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Original Article

FORMULATION AND OPTIMIZATION OF BUDESONIDE COLON-TARGETED TABLETS USING CONTROLLED POROSITY OSMOTIC PUMP TECHNOLOGY

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ABSTRACT

Objective: Formulation and optimization of Budesonide (BDU) controlled porosity osmotic pump tablets (CPOP) to treat Nocturnal Asthma (NA) by adopting the Quality by design approach was set as objective of this research work.

Methods: Solubility of Budesonide was enhanced by converting in to the form of BUD Solid dispersions, using poloxamer 188. Controlled Porosity Osmotic pump (CPOP) tablets of budesonide were formulated by wet granulation technique. Quality by design approach using Box-Behnken design was adopted to optimize the selected critical factors. The optimized formulation was compared with the marketed extended-release formulation.

Results: The percentage of drug released at 4 h (D4), 7 h (D7), and 10 h (D10) were identified as response factors during the optimization phase. Statistical analysis showed that a combination of 200 mg of the SPM coat, 19.72 mg of Eudragit S 100 for the enteric coating, and 69.74 mg of guar gum in the core could achieve drug release rates of 9.4% after 4 h, 55.9% after 7 h, and 96.6% after 10 h of administration for the CPOP tablets.

Conclusion: The results indicated that the CPOP tablets were successfully formulated for colon-targeted drug release.

Keywords: Design of experiments, CPOP tablets, Box-behnken design, ANOVA test, Enteric coating, Semipermeable membrane, Polysaccharides

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INTRODUCTION

Asthma is a chronic disorder in many people across the globe. There have been numerous studies on asthma concluding the symptoms got worsen in the night during sleep. This kind of asthma is called as '*nocturnal asthma (NA)*'. According to National Heart, Lung and Blood Institute (NHLBI, A branch of National Institute of Health, USA), the lung function because of NA becomes worsen in the night with increased symptoms and airway resistance, thus requiring medication at that time [1]. Asthmatic attacks are less common in the first half of night. The air-way resistance increases progressively through the night and much greater during the sleep [2, 3]. Hence, this chronopathology of NA suggests that administration of anti-asthmatic drugs that are developed based on Chrono pharmaceutical technology is most desirable in consideration of the patient convenience. This can be achieved only through formulating Colon Targeting Drug Delivery Systems (CTDDS). These systems are formulated such that they prevent the drug release in the upper GIT and allow the drug to release only after crossing the ileocecal valve that connects the ileum to colon. After administration, passage of intact solid dosage form to the colon generally requires around 6-8 h (around 2-3 h to cross stomach and around 4-5 h to cross small intestine). Administration of these solid CTDDS after night meal at around 9 pm can produce the dosage form in the colon at around 4 am in the next day morning. So, the immediate release of any anti-asthmatic drug loaded can produce the desired plasma concentration at the most needed time to prevent the early morning attacks of asthma.

Budesonide (BUD) is one of the treatment options to treat patients with mild to moderate asthma symptoms. Budesonide belongs to the class of corticosteroids acts as bronchodilator to relieve the pain and inflammation associated with asthma attacks [4, 5]. Budesonide has high first-pass metabolism (around 90% of the dose) form the upper GIT resulting absorption of only around 10% of the administered dose. In contrast, this drug exhibited significantly high absorption around 60-80% from the ileum and colon [6, 7]. Further, it is well evidenced that budesonide can cause bleeding in the upper GIT [8] which is asymptomatic and can be discovered only when serious hemorrhage occurs. These facts suggest that it is of great necessity for Budesonide to be released only in the lower GIT i. e. in the ileum and colon for better absorption as well as preventing GI bleeding. Hence, this drug is also best-suitable for developing into CTDDS.

As per literature BUD belongs to the class-II of Biopharmaceutical classification system (BCS), which is characterized by poor solubility and high permeability [9]. Such type of APIs exhibits dissolution limited bioavailability. As the current study focusing on the targeted drug release site is colon [10, 11], and by considering the less availability of fluids in colon, it is necessary to improve the solubility of BUD. Different approaches are available in the literature to improve the solubility of the drugs; among all the approaches, solid dispersion was found to have various advantages like ease of preparation, reduced cost for preparation, improve wettability. Osmotic drug delivery systems are the most promising drug delivery systems with controlled drug release manner with aid of osmotic pressure [12].

Controlled Porosity Osmotic Pumps (CPOP) is one of the most dependable osmotic drug delivery systems to have desired drug release for the diseases associated with circadian rhythms like asthma [13] CPOP systems have unique advantage over conventional osmotic systems that they don't need mechanical drilling of orifice on the semipermeable membrane (SPM) for drug release. Instead, the SPM contains a substance that is dissolved/eroded/degraded in the favorable conditions upon administration and provide numerous micropores to allow the drug release [14, 15]. Use of natural polysaccharides like chitosan and guar gum gained an advantage because of its gelling property. These polysaccharides are degraded by the enzymes of colonic microflora once reaches to the colonic region.

Present research consisted of enhancing solubility of the BUD by solid dispersions, developing CPOP tablets with polysaccharides and coating them with enteric polymers to so as to minimize the drug release in the upper GIT and achieving the targeted release in the lower GIT. Quality by design (QbD) [16] was applied to study the influence of several factors on the drug release form the CPOP tablets also to optimize the formulation towards achieving the desired drug release profile.

