FORMULATION AND EVALUATION OF BUDESONIDE MINI-TABLET IN ENTERIC-COATED CAPSULE FOR THE TREATMENT OF ULCERATIVE COLITIS USING A FACTORIAL DESIGN APPROACH

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Abstract

The Enteric Capsule Drug Delivery Technology (ECDDT) was designed to enable oral administration while ensuring complete enteric protection and swift release in the upper gastrointestinal (GI) tract, without the need for coatings. The utilisation of ECDDT can potentially mitigate programme risk and expedite development timelines by removing the preparatory and applicative measures involved in enteric coating. Mini-Tablets present a viable option for administering low porosity pellets, as they share the same dimensions and morphology, exhibit uniform surface characteristics, demonstrate minimal inter-batch variation, and are readily manufacturable. Current study used a 3^2 factorial design (Stat-Ease Design Expert v12) to formulate a mini-tablet in an enteric-coated capsule to treat ulcerative colitis utilising ECDDT and mini-tablets. Budesonide, a corticosteroid, was used as a model drug to study the effects of independent variables like HPMC K4M as a release retarding polymer at 2-6% and Cros povidone as a super disintegrant at 2-5% on in vitro drug release to meet desired Q points of dissolution.

Keywords: Budesonide, HPMC K4M, Cros povidone, factorial design, release retarding agent.

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DOI: 10.48047/ecb/2023.12.si5a.0557

INTRODUCTION

Inflammation and ulcers (sores) in the digestive system are symptoms of the inflammatory bowel disease (IBD) known as ulcerative colitis. The innermost lining of the large intestine, often known as the colon and rectum, is impacted by ulcerative colitis. In the majority of people, symptoms typically appear gradually rather than abruptly. [1] Draining and perhaps life-threatening consequences are possible with ulcerative colitis. Although there is no known cure, there are a number of innovative treatments that can significantly lessen the disease's signs and symptoms and result in a long-lasting remission. [2]

Typically, either drug therapy or surgeries are used as treatments. The treatment of ulcerative colitis may be successful with a variety of drug classes. Some individuals may not respond adequately to some drugs [3]. The initial line of treatment for ulcerative colitis is frequently anti-inflammatory drugs, which are suitable for the majority of patients with this condition. [4]

The enteric coated drug-delivery technology (ECDDT), which offers complete enteric protection without the need for a separate enteric coating, is described in recent technical research. ECDDT can provide quicker development timelines and decreased programme risk by doing away with the preparation and application stages required for enteric coating [5, 6]. It has been demonstrated that this cutting-edge technology makes it possible to develop products that require enteric protection and/or targeted release to the upper gastrointestinal tract by enabling the oral delivery of sensitive molecules and acting as a valuable tool for product development. [7]

Making mini-tablets that meet the USP dissolution Q values of budesonide [8] is the most difficult aspect of the study to prevent dose dumping. A factorial design was used to develop mini-tablets based on budesonide. To investigate the effect of independent factors on dependent variables, a two-factor, three-level factorial design was used with Stat-Ease Design Expert v12. According to the experimental design, nine formulations were generated. Excipient levels in factorial designs were chosen in accordance with the 6th Edition; Handbook of Pharmaceutical Excipients [9]. Mini-tablets were compressed and evaluated for precompression and post compression parameters before being encapsulated in enteric-coated capsules. In Vitro drug release, Release Kinetics and Stability were conducted on a mini-tablet in an enteric-coated capsule.

MATERIALS AND METHODS

Materials

Budesonide drug was obtained as gift sample from Remedium Laboratories Pvt. Ltd, Hyderabad. Enteric Coated Capsule was obtained from XPRS Nutra, West Jordan. Microcrystalline Cellulose, Cros povidone, HPMC K4M, Magnesium stearate & Talc were purchased from Signet Excipients Pvt. Ltd, Bangalore.

Methods

Assessment of Enteric Coated Capsules

Enteric coated capsules were assessed for maintaining the integrity in acidic pH. 6 units with 3mg of Budesonide drug in each capsule were subjected to dissolution for 2 Hours in 0.1N Hydrochloric acid according to USP Dissolution method. Specification of NMT 5% release of Budesonide after 2 Hours. (Dissolution Conditions Volume: 1000mL, Medium: 0.1N Hydrochloric Acid, Temperature: 37°, RPM: 75, Time: 2 Hours, Intervals (Minutes): 30, 60, 90 & 120, Apparatus: USP Type II)

Compatibility Study of Drug and Excipients using FT-IR:

Budesonide and Excipients compatibility were evaluated using Bruker Alpha II FT-IR. Potassium Bromide pellet method is employed for the current study.

Formulation of Mini-Tablets with Factorial Design Approach

Budesonide based Mini Tablets were prepared by using factorial design. A 2-factor three-level factorial design was employed using Stat-Ease Design Expert v12 to study the effect of independent variables on dependent variables. A total of 9 formulations were prepared according to the experimental design. The amount of HPMC K4M (X1) and Cros povidone (X2) were selected as independent variables. The time dissolution response of drug in 1hr (Q1), 2hr (Q2) and 6 hrs (Q3) was selected as dependent variable. Excipient levels in factorial design were selected according to handbook of pharmaceutical excipients 6th Edition. [9]

Std	Run	Factor 1 A:HPMC K4M %	Factor 2 B:Crospovidone %	Response 1 Dissolution @ 1 Hour %	Response 2 Dissolution @ 2 Hour %	Response 3 Dissolution @ 6 hours %
3	1	2	2			
7	2	4	5			
4	3	6	3			
8	4	2	5			
5	5	4	3			
9	6	6	5			
6	7	4	2			
2	8	2	3			
1	9	6	2			

Figure 1: Trials based on Stat-Ease Design Expert

Name	Units	Type	Changes	Std. Dev.	Low	High
HPMC K4M	%	Factor	Easy	0	2	6
Crospovidone	%	Factor	Easy	0	2	5
Dissolution @ 1 Hour	%	Response				
Dissolution @ 2 Hour	%	Response				
Dissolution @ 6 hours	%	Response				

Figure 2: Trials with Independent Factors at Low and High Level based on Design Expert

Formulation Development

All the ingredients were weighed according to the quantities specified in Table 1 and passed through #60mesh separately. Then the ingredients were mixed in geometrical order and compressed into tablets of 40mg by using 8-station rotary mini press tablet machine using 5mm punch. Compressed tablets were filled into Enteric Coated capsule of size#0. Each capsule contains 1 mini-tablet. The dose of each capsule is 3mg.

