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Original Article

Formulation Development of Cevimeline Hydrochloride Mouth Dissolving Tablets Using 2^3 Factorial Design Approach

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ABSTRACT

In the present work, the mouth dissolving tablets of cevimeline hydrochloride were prepared to target those patients suffering from Sjogren syndrome, due to this syndrome patient faces problems such as difficulty in swallowing tablets or capsules because of dryness in mouth, resulting in noncompliance and ineffective therapy. Mouth dissolving tablets were prepared by direct compression method. The preliminary trial batches were formulated with three super-disintegrant *viz*. crospovidone, sodium starch glycolate, croscarmellose sodium in different concentration along with pearlitol SD 200 alone and in combination with microcrystalline cellulose (Avicel102). The prepared batches were evaluated for weight variation, hardness, thickness, mechanical strength, wetting ability, disintegration time and *in vitro* drug release. Amongst all four-formulation batches, batch no A4 containing crospovidone 8 mg, mannitol & MCC in the ratio of 10:1 has shown disintegration time of 8 seconds along with 96% drug release within 30 min. The compatibility study of drug and excipients was carried out by using FTIR and DSC. Based on the results, trial A4 was selected for further optimisation by using 2^3 factorial design. Among all trials generated by 2^3 factorial design, D4 shows most satisfactory result like disintegration time about 8 sec and drug release 98 % in 30 min, hence formulation D4 considered as optimised formulation.

Keywords: Sjogren disease, Cevimeline hydrochloride, Superdisintigrant, Mouth dissolving tablets, Factorial design

INTRODUCTION

The Sjogren's syndrome is a chronic autoimmune inflammatory disease in which moisture-producing glands are damaged, significantly decreasing the quantity and quality of saliva and tears [1-2]. For the treatment of Sjogren syndrome, the cevimeline hydrochloride capsules are available in market. In this condition, many patients express difficulty in swallowing (dysphasia) tablets and capsules among all age groups, especially in elderly and paediatrics, resulting non-compliance and ineffective therapy [3]. To overcome this problem with the help of recent advances in Novel Drug Delivery System (NDDS) is mouth dissolving tablets that can dissolve or disintegrate in oral cavity, have attracted a great deal of attention [4]. Indeed, the mouth-dissolving tablet is an important and attractive alternative to liquid dosage form. Syrups are best for paediatrics but they are bulky and drugs are not as stable in liquid form as compare to solid form like tablets. The major advantage is that can be administered without water, which is suitable for mentally ill patients who cannot access water easily as well as for geriatric and paediatric patients. The other benefits include rapid onset of action, increase bioavailabity and good stability [5-7]. Recently useful dosage forms such as rapidly disintegrating or dissolving tablets, have been developed and applied clinically. When such tablets are placed in the oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration. The objective of this study was to formulate directly compressible tablets of cevimeline Hydrochloride with sufficient mechanical

integrity, maximum drug release and acceptable palatability with better mouth feel for the treatment of Sjogren syndrome. As cevimeline Hydrochloride shows peak plasma concentration/half-life at 4-5 hours after oral administration as well as it is tasteless and highly water-soluble drug, so it can be considered good candidate for mouth dissolving tablet [8-9].

MATERIALS AND METHODS

Materials

Cevimeline Hydrochloride and Crospovidone, Sodium Starch Glycolate, Mannitol, Avicell-102, Magnesium Stearate and Talc were obtained as a gift sample from Aurobindo Research Centre Hyderabad. All other chemicals used were of analytical grade.

Selection of Excipients

The concentration of each excipients was selected as per their maximum potency per dose of each ingredient. By referring the Handbook of pharmaceutical excipients and Inactive Ingredients Guidelines limit are given in (Table 1**)** [10-12].

Solubility Studies

Solubility study of CEVH was performed in different solvents such as distilled water, 0.1 N Hcl, 4.5 pH Phosphate buffer and 6.8 pH phosphate buffer. An excess of CEVH was dissolved separately in 10 ml of above solvents and ultra-sonicated for 24 hours at room temperature. Then solution was then filtered and after making suitable dilutions, the amount of drug dissolved in various solvents was analysed spectrophotometrically using UV spectrophotometer (v-530, Jasco) at 207 nm (Table 2).

Standard calibration curve of CEVH

Calibration curve of CEVH was recorded in the range of 200 to 400 nm using 6.8 pH phosphate buffer. The absorbance was measured by UV spectrophotometer (Jasco307) at 207 nm (Figure 1), and the graph was plotted (Figure 2). This graph was used for estimation of drug content, *In-vitro* drug release in the formulated CEVH's MDT.

Preliminary trial of CEVH loaded MDT

CEVH's MDT formulated by direct compression method. The batch size was kept as 50 tablets. Required amounts of all excipients were weighed and sifted together through sieve # 60. Then it was transferred into mortar pestle and mixed together until it has been uniformly mixed. The powder blend was compressed on compression machine (Cadmach) using 4 mm Round punch (Table 3) [13].

Evaluation of CVEH MDT

Weight variation: Twenty tablets were randomly selected from each batch and weighed using a (Electrolab). The mean SD was calculated.

Thickness: Ten tablets from each formulation batch were taken randomly and their thickness was measured with a vernier callipers (Digimatic, Japan) the mean SD values were calculated.