MATERIALS AND METHODS

Materials

Budesonide received as gift sample from Hetero Drugs Pvt. Ltd, Hyderabad, Poloxamer-188, PEG-6000, guar gum, mannitol, Cellulose Acetate (CA) 320S, CA 398-10 was purchased from Sigma Aldrich Chemicals Co., USA, Eudragit S 100 were received as gift sample from Evonik industries, Povidone K-30 was received as gift sample from JRS Pharma. All other solvents and reagents used were of analytical grade.

Preparation of BUD-solid dispersion

BUD solid dispersions (BSDs) were prepared using solvent evaporation method [17, 18]. Briefly drug and carrier (poloxamer-188) were dissolved at 1:1, 1:5 and 1:2 ratio in round-bottomed flask containing isopropyl alcohol (IPA) and were named as BSD1, BSD2 and BSD3, respectively. Further these mixtures were subjected for evaporation of solvent using rotavapor. The dried BSDs were collected and stored until further usage.

Characterization of the BSDs

Solubility was performed using shake flask method. Briefly 10 ml of water was taken in a conical flask and excess amount of BSD was added to the media subjected for shaking until 24 h. After 24 h. the mixture was filtered and the filtrate was estimated for drug content using UV spectrophotometer [19]. X-ray diffraction studies were performed for the BUD API and formulated BSDs to detect changes in crystallinity using Thermo Fisher Scientific X-Ray Diffractometer [20, 21].

Formulation development of CPOP tablets

Colon-targeted CPOP tablets were formulated with core containing the solid dispersion of BDU, osmogenic agent and rate-controlling polymer. CPOP tablets were prepared at various combinations of the factors according to the design and were characterized. Design of experiments (DoE) analysis was carried out to identify the most significant factors based on their influence on the drug release from the tablets. To design the Budesonide CPOP Tablets, three factors were optimized by Box-Behnken design (BBD) [22, 23]. Factor A: The weight of the SPM coating, composed of cellulose acetate and the pore-forming agent PEG-6000, was optimized to support the osmotic drug release mechanism for budesonide. Factor B: The amount of guar gum (a polysaccharide) in the CPOP tablets controls the release of budesonide, specifically in colonic regions where the galactosamine enzyme is present. Factor C: The concentration of Eudragit S 100 was optimized to create an effective enteric coating for CPOP tablets. For optimization studies, three response factors % Drug released after 4 h (D4) as R1, % Drug released after 7 h (D7) as R2, % Drug released after 10 h (D10) as R3. The combinations of the above factors at their levels according to the Box-Behnken design were shown in table 1.

Table 1: List of dependent and independent variables in box-behnken design for budesonide colon-targeted tablets

Factor	Name	Units	Level used	
			LOW (-1)	HIGH (+1)
A	Semipermeable Membrane	(mg)	200	400
B	Guar gum	(mg)	40	160
C	Eudragit S100	(mg)	10	20
Response	**Name**	**Units**	**Goal**	
R_1	Drug released after 4 h (D_4)	%	≤10%	
R_2	Drug released after 7 h (D_7)	%	≤60%	
R_3	Drug released after 10 h (D_{10}) (D10)	%	≥95%	

Core tablet preparation

Core CPOP tablets were prepared using conventional wet granulation technology using Povidone K-30 as binder and water as granulating aid [24]. Core composition of CPOP contains Solid dispersion of BSD and osmogen (Mannitol). The wet granules were dried, lubricated and compressed with 8 mm round punches to get 1.8 mm thickness tablets.

Application of semipermeable coating to CPOP

The prepared SPM mix was applied on core tablets using a sandwich compression approach. Half quantity of SPM mix per unit was placed in 12 mm die cavity, followed by the core tablet was placed in the cavity and compressed with minimal force and the remaining half quantity of SPM mix was also added to the die cavity and compressed to form the CPOP tablets [25]. Enteric coating was applied on the formulated CPOP tablets using Eudragit S 100 polymer [26].

Evaluation of CPOP tablets

Physical characterization of CPOP tablets

The manufactured CPOP tablets were evaluated for thickness, tensile strength, packing fraction, friability and % drug content as per the commonly used procedures.

Drug release study

The drug release study for the CPOP tablets was conducted using a USP type-2 apparatus at 100 RPM for 2 h in 500 ml of 0.1N HCl, followed by a pH 7.4 phosphate buffer up to 10 h [27]. To the dissolution media galactomannanse from *Aspergillus niger* was added after 3 h of the dissolution in buffer stage to make the dissolution medium simulated to colonic medium for the digestion of guar gum [28, 29]. The sample was collected after 2 h in acid stage, after 2 h in buffer stage (cumulative time point of 4 h to acid stage-D4), after 5 h in buffer stage (cumulative time point of 7 h to-D7), after 8 h in buffer stage (cumulative time point of 10 h to-D10).

Optimization of critical factors

Factors having a significant impact on the response factors were optimized using Box-Behnken design [30]. The model-suggested formulations were made and further optimization was also done to get the best suitable formulation with desired responses (R1-% drug release after 4 h (D4), R2-% drug release after 7 h (D7), R3-% drug release after 10 h (D10). The general model corresponds to the following equation:

$$Y_0 = b_0 + b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC + b_{23}BC + b_{11}A^2 + b_{22}B^2 + b_{33}C^2 \quad (1)$$

Where Y is the measured response associated with each factor level combination; b0 is an intercept; b1 to b23 are the regression coefficients; and X1, X2, and X3 are the independent variables. The formulation compositions of the Budesonide CPOP tablet are presented in table 2.