Table 1: Budesonide Mini-Tablets Formulations

S. No	Ingredient (mg)	BF1	BF2	BF3	BF4	BF5	BF6	BF7	BF8	BF9
1	Budesonide	3	3	3	3	3	3	3	3	3
2	HPMC K4M	0.8	1.6	2.4	0.8	1.6	2.4	1.6	0.8	2.4
3	Cros povidone	0.8	2	1.2	2	1.2	2	0.8	1.2	0.8
4	Microcrystalline Cellulose 112	34.8	32.8	32.8	33.6	33.6	32	34	34.4	33.2
5	Magnesium Stearate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
6	Talc	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Total Tablet Weight (mg)		40	40	40	40	40	40	40	40	40

Evaluation of Mini-Tablets

Pre-Compression

Bulk density, Tapped density, Angle of repose, Compressibility Index and Hausners ratio were evaluated according to USP General chapter <1174> to assess the flow property of the blend before compression. [10]

Post-Compression:

Compressed tablets were evaluated for post compression parameters according to the procedure mentioned in the following USP general chapters Weight Variation & Drug Content <905> [11], Hardness, Thickness & Friability <1217>. [12-19]

In-Vitro Drug Release Study

In-Vitro dissolution was performed according to the procedure mentioned in Budesonide USFDA dissolution database. Mini-Tablets encapsulated enteric coated capsules were assessed for maintaining the integrity in 0.1N HCL acidic pH for 2 hours while maintaining dissolution conditions (1000mL, 75 RPM; 37°±5°C; followed by (7.5 pH Phosphate Buffer; 1000mL, 75RPM; 37°±5°C; 8 Hours) at sampling intervals of 0.25, 0.5, 1, 2, 4, 6, 8 Hours). Samples obtained were determined by UV-visible spectrophotometer at 247nm. [20]

Stability Studies

Stability studies were performed according to the ICH guidelines Q1A (R2) for the optimized formulation. The stability study is an indicative method for determination of durability of quality and quantity of therapeutic agents with the passes of time under the influence of various atmospheric conditions such as temperature, humidity, light and to establish a shelf life for the drug product and recommended storage conditions at 40°C ± 2°C/75% RH ± 5% RH. [21].

Differential Scanning Colorimetry (DSC):
Further stability studies were confirmed by Differential Scanning Calorimetry. Thermal analysis of Optimized Formulation before and after stability was performed using thermal analyzer (Mettler Toledo-DSC 3) Temperature axis and cell constant were calibrated by utilizing indium (In). This technique allows a rapid assessment of possible interaction by disclosing transition in exhibition, dissipation of endothermic or exothermic peaks, and transition in the pertinent enthalpy standards in thermal curves of drug-excipients combinations.

Release Kinetics
The drug release kinetics study was conducted on optimized formulation related to various kinetic models, namely, zero-order kinetics, first-order kinetics, Higuchi and Korsmeyer-Peppas models, and then the regression analysis (R^2) and diffusion coefficient (n) were determined.[22]

RESULTS AND DISCUSSION

Assessment of Enteric Coated Capsules
Samples were collected at respective intervals and analysed in UV. There are no traces of drug found at the end of 2 hours. Results indicates that capsules are having integrity and resistance in acidic pH. Capsules were found to be an ideal candidate for enteric drug delivery system.

Figure 3: Enteric Coated Capsules with Sinker & Budesonide Mini-Tablets

Compatibility Study of Drug and Excipients using FTIR:
The FT-IR spectrophotometer was used to identify the possibilities of any interaction between the formulation components. As showed in the Table 2 & Figures 4-5, there was no substantial differentiation in the FT-IR spectra of the drug and when compared to the spectra of the Formulation mixture.

