character of the Budesonide from the colon targeted tablets.

TF9's exceptional friability, combined with its minimal weight variation (0.32%), consistent thickness (0.47±0.03 mm), and precise hardness (4±0.01 kg), underscores its overall superiority in quality and consistency. TF9 is identified as the optimized batch based on its drug content of 99.75±0.01%, hardness measurement of 4±0.01 kg, friability measurement of 0.29%. The kinetic equations were used i.e., Zero order, First-order and Higuchi model. Both the kinetic rate constant (k) and the determination coefficient (R^2) were calculated and presented in graphs. The best fit model with the highest determination coefficient (R^2 is 0.9823) value for optimized batch was Zero order.

Aknowledgement

The authors would like to thank Invitox, R&D Institute, Pune, Maharashtra, India, for their laboratory, instrumentation analysis and for in vivo study support. Authors are also thankful to Dr. Amit Kasabe for his kind support throughout research.

REFERENCES

1. Rayaprolu BM, Strawser JJ, Anyarambhatla G. Excipients in parenteral formulations: selection considerations and effective utilization with small molecules and biologics. Drug development and industrial pharmacy. 2018 Oct 3;44(10):1565-71.
2. Vargason AM, Anselmo AC, Mitragotri S. The evolution of commercial drug delivery technologies. Nature biomedical engineering. 2021 Sep;5(9):951-67.
3. Ezike TC, Okpala US, Onoja UL, Nwike PC, Ezeako EC, Okpara JO, Okoroafor CC, Eze SC, Kalu OL, Odoh EC, Nwadike U. Advances in drug delivery systems, challenges and future directions. Heliyon. 2023 Jun 24.
4. Adepu S, Ramakrishna S. Controlled drug delivery systems: current status and future directions. Molecules. 2021 Sep 29;26(19):5905.
5. Prajapat P, Agrawal D, Bhaduka G. A brief overview of sustained released drug delivery system. Journal of Applied Pharmaceutical Research. 2022 Sep 30;10(3):05-11.
6. Khalane L, Alkunte AT, Birajdar AR. Sustained release drug delivery system: a concise review. Pharmatutor: pharmacy infopedia. 2016.
7. Amidon S, Brown JE, Dave VS. Colon-targeted oral drug delivery systems: design trends and approaches. Aaps Pharmscitech. 2015 Aug;16: 731-41.
8. Jain M, Venkataraman J. Inflammatory bowel disease: An Indian perspective. Indian Journal of Medical Research. 2021 Apr 1;153(4):421-30.
9. Sethi S, Harikumar SL. Review on advances in colon targeted drug delivery system. International Journal of Pharmaceutical Sciences And Research. 2012 Sep 1;3(9):2989.
10. Marieb EN, Hoehn K. Human anatomy & physiology. Pearson education; 2007.
11. Hebden, Blackshaw, Perkins, Spiller. Limited exposure of the healthy distal colon to orally-dosed formulation is further exaggerated in active left-sided ulcerative colitis. Alimentary pharmacology & therapeutics. 2000 Feb;14(2):155-61.
12. Alvarez-Fuentes J, Fernández-Arévalo M, González-Rodríguez ML, Cirri M, Mura P. Development of enteric-coated timed-release matrix tablets for colon targeting. Journal of drug targeting. 2004 Dec 1;12(9-10):607-12.
13. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut. 1988 Aug 1;29(8):1035-41.
14. Budesonide: Uses, Interactions, Mechanism of Action | DrugBank Online
15. Abla KK, Mneimneh AT, Allam AN, Mehanna MM. Application of Box-Behnken design in the preparation, optimization, and in-vivo pharmacokinetic evaluation of oral tadalafil-loaded niosomal film. Pharmaceutics. 2023 Jan 3;15(1):173.
16. Nama M, Gonugunta CS, Reddy Veerareddy P. Formulation and evaluation of gastroretentive dosage forms of clarithromycin. Aaps PharmSciTech. 2008 Mar;9:231-7.
17. Khan FN, Dehghan MH. Enhanced bioavailability of atorvastatin calcium from stabilized gastric resident formulation. Aaps Pharmscitech. 2011 Dec;12(4):1077-86.
18. Pathare VB, Shendge RS, Shinde PS, Pandit SR, Pulate AJ. Formulation and In Vitro evaluation of Oral Colon Targeted Sustained Released Tablet of Budesonide. Turkish Journal of Physiotherapy and Rehabilitation.;32(3).
19. Mehta R, Chawla A, Sharma P, Pawar P. Formulation and in vitro evaluation of Eudragit S-100 coated naproxen matrix tablets for colon-targeted drug delivery system. Journal of advanced pharmaceutical technology & research. 2013 Jan 1;4(1):31-41.
20. Zheng, L., Gao, Z. Q., & Wang, S. X. (2000). Chronic ulcerative colitis model in rats. World journal of gastroenterology, 6(1), 150.
21. Lin TY, Chen CW. Overview of stability study designs. Journal of biopharmaceutical statistics. 2003 Jan 7;13(3):337-5