RESULTS AND DISCUSSION

Characterization of the BSDs

The solubility of the BSDs was observed in the range of 0.439 mg/ml to 0.845 mg/ml, which was about 10–20 folds increment in comparison with API solubility of 0.041 mg/ml [31]. Among all the formulations the BSD3 was found to have highest solubility of 0.845 mg/ml, followed by BSD2 with 0.706 mg/ml solubility, followed by BSD1 with 0.439 mg/ml solubility. The results are displayed in fig. 1.

Table 2: Formulation compositions of the budesonide CPOP tablets

Run	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
	A	B	C	R1	R2	R3
	mg	mg	mg	%	%	%
1	300	40	20	9.7	49.6	92.7
2	200	40	15	12.5	61.8	100.5
3	300	40	10	9.4	56.5	91.1
4	200	160	15	14.2	62.3	96.4
5	400	40	15	9.5	50.9	90.8
6	*300*	*100*	*15*	*7.2*	*42.7*	*81.6*
7	200	100	20	8.4	55.6	91.5
8	300	160	10	10.9	60.5	95.7
9	*300*	*100*	*15*	*7.2*	*42.7*	*81.6*
10	400	100	10	7.9	49.1	84.3
11	300	160	20	5.8	37.9	79.4
12	200	100	10	8.1	48.2	92.3
13	*300*	*100*	*15*	*7.2*	*42.7*	*81.6*
14	400	160	15	6.3	41.4	83.1
15	*300*	*100*	*15*	*7.2*	*42.7*	*81.6*
16	400	100	20	6.3	56.9	90.9
17	*300*	*100*	*15*	*6.3*	*42.7*	*81.6*

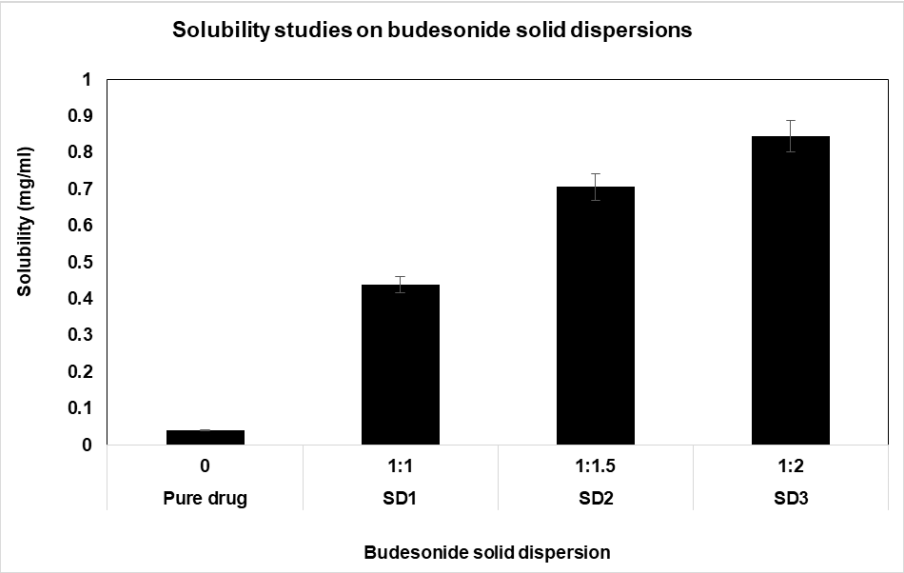

Fig. 1: Comparison of budesonide solubility profiles in pure form and solid dispersion forms (1:1, 1:1.5 and 1:2), *All the results are presented as mean±standard deviation for *n* = 3

The Solid dispersions dissolution rate depends on the proportion of the poloxamer 188 in the solid dispersions. An enhancement of dissolution rate of budesonide is because of its amorphous state, which increases the as increase of the weight fraction of the poloxamer 188 up to its saturation solubility. From the solubility data it was found that there is drastic improvement in solubility with an increment in the carrier concentration i. e. poloxamer 188. As the desired solubility achieving with 1:2 drug and carrier ratio, the same will be used for further preparation of CPOP tablets.

XRD studies were also performed for the formulated SDs to know the crystallinity of the formulation. XRD was performed for both the API and the prepared BSDs. The XRD spectrum of Budesonide API was found to have the share, high intense peaks, which indicating the crystal nature of API, whereas the XRD spectrum formulated BSDs was found to have the broad, less intense peaks, which is confirming the form conversion of API from crystalline to amorphous after solid dispersion formation [32]. The XRD spectrum is displayed in fig. 2.

Physicochemical properties of the CPOP tablets

The optimized formulations were evaluated for physical property evaluation. The results were shown in table 3. From the physical property evaluation, it was clear that the formulated CPOP tablets were rigid enough to maintain their integrity throughout lifecycle [33]. Friability data of the optimized formulations were found to be within limit as per USP (<1.0%).

Drug release study

Dissolution was performed for optimized formulations as mentioned above. Dissolution results were displayed in fig. 3. All the 13 batches were shown less than 10% drug release as per USP enteric coating criteria [34]. The D4 was found to be in the range of 5.8 to 14.2%, D7 was found to be in the range of 37.9 to 62.3%, as per the objective of the study, almost 100% drug release was observed after 10 h (D10). From the dissolution data it is evident that there is control over the drug release as per the required pattern for colon-targeted drug delivery. After 5 h, with addition of the galactomannanse from *Aspergillus niger* to the dissolution medium, there is an increase in % drug release rate, which might be due to the soluble nature of polysaccharide matter present in the SPM thereby forming pores on the surface of the CPOP tablets to facilitate the drug release [35, 36]. The compartitive dissolution studies of optimized formulation and the marketed formulation displayed in fig. 4.