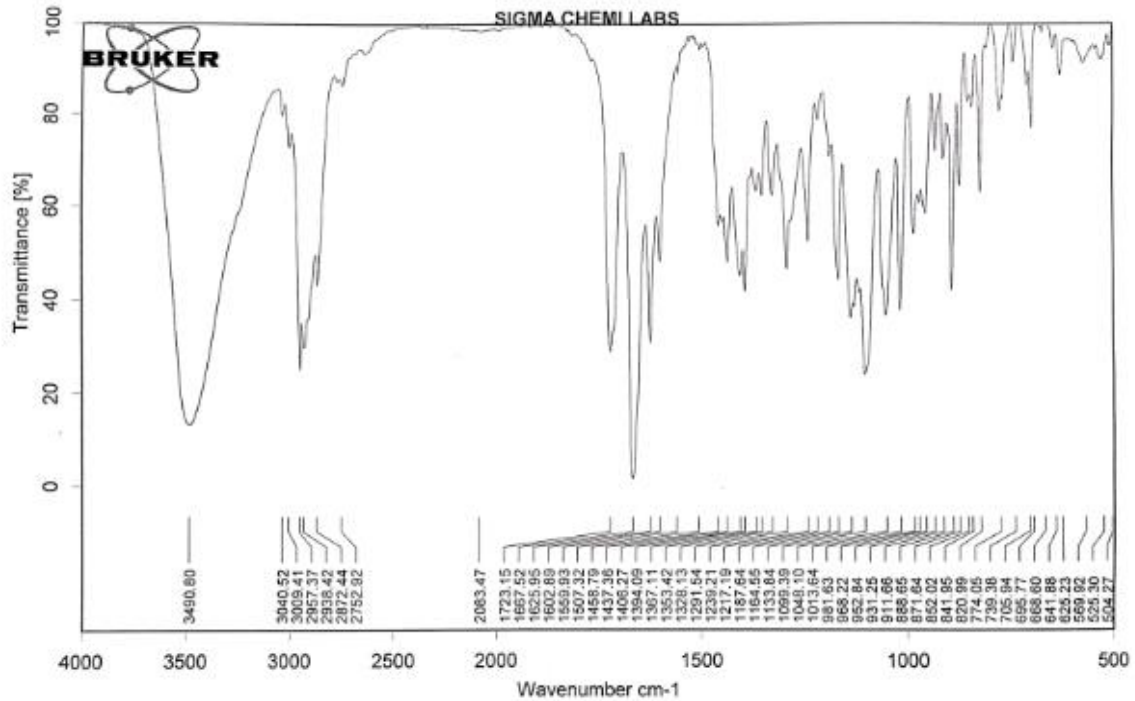

Figure 4: FT-IR Spectra of Budesonide Pure Drug

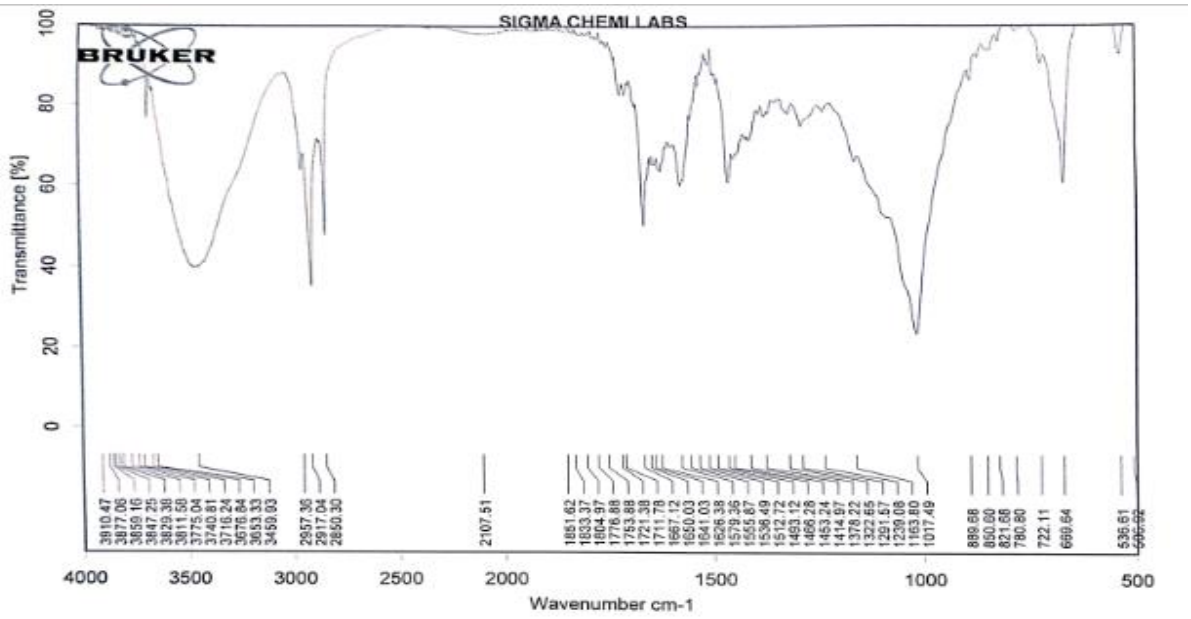

Figure 5: FT-IR Spectra of Formulation Mixture

Table 2: FT-IR Interpretation for Budesonide

Figure. No.	Compatibility	Wave numbers cm^{-1}				
		O-H Stretching	**C-H Stretching**	**C=O non-conjugated acetyl Stretching**	**C=O conjugated dihydrobenzo quinone Stretching**	**Observation**
Figure 4	Pure Drug	3490.80	3040.52	1723.15	1667.52	No Possible Interaction found
Figure 5	Formulation Mixture	3459.93	2957.36	1512.72	1667.12.24	

IR spectrum of Budesonide shows a broad peak at 3490.80 cm^{-1} may be due to O-H stretching, 3040.52 cm^{-1} may be due to C-H stretching, 1723.15 cm^{-1} may be due to non-conjugated acetyl C=O stretching and 1667.52 cm^{-1} may be due to conjugated dihydrobenzo quinone C=O stretching. IR Spectra interpretation of drug was done with individual excipients and formulation mixture and observed that there is no appreciable change in the positions of the characteristic bands. Since there is no change in the nature and position of the bands in the formulation, it can be concluded that the drug maintains its identity without undergoing any chemical interaction with the excipients used.

Evaluation of Mini-Tablets

Table 3: Precompression Evaluation Parameters of Budesonide Powder Blend

Formulations	BF1	BF2	BF3	BF4	BF5	BF6	BF7	BF8	BF9
Angle of repose (°)	28.34	26.18	28.37	25.12	25.48	26.22	27.42	24.14	29.38
Bulk density (gm/cc)	0.78	0.84	0.74	0.8	0.76	0.78	0.84	0.82	0.7
Tapped density (gm/cc)	0.85	0.9	0.83	0.86	0.86	0.84	0.94	0.86	0.8
Compressibility Index (%)	8.24	6.67	10.84	6.98	11.63	7.14	10.64	4.65	12.50
Hausner's ratio	1.09	1.07	1.12	1.08	1.13	1.08	1.12	1.05	1.14

Table 4: Post compression Evaluation Parameters of Mini-Tablets

Formulation	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
BF1	39.33	2.07	1.8	0.18	98.54
BF2	38.00	1.97	2.3	0.15	97.22
BF3	41.33	1.87	2.8	0.17	101.73
BF4	39.33	2.70	2	0.16	99.34
BF5	40.00	1.73	2.5	0.19	99.28
BF6	39.33	2.00	2.6	0.13	98.94
BF7	38.67	2.00	3	0.21	98.42
BF8	39.00	2.47	2.4	0.15	99.12
BF9	41.00	1.83	3.4	0.17	100.01

Results obtained in Table 3; were found within the limits and showed good flow properties for all the formulations. Results obtained in Table 4; were found within the acceptable limits for friability and weight variation. Thickness was found in the range of 1.73-2.70mm; Hardness was found in the range of 1.8-2.8 kg/cm^2 and Drug content was fund in the range of 97.22-101.73 %.

In-Vitro Drug Release Study

Table 5. In-Vitro Drug Release Studies of Budesonide Mini-Tablets in Enteric Coated Capsules

Dissolution (in hours.)	BF1	BF2	BF3	BF4	BF5	BF6	BF7	BF8	BF9
Initial 2 Hours in 0.1N HCL									
2 Hours	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
8 Hours Dissolution in 7.5 pH Phosphate Buffer									
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.25	10.93	9.93	9.93	12.94	8.92	9.93	8.92	16.95	5.91
0.5	15.00	15.99	13.99	24.03	10.97	18.00	10.97	21.04	9.96
1	23.97	24.97	22.09	35.00	20.96	25.98	17.95	29.99	16.95
2	49.17	47.17	32.23	62.26	42.13	52.19	28.07	58.23	25.06
4	73.09	64.00	52.45	75.28	64.94	73.14	57.74	71.18	58.62
6	90.50	86.38	80.80	95.71	90.34	86.55	80.09	89.59	80.98
8	100.98	100.85	98.25	100.19	98.81	100.01	93.53	101.06	88.41

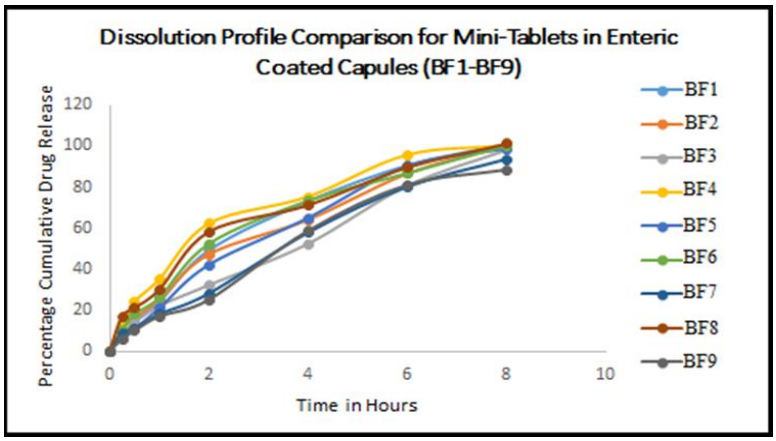

Figure 6: Cumulative Percentage Drug Release of Budesonide Mini-Tablets in Enteric Coated Capsule Formulation (BF1-BF9)

Statistical Analysis by Design Expert Software

The response Q1h, Q2h and Q6h also followed interactive (2FI) model and Design-Expert®

Table 6: Budesonide Mini-Tablets in Enteric Coated Capsules compositions with their Observed Responses

		Factor 1	Factor 2	Response 1	Response 2	Response 3
Std	**Run**	**A:HPMC K4M**	**B:Crospovidone**	**Dissolution @ 1 Hour**	**Dissolution @ 2 Hour**	**Dissolution @ 6 hours**
		%	%	%	%	%
3	1	2	2	23.97	49.17	90.5
7	2	4	5	24.97	47.17	86.38
4	3	6	3	22.09	32.23	81.46
8	4	2	5	35	62.26	95.71
5	5	4	3	20.96	42.13	90.34
9	6	6	5	25.98	52.19	86.55
6	7	4	2	17.95	28.07	80.09
2	8	2	3	29.99	58.23	89.59
1	9	6	2	16.95	25.06	80.98

Response 1: Dissolution @ 1 Hour (%)

Dissolution@1 Hour (%) =25.4086 + -10.1921 * HPMC K4M + 9.66087 * Crospovidone + -0.162857 * HPMC K4M * Crospovidone

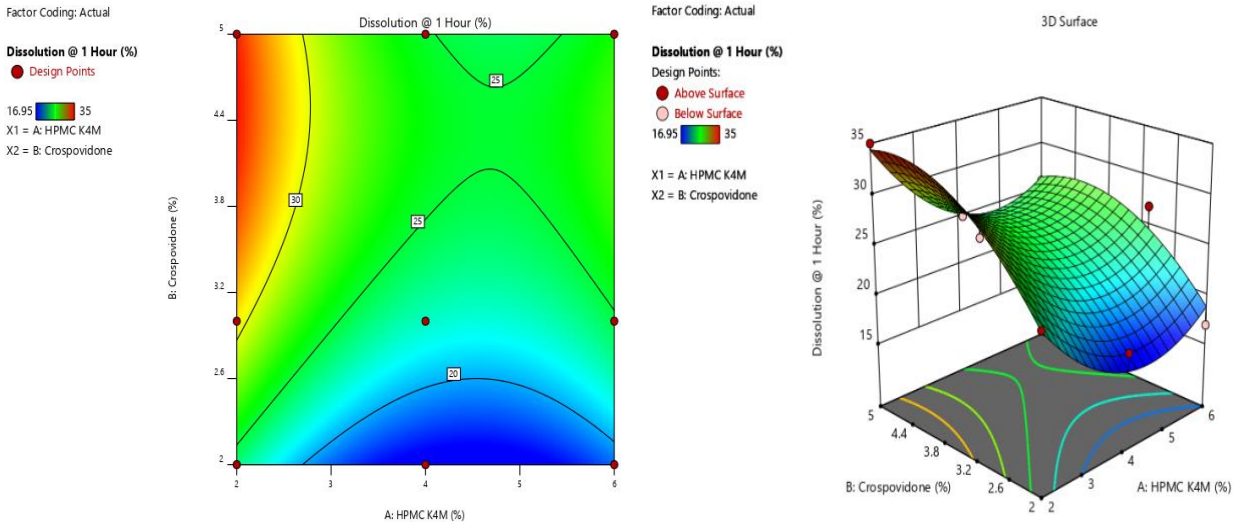

Figure 7: Response Surface Plot for Dissolution@1 Hour (%)