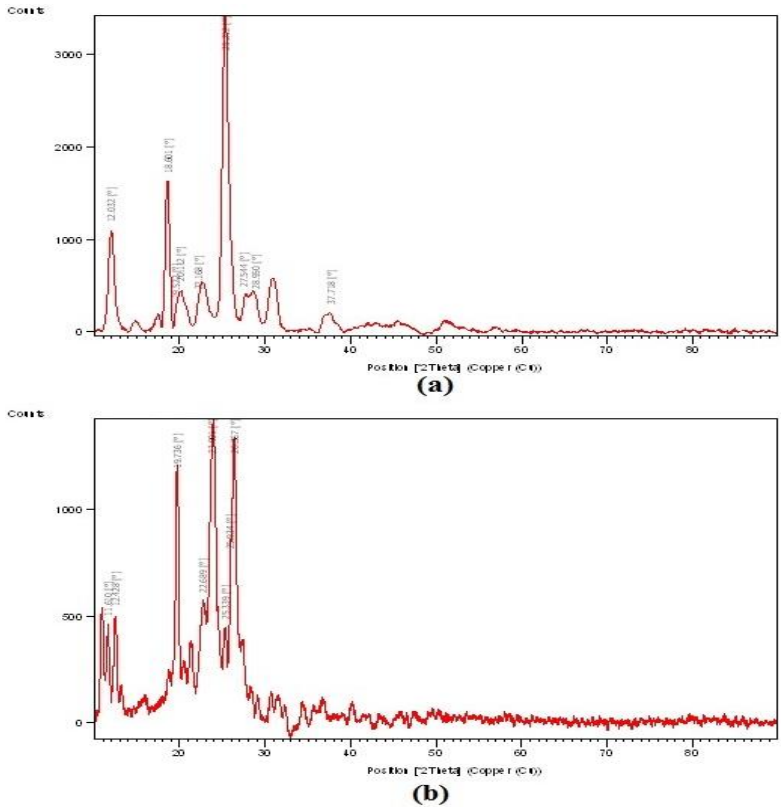

Fig. 2: XRD spectrum of a) Pure budesonide, b) Budesonide solid dispersion

Table 3: Post-compression physical properties of the screening formulations OF1 – OF13

S. No.	Formulation	Thickness (mm)	Tensile strength (N/mm²)	Packing fraction (P_f)	Friability (%)	Drug content (%)
1	OF1	2.08±0.04	0.63±0.06	0.93±0.04	0.18±0.06	98.7±2.6
2	OF2	2.12±0.06	0.61±0.07	0.94±0.03	0.21±0.05	98.2±1.2
3	OF3	2.11±0.03	0.65±0.04	0.91±0.07	0.24±0.02	101.9±0.8
4	OF4	2.09±0.08	0.66±0.08	0.95±0.08	0.13±0.06	100.5±1.6
5	OF5	2.52±0.06	0.62±0.05	0.92±0.05	0.16±0.03	99.4±2.1
6	OF6	2.58±0.12	0.59±0.04	0.93±0.03	0.21±0.06	98.5±2.4
7	OF7	2.56±0.05	0.63±0.02	0.90±0.06	0.14±0.05	101.7±1.5
8	OF8	2.61±0.03	0.60±0.05	0.95±0.02	0.18±0.03	100.2±1.8
9	OF9	2.63±0.07	0.64±0.03	0.93±0.03	0.12±0.02	98.9±2.2
10	OF10	3.13±0.11	0.58±0.09	0.91±0.04	0.25±0.03	101.3±1.9
11	OF11	3.10±0.06	0.63±0.05	0.94±0.03	0.27±0.04	99.8±2.7
12	OF12	3.08±0.09	0.60±0.07	0.95±0.08	0.15±0.03	98.4±3.1
13	OF13	3.12±0.06	0.62±0.03	0.93±0.05	0.16±0.06	100.6±1.3

*All the results are presented as mean±standard deviation for n = 3

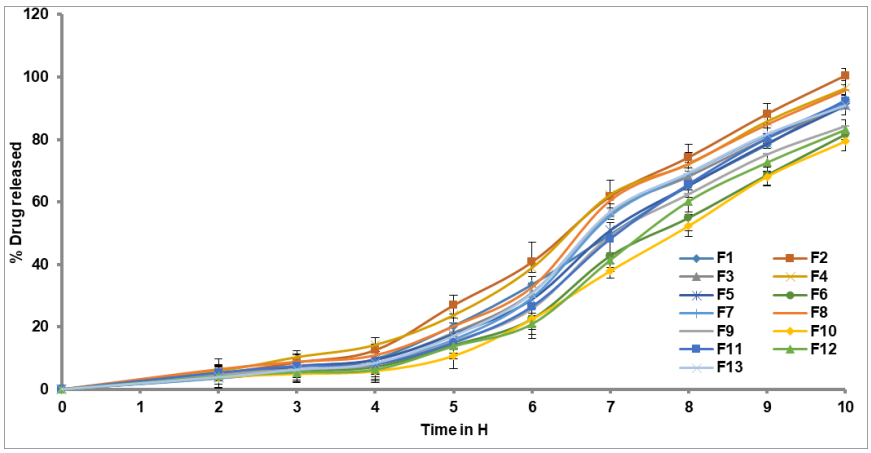

Fig.3: *in vitro* drug release profile of optimized BDU CPOP tablets,
***All the results are presented as Mean±Standard deviation for n = 3**