The codes and actual equation of Dissolution for 1 Hour (%) suggests that factor A (% HPMC K4M), AB has negative dominant effect and factor B (% Crospovidone) has positive dominant effect. This is further interpreted from ANOVA results and equation that increase in Crospovidone concentration in proportion to HPMC K4M will result in significant increase in release rate to achieve the desired Q points.

Response 2: Dissolution @ 2 Hour (%)

Dissolution @ 2 Hour (%) = 42.981 + -5.015 * HPMC K4M + 6.34071 * Crospovidone

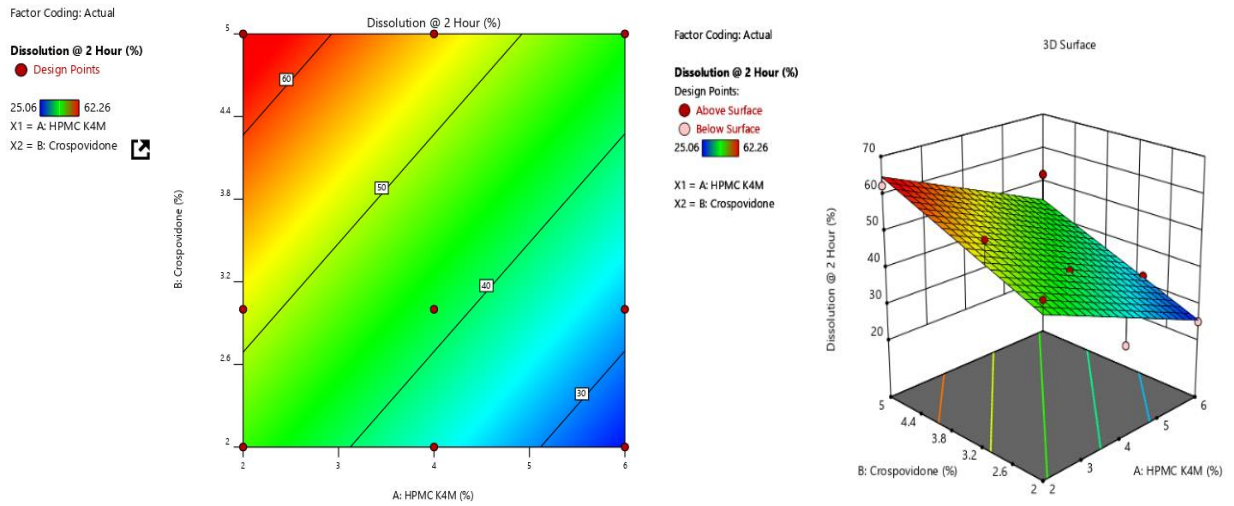

Figure 8: Response Surface Plot for Dissolution@2 Hour (%)

The codes and actual equation of Dissolution for 2 Hour (%) suggests that factor A (% HPMC K4M) has negative dominant effect and factor B (% Crospovidone) has positive dominant effect. This is further interpreted from ANOVA results and equation that increase in Crospovidone concentration in proportion to HPMC K4M will result in significant increase in release rate to achieve the desired Q points.

Response 3: Dissolution @ 6 Hour (%)

Dissolution @ 6 Hour (%) = 89.7867 + -2.23417 * HPMC K4M + 1.79833 * Crospovidone.

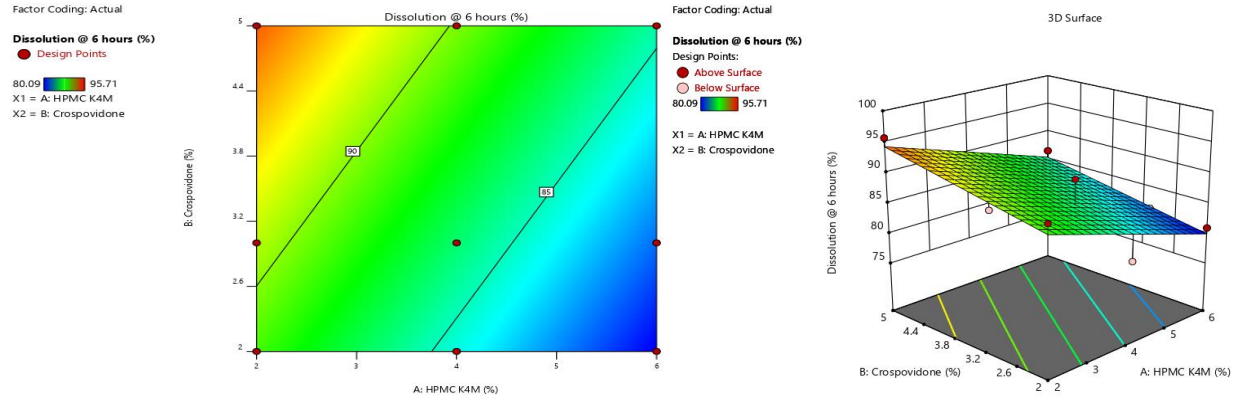

Figure 9: Response Surface Plot for Dissolution@6 Hour (%)

The codes and actual equation of Dissolution for 6 Hour (%) suggests that factor A (% HPMC K4M) has negative dominant effect and factor B (% Crospovidone) have positive dominant effect. This is further interpreted from ANOVA results and equation that increase in Crospovidone concentration in proportion to HPMC K4M will result in significant increase in release rate to achieve the desired Q points.

Upon Interpretation of data, it was observed that rapid release rates were higher in formulations prepared with higher concentrations of Crospovidone in proportion to the HPMC K4M (BF2, BF4&BF8). Retardation of release rates were observed with formulations prepared with higher concentrations of HPMC K4M in proportion to the Crospovidone (BF3, BF7 & BF9). Mixed order release was observed with the formulations (BF1, BF5 & BF6).

A multi-criteria decision optimization of approaches was employed for formulation optimization with desired responses. Optimization was performed with constraints of Q1h in the range of 25-45%, Q2h in the range of 50-75% and Q6h in the range of NLT 80%, to get optimized formula solutions with higher desirability function.

Optimization

The optimized formulation which will fit into the model is (BF4), based on the response surface plots given in Figure 10 & Table 7.

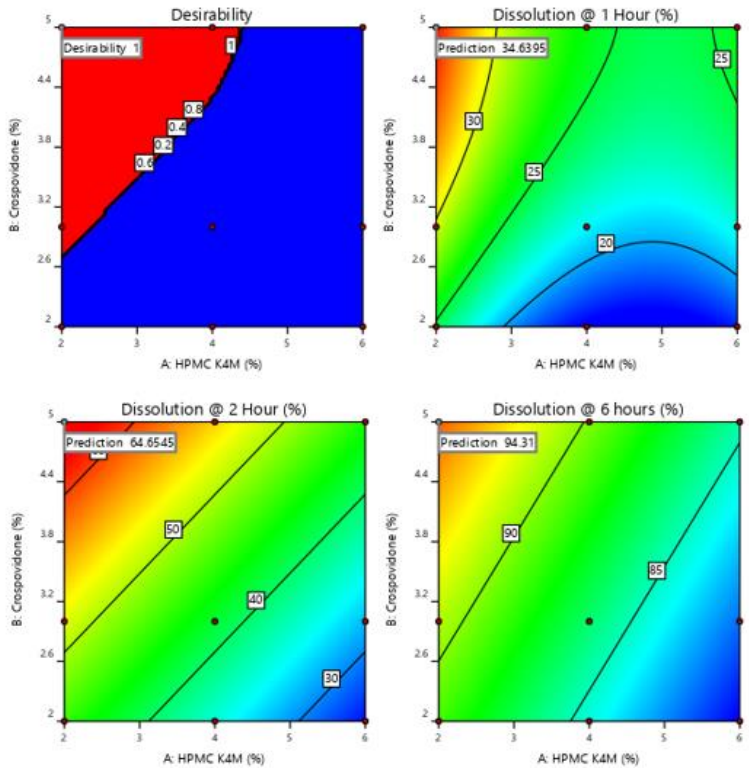

Figure 10: Response Surface Plot for Optimization of Budesonide Mini-Tablets in Enteric Coated Capsules

Table 7: Point Prediction & Confirmation

Solution 6	BF4-O	Predicted Mean	Predicted Median	Std Dev	95% PI low	95% PI high
Dissolution @ 1 Hour	35	34.6395	34.6395	1.08609	29.9343	39.3448
Dissolution @ 2 Hour	62.26	64.6545	64.6545	6.16162	46.3363	82.9728
Dissolution @ 6 hours	95.71	94.31	94.31	3.05382	85.2311	103.389

Stability studies

Short term accelerated stability data obtained for optimized formulation (BF4-O) revealed that drug content, In-Vitro dissolution and DSC found within acceptable limits. Thus, the formulation can be said to be stable.

Table 8: Stability studies of Budesonide Mini-Tablets in Enteric Coated Capsules

	Budesonide at 40°C ± 2°C/75% RH ± 5% RH	
Formulation	**Optimized Trial (BF4-O)**	
	Initial	**After 3 months**
Dissolution Time (Hours)	**% Cumulative Drug Release**	
0	0.00	0.00
0.25	12.94	11.93
0.50	24.03	25.03
1	35.00	36.19
2	62.26	61.45
4	75.28	74.79
6	95.71	96.23
8	100.19	98.71
Average Drug Content %	99.34	99.21

Differential Scanning Colorimetry (DSC):

DSC – spectrum of optimised formulation (BF4-O) before and after stability studies were depicted in figures 11 and 12. Endothermic Peak for Budesonide before stability was observed at 282.37°Cand 284.63°C after stability. DSC spectrum showed that there was no possible interaction and degradation found in the samples analysed.