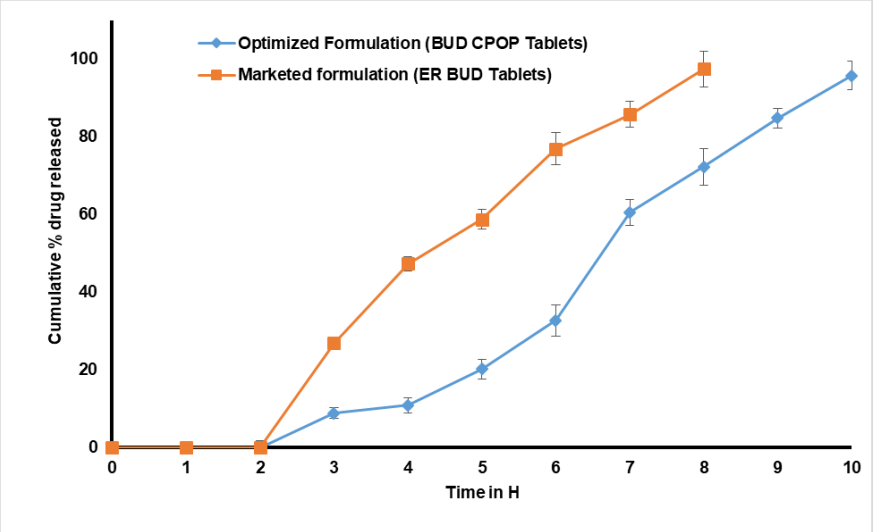

Fig. 4: *In vitro* dissolution profile of BUD CPOP colon target tablets and marketed BUD extend release tablets, *All the results are presented as mean±standard deviation for *n* = 3

Design of experimental analysis of the responses

To find the model fitness, sequential model sum of square analysis was applied to find suitable regression model for every response with the selected factors by the Design Expert software [37]. From the results, as given by the software, it was observed that the linear model was the best fit to explain the impact of factors for all the three responses. This suggested linear model was subjected to diagnosis tests to confirm its suitability and significance by ANOVA test, normal plot of residuals as well as predicted vs actual plots illustrated in fig. 4.

ANOVA test results are shown in table 4 and it's confirmed the suitability of the selected design for all the selected factors and the occurred responses [38]. The *p*-value was found to be less than 0.05, which is confirming the significance of model terms. The normal plot of residuals and the predicted versus actual plot are displayed in fig. 4. All the data points in the normal plot of residuals were aligned linearly without any sigmoid shape alignment. The predicted vs actual plots illustrated that the points were uniformly aligned around the 45 line. These observations are concluding that the selected models for the three responses are suitable and the same can be moved for optimization stage [37].

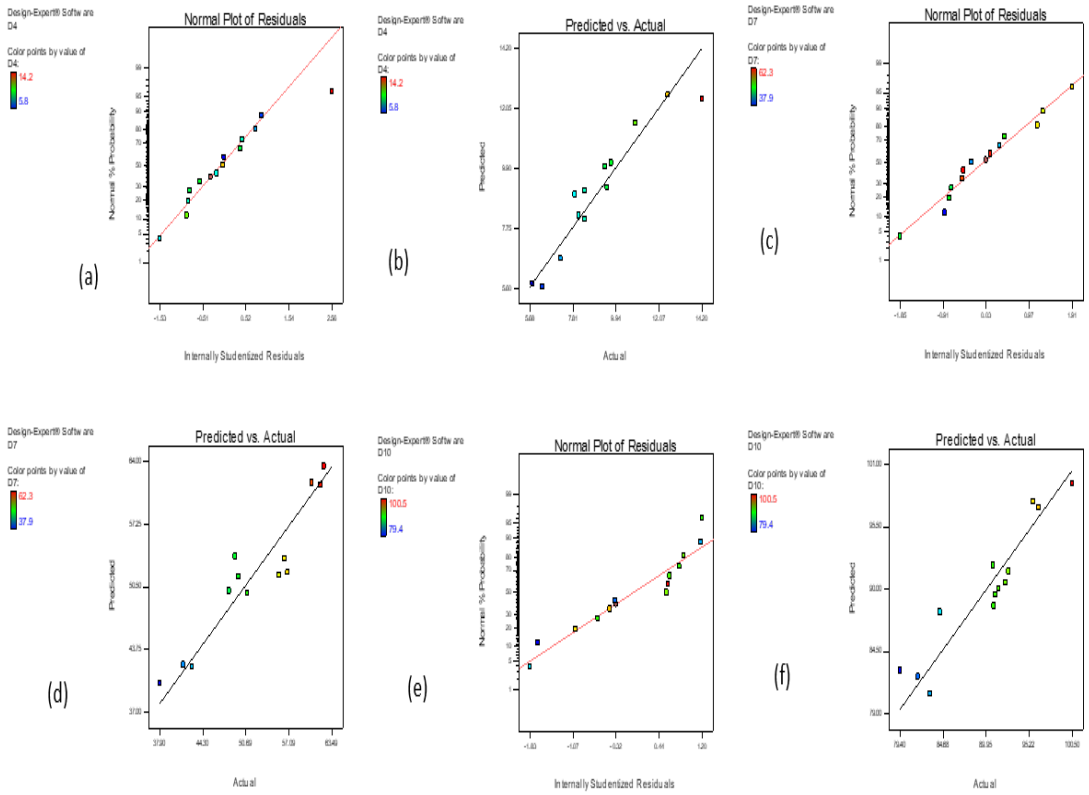

Fig. 4: a) Normal plot of residuals for the Response D_4, b) Predicted versus actual plot for the Response D_4, c) Normal plot of residuals for the response D_7 d) Predicted versus actual plot for the Response D_7, e) Normal plot of residuals for the response D_{10} d) Predicted versus actual plot for the response D_{10}