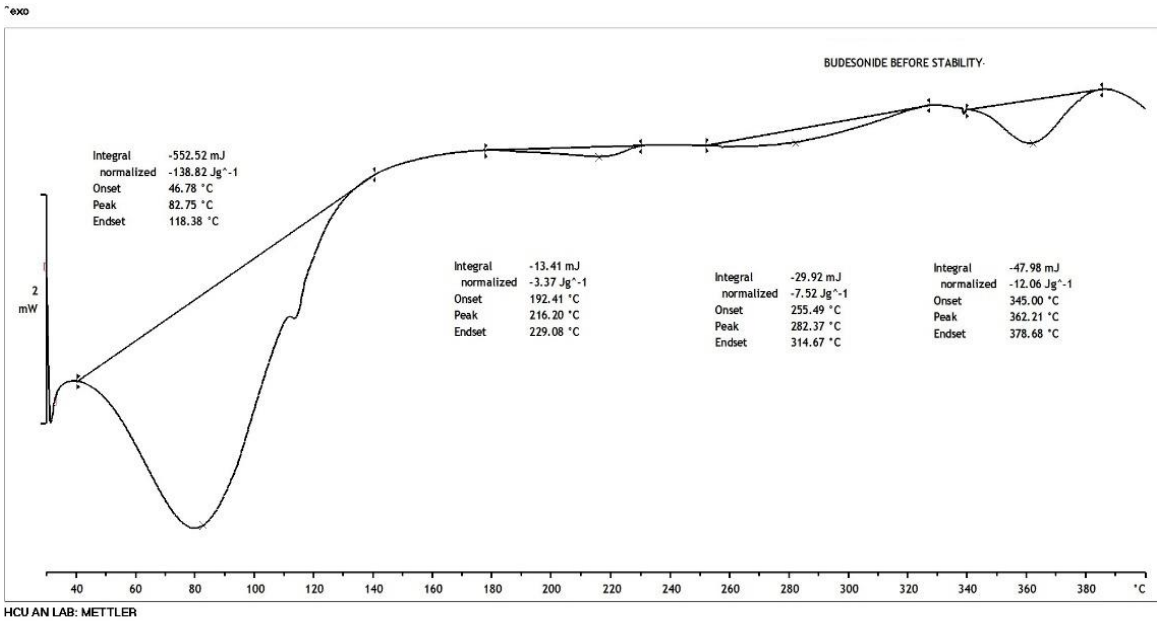

Figure 11: DSC studies of the Optimized Formulation (BF4-O) before Stability

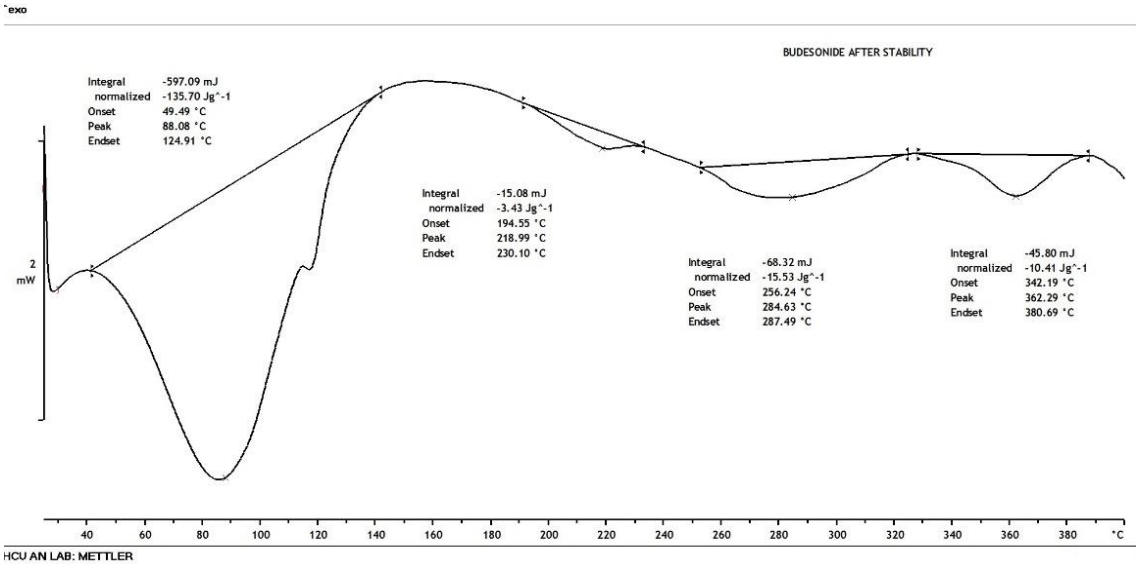

Figure 12: DSC studies of the Optimized Formulation (BF4-O) after Stability

Release Kinetics

The estimations of Ko, R^2 & n values were shown in Table 9 and graphical plot for optimized formulation was depicted in Figure 13. Upon interpretation of data, revealed that optimized formulation (BF4-O) follows First order release kinetics and Higuchi Diffusion model based on R^2 value and Non-Fickian Transport mechanism as n value of optimized formulation BF4-O is 0.585. According to Korsemeyer-peppas model; n value between 0.5-1.0 suggests Non-Fickian Transport Mechanism.

Table 9: Kinetic Data for Optimized Formulation BF4-O

Kinetic Models	Ko	R^2	N
Zero Order	17.907	0.8885	12.053
First Order	2.051	0.9681	-0.237
Korsmeyer-Peppas	1.529	0.9758	0.585
Higuchi	1.159	0.9826	38.047