Table 4: Results of ANOVA test for response surface linear model for the response D4

Response	Source	SS[a]	Df[b]	MSS[c]	F value	p-Value	Inference[d]
D4	Model	60.56	3	20.19	27.47	<0.0001	Significant
	A-SPM coat weight	36.98	1	36.98	50.31	<0.0001	Significant
	B-PS Conc.	10.58	1	10.58	14.39	0.0043	Significant
	C-Amount of RCP	13.01	1	13.01	17.69	0.0023	Significant
	Residual	6.61	9	0.73			
	Core Total	67.18	12				
D7	Model	672.23	3	224.08	23.36	0.0001	Significant
	A-SPM coat weight	262.21	1	262.21	27.33	0.0005	Significant
	B-PS Conc.	284.41	1	284.41	29.65	0.0004	Significant
	C-Amount of RCP	125.61	1	125.61	13.09	0.0056	Significant
	Residual	86.33	9	9.59			
	Core Total	758.56	12				
D10	Model	410.19	3	136.73	22.78	0.0002	Significant
	A-SPM coat weight	153.13	1	153.13	25.51	0.0007	Significant
	B-PS Conc.	64.98	1	64.98	10.83	0.0094	Significant
	C-Amount of RCP	192.08	1	192.08	32.00	0.0003	Significant
	Residual	54.02	9	6.00			
	Core Total	464.20	12				

Note: [a]-Sum of Squares; [b]-Degrees of Freedom; [c]-mean Sum of Squares; [d]-p-Value less than 0.05 indicates model terms are significant

The effects of the selected factors on the responses are illustrated in fig. 5. The factors A and C were found to be negative on drug release whereas the factor B has positive impact on drug release. With increase in SPM coating weight, the thickness of the coating will also increase thereby decrease in drug release rate. This could be due to the increased resistance for water permeation; thereby, limited pressure development would result in decreased drug release at thicker coats [39, 40]. The drug release was found to be sustained after 5 h of dissolution, with increased concentration of polysaccharide i. e guargum. The impact of polysaccharide concentration on drug release was found to be more in case of D7 and D10 rather D4. This could be attributed to the addition of galactomannanse from *Aspergillus niger* to dissolution medium after 5 h. Galactomannanse is an enzyme that is secreted in the intestinal microflora and is responsible for the digestion of the polysaccharides in the intestine [28, 29].

The goal of drug release of prepared BUD CPOP tablets was to be pulsatile drug release pattern. The effect of the formulation factors on drug release was more complex. To study the effect of formulation factors (A, B and C) on the drug release of prepared tablet responses (R1: after 4h (D4), R2: after 7 h (D7), and R3: after 10h (D10), multiple linear regression analysis was done using polynomial equation (1,2 and 3).

$$R1 = +7.02 - 1.65A - 0.4875B - 0.7625C - 1.23AB - 0.4750AC - 1.35BC + 1.16A^2 + 2.44B^2 - 0.5100C^2 - \ldots\ldots\ldots\ldots (1)$$

$$R2 = +42.70 - 3.70A - 2.09B - 1.79C - 2.50AB + 0.1000AC - 3.93BC + 6.36A^2 + 5.04B^2 - + 3.39C^2 - \ldots\ldots\ldots\ldots (2)$$

$$R3 = +81.60 - 3.95A - 2.56B - 1.11C - 0.9000AB + 1.85AC - 4.48BC + 5.56A^2 + 5.54B^2 + 2.59C^2 - \ldots\ldots\ldots\ldots (3)$$

The equations revealed that all three factors A: SPM coat weight, B: Amount of PS and C: amount of Eudragit S 100 impact on the BUD release from the CPOP tablets. To simulate the intestinal conditions in the *in vitro* drug release studies, this enzyme is added to the dissolution medium after 5 h of the test [41]. So that, the drug release observed here can be correlated to the *in vivo* conditions. Might be the presence of this enzyme in dissolution media (mimicking the colon fluid conditions) accelerating the digestion of the polysaccharide, followed by the formation of pores on the surface of the tablet to facilitate the drug release [42]. These results signified that controlling the levels of the SPM coat weight, Amount of Eudragit S 100 and the amount of PS, the drug release from the CPOP tablets can be controlled and can achieve the desired colon-targeted drug delivery [43].