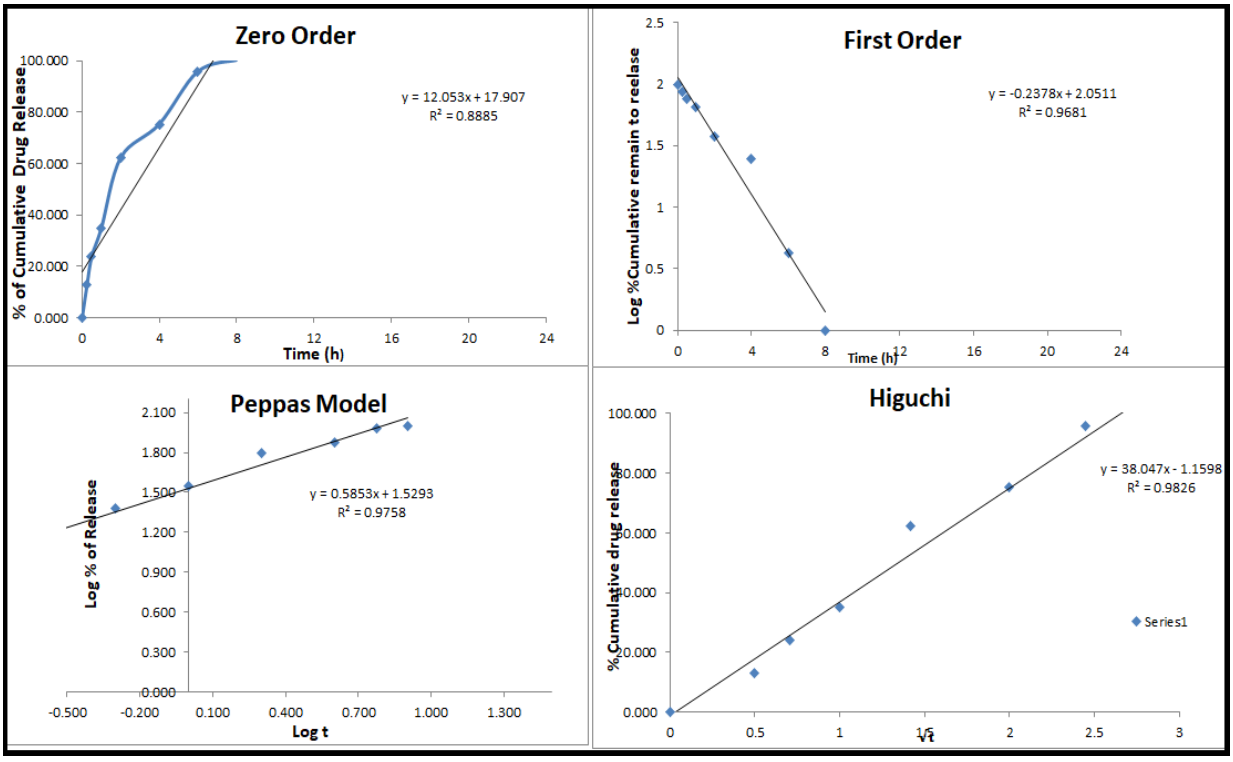

Figure 13: Kinetic Modelling Graphs for Optimized Formulation BF4-O

CONCLUSION

The physicochemical properties of the produced mini-tablets were satisfactory. The Mini-Tablets were developed with the use of 3^2 full factorial design and optimisation methodologies. Based on statistical information gathered via a factorial design approach, BF4-O was thought to be an optimized formulation. The drug content, in vitro dissolution, and DSC of the improved formulation (BF4-O) were all within acceptable ranges, according to short-term accelerated stability studies. Thus, it can be stated that the formulation is stable. ECDDT demonstrates to be a potential method for delivering medications that are sensitive to acid without enacting the enteric coating techniques included in commercialised formulations.

REFERENCES

1. Crohn's and Colitis Canada. If your child has crohn's or colitis. (https://crohnsandcolitis.ca/Living-with-Crohn-s-Colitis/If-your-child-has-Crohn-s-or-colitis) Accessed 7/20/2020.
2. Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of Paediatric Ulcerative Colitis. (https://journals.lww.com/jpgn/Fulltext/2018/08000/Management_of_Paediatric_Ulcerative_Colitis,_Part.24.aspx) JPGN. 2018;67(2):257-291. Accessed 7/20/2020.
3. GI Kids. Diet & Nutrition to Manage IBD. (https://gikids.org/inflammatory-bowel-disease/treatment/diet/) Accessed 7/20/2020.
4. Crohn's & Colitis Foundation of America. Surgery for Crohn's Disease and Ulcerative Colitis. (https://www.crohnscolitisfoundation.org/sites/default/files/legacy/assets/pdfs/surgery_brochure_final.pdf) Accessed 7/20/2020.
5. Pawar VK, Meher JG, Singh Y, Chaurasia M, Reddy BS, Chourasia MK. Targeting of gastrointestinal tract for amended delivery of protein/peptide therapeutics: strategies and industrial perspectives. Int J Pharm. 2014; 196:168-183.
6. H2 Pharma Consulting, Ltd. (Maidstone, Kent ME14 5FR, UK).
7. Choonara BF, Choonara YE, Kumar P, Bijukumar D, du Toit LC, Pillay VA. Review of advanced oral drug delivery technologies facilitating the protection and absorption of protein and peptide molecules. Biotechnology Advances. 2014;32:1269-1282.
8. https://www.accessdata.fda.gov/drugsatfda_docs/anda/2011/090410Orig1s000Approv.pdf
9. Raymond C. Rowe., Paul J Sheskey., Marian E Quinn.,2009. Handbook of pharmaceutical excipients; 6th edition.
10. Carr, R.L. Evaluating Flow Properties of Solids. Chem. Eng. 1965, 72, 163–168.
11. https://www.usp.org/sites/default/files/usp/document/harmonization/genmethod/q0304_stage6_monograph_25_feb_2011.pdf
12. Davies, P.N.; Newton, J.M. In Pharmaceutical Powder Compaction Technology; Alderbom, G., Nystrom, C., Eds.; Marcel Dekker: New York, 1995; Chapter 7.
13. Gold, G.; Duvall, R.N.; Palermo, B.T. New instrumentation for determining flexure breaking strength of capsule-shaped tablets. J. Pharm. Sci. 1980, 69(4), 384–386.
14. Diem, K., Ed. Documenta Geigy, Scientific Tables, 6th ed.; Geigy Pharmaceuticals: Ardsley, New York, 1969; 214.
15. Fell, J.T.; Newton, J.M. Determination of tablet strength by the diametral-compression test. J. Pharm. Sci. 1970, 59(5), 688–691.
16. Tomoshenko, S. Theory of Elasticity; Mc Graw-Hill: New York, 1934; 82–85, 104–109.
17. Frocht, M.M. Photoelasticity; John Wiley & Sons: New York, 1948; 2, 32–39, 118–129.
18. Stanley, P.; Newton, J.M. The tensile fracture stress of capsule-shaped tablets. J. Pharm. Pharmacol. 1980, 32(12), 852–854.
19. Pitt, K.G.; Newton, J.M.; Stanley, P. Tensile fracture of doubly-convex cylindrical discs under diametral loading. J. Mater. Sci. 1988, 23, 2723–2728.
20. https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm
21. ICH Q1C: "Stability Testing of New Dosage Forms"
22. Suvakanta Dash, Padala Narasimha Murthy, Lilakanta Nath, Prasanta Chowdhury; Acta Poloniae Pharmaceutica-Drug Research, Vol. 67 No. 3 pp. 217-223, 2010.