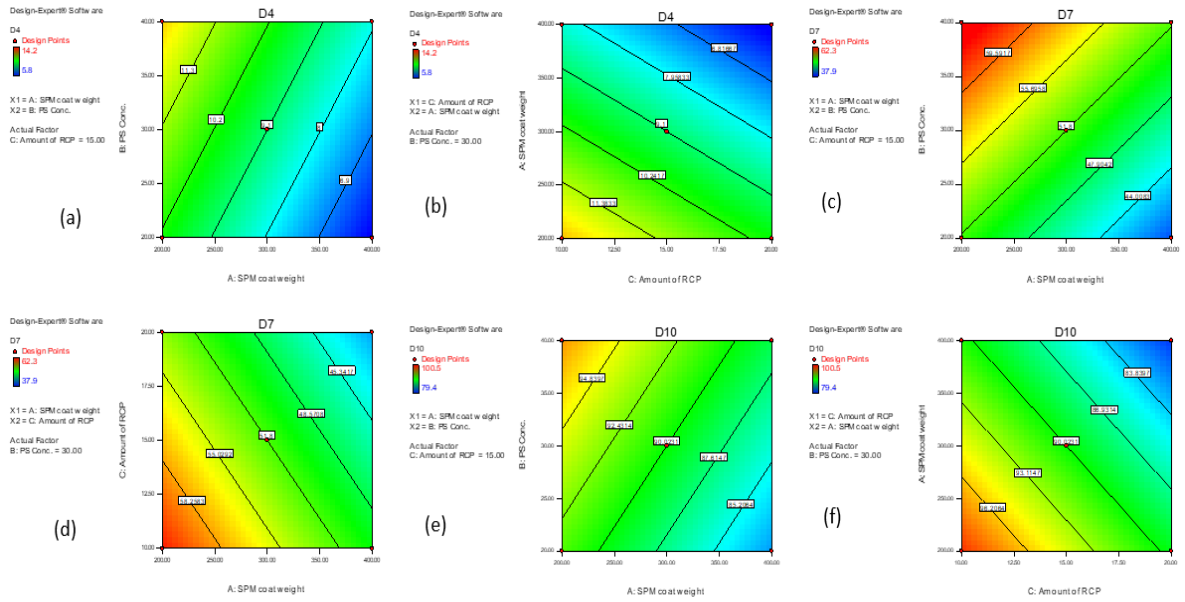

Fig. 5: Contour plot showing the effects of a) the factors A and B on the D4; b) the factors A and C on the D4; c) the factors A and B on the D7, d) the factors A and C on the D7, e) the factors A and B on the D10, f) factors A and C on the D10

Optimization of formulation

Formula optimization was performed to find the best suitable combination of the factors to achieve the desired responses. The desirability of responses is to have the minimum drug release (below 10%) after 4 h, half amount of drug release at 7 h (less than 60%) and the maximum amount of drug release at 10 h (above 90%) after dissolution to meet the objective of the formulation development of CPOP tablets of attaining maximum drug release in colon region that is after 6 h of administration.

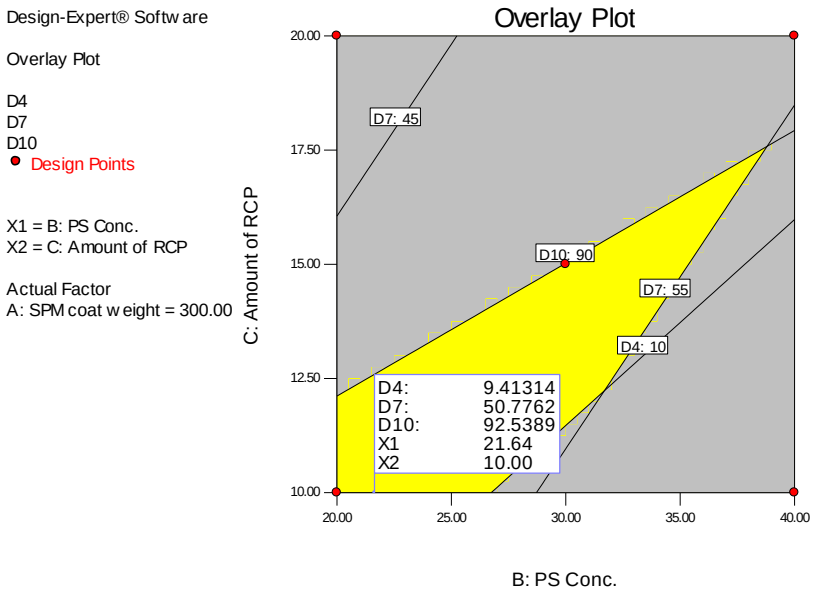

Fig. 6: Overlay plot showing the Design space (the yellow region: the yellow color part of the plot suggests the best possible combinations of factors B and C to get desired responses)

The overlay plot of graphical optimization with set of desirability function is displayed in fig. 6. The yellow color part of the plot suggests the best possible combinations of factors B and C to get desired responses. The plot indicates the combination of factor A at 200 mg SPM coat weight can produce CPOP tablets with desired drug profile. The combination of factors and the predicted drug release profiles are displayed in table 5.

Table 5: Comparison of the predicted and observed values of the responses for the optimized budesonide CPOP tablets

Factors combination	Responses	Predicted values	Observed values	% Error
A: SPM coat weight (200 mg)	R1: D4 (%)	9.9	9.4	5.05
B: PS conc. (69.74 mg)	R1: D7 (%)	56.94	55.9	-1.86047
C: Amount of Eudragit S 100 (19.72 mg)	R1: D10 (%)	95.0	96.6	1.656315

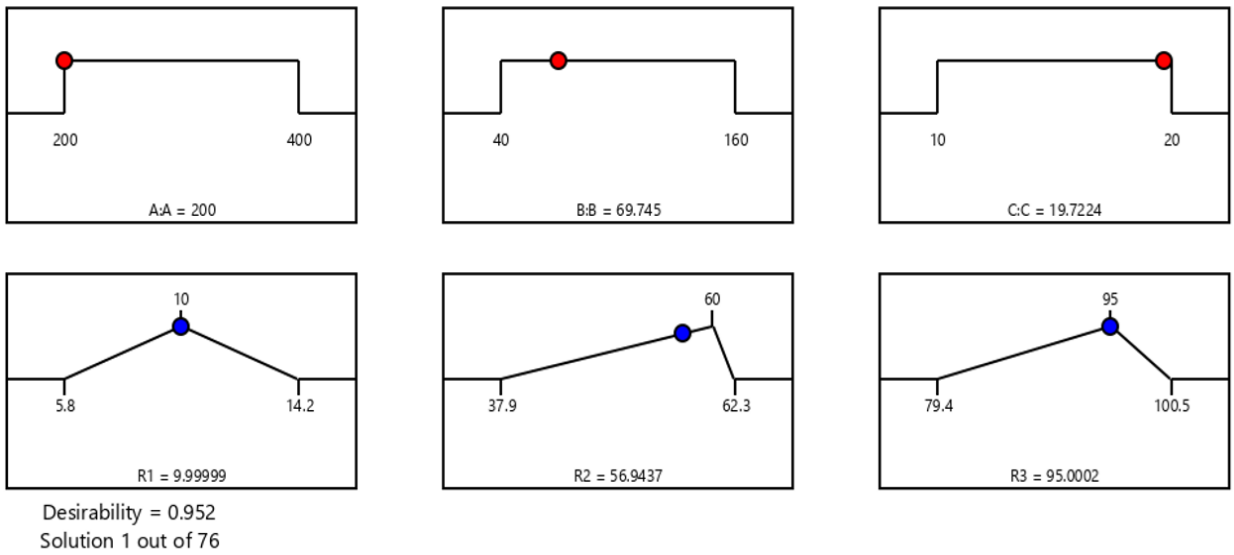

Fig. 7: Numerical optimization of BUD loaded CPOP tablets using box-bhenken design

A new batch of CPOP tablets was formulated with the design-suggested combination and evaluated for dissolution profile (fig. 7). The observed values were found to be correlating with predicted values by design space. So, the combination was selected as optimum formulation of Budesonide CPOP tablets for colon-targeted drug delivery. The difference between observed and predicted values was calculated using the following equation (4).

$$\text{Error (\%)} = (\text{difference between observed and predicted values})/\text{predicted value} \times 100 \quad \ldots\ldots (4)$$

The optimized formulation containing BUD showed with small error values (R1: 5.05, R2:-1.860, and R3: 1.65. This reveals that mathematical models obtained from the Box-Behnken design were well-fitted [44]. Comparison of in vitro dissolution profile of BUD CPOP colon target tablets and marketed BUD extended-release tablet was shown in fig. 8. The drug release was entirely inhibited at stomach pH, indicating that the concentration of the enteric-coated polymer was effective [45]. This demonstrates the reliability of the optimized procedure in predicting the operating parameters for the preparation of BUD CPOP tablets for colon targeting.

CONCLUSION

Budesonide SD was formulated to improve the dissolution rate with the help of poloxamer 188 as a carrier by solvent evaporation method. The formulated solid dispersions were found to have improved solubility in comparison with BUD plain drug. The solid dispersions were further evaluated to know the changes in crystallinity using X-ray diffractometer and from the XRD studies, it was found that the crystal form of the BUD was changed into amorphous form. The CPOP tablet was manufactured using QbD as a tool to optimize by the Box-Behnken design. Further, the significance of the model for each response was analysed by the ANOVA. From the optimization study it was concluded that increment in rate controlling polymer in core and the increment of semipermeable coat weight are controlling the drug release, whereas the increased polysaccharide content in semipermeable coat mixture leads to the higher drug release after 6 h and the model is validated using the correlation between observed and predicted values. The current study concluded that CPOP tablets effectively controlled drug release during their transit through the gastrointestinal tract (GIT) and provided targeted drug delivery for treating conditions related to circadian rhythms.

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ABBREVIATION

BDU: Budesonide, CPOP: Controlled Porosity Osmotic Pump Tablets, NA: Nocturnal Asthma, QbD: Quality By Design, ANOVA: Analysis of Variance, NHLBI: National Heart, Lung and Blood Institute, CTDDS: Colon Targeting Drug Delivery Systems, GIT: Gastro-Intestinal Tract, GI: Gastro Intestine, API: Active Pharmaceutical Ingredient, SPM: Semipermeable Membrane, PEG: Poly Ethylene Glycol, CA: Cellulose Acetate, BSD: BUD solid dispersions, IPA: Isopropyl Alcohol, BBD: Box-Behnken Design, DoE: Design of experiments, USP: United States of Pharmacopoeia, HCl: Hydrochloric acid, XRD: X-Ray Diffraction.

AUTHORS CONTRIBUTIONS

Ismail. Y conceptualized the review, planned it, and examined the study; and Ismail. Y edited, reviewed, and oversaw the document; Vijaya Kumar Voleti produced the majority of the manuscript, conducted a literature search, created the tables, figures, and references; After reading the published version of the manuscript, all writers have given their approval.

CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interest

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