Hardness and friability: Hardness of disintegrating tablets were tested using electrolab digital tablet hardness tester and friability by using roche friability test apparatus [14].

Wetting time: Two folded circular tissue papers were placed in a petri dish of 10 cm diameter, 10 mL of water containing 1% of methyl blue water-soluble dye was added to the petri dish. Tablet was placed in petri dish to measure the time required for water to reach the upper surface of tablet until it becomes completely wetted. This was noted as the wetting time [15].

***In-Vitro* disintegration time:** The process of breakdown of tablet in to smaller particles is called as disintegration. Orally disintegrating tablet was disintegrated due to water uptake by superdisintigrant *via* capillary action. Test carried out with specification (Electrolab disintegration apparatus-II), distilled water at 37°C ± 2°C as media. The time required to complete disintegration of tablet with no palatable mass left behind in apparatus was measured (Table 4) [16].

***In-Vitro* drug release study:** *In-Vitro* drug release study of CEVH's MDT was performed using USP-II appratus (Electrolab TDD06P), paddle speed at 50 rpm and dissolution medium volume about 900 mL of 6.8 pH phosphate buffer and temperature about $37^0 \pm 2^0$ was maintained. Sample (5 mL) were collected at predetermined interval (5, 10, 15,30,45,60 min) and replaced with equal volume of fresh medium at each interval. The sample, which is withdrawn at specified time, was filtered and analysed with UV-Visible Spectrophotometer at λ 207 nm. Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug release (Table 5) [17]

Optimization of Formulation

Formulation A4 was selected for further optimization. The 2^3 Factorial design along with three replicates was applied to examine combined effect of two formulation variables for which 13 trials of CEVH tablets were generated (Table 7). The amount of crospovidone and Avicel-102 were taken as independent variables while disintegration time (DT), % Friability and wetting ability were taken as dependent variables (Table 6). Based on the preliminary feasibility study, a DOE with factorial design was performed to optimize Avicel-102 and Crospovidone concentration used in the formulation. The percentage of friability, disintegration time and wetting ability of tablets was identifying as CQA of the formulation composition, the ranges for the response were based on these three factors and it summarizes the study design and acceptance criteria.

A constant tablet weight about 150 mg was compensated with quantity of Mannitol to achieve targeted weight. The goal of formulation development was to the optimization of Avicel-102 and Crospovidone concentration and to understand if there were any interaction within the variables using Design-Expert® 11 software (Table 8) [18].

Stability Study

The stability studies were carried out as per ICH guidelines on the most acceptable formulation (D4). Formulation was packed in aluminium foils. The stability studies were performed at 40 ± 2 °C / 75 ± 5 % RH conditions for 6 month. At the end of study, samples were analysed for the physical evaluation and *in vitro* drug release etc (Table 9) [19-20].

Kinetics Release Study for Optimized Formulation D4

The dissolution release data of the optimized formulation D4 was processed into graphs to understand the linear relationship, i.e., kinetic principles (Figures 5-9). The data were processed for regression analysis using MS - Excel statistical functions. The parameters and equations were given in the (Table 10) is indicated that the release kinetics of the drug followed Zero-order kinetics from optimized formulation.

RESULT AND DISCUSSION

Compatibility Study

FTIR study: FTIR spectra of Cevimeline hydrochloride and mixture of Cevimeline hydrochloride and Excipients were taken and compared (Figure 10 and Figure 11). The result revealed that there was no appearance of any extra peaks and disappearance of existing peaks, which indicated that there was no interaction between drug and polymer used.

DSC study: The supporting evidence for compatibility between drug and excipients was obtained from DSC studies. and thermogram of cevimeline HCL show sharp endothermic peak at 205°C corresponding to the melting point of drug. The optimized formulation of cevimeline hydrochloride with endothermic peak at 205°C. In the DSC, which reflects that there is no interaction between drug and excipients. (Figure 12 and Figure 13)

Formulation development: Based on dissolution data of office of generic drug Q point is 80% release in 1 hr. The first trial of batch no A1 was taken with Cevimeline HCl tablets by using Crospovidone as a disintegrant and mannitol as diluents and tablets compressed by using direct compression method. The disintegration time was observed 15 to 20 seconds and dissolution results resemble with Q point, but the friability was more than 1% and also capping was obtained.

The second trail batch A2 was taken by changing disintegrant as sodium starch glycolate, but the disintegration time get increased up to 50 to 120 second and dissolution results did not match with Q point limit. The third trail of batch A3 was taken by changing disintegrants as croscarmellose cellulose. The trial resulted in increase in disintegration time i.e. 120 to 180 second but dissolution results was found below the Q point limit. The fourth trail A4 was taken similar as to A1 trail but in this trial the combination of diluent Mannitol & MCC-102 was used in the ratio of 9:1. The disintegration results of this batch were good and dissolution time greater than Q point i.e. 10-15.

Factorial Design

In the 23 central composite full factorial design the dependable variables of formulation batches D1 to D13 such as disintegration time in seconds, friability in % and wetting time in seconds showed a wide variation i.e. 8-50 seconds, 0.27-0.83 %, and 9-20 seconds respectively. The obtained data from DOE batches showed that the dependent variables i.e. DT and wetting time were strongly independent on the selected dependant variables. The factorial equations can be used to draw conclusion after considering the magnitude of coefficient and mathematical sign it carries positive or negative. The analysis of variance (ANOVA) was performed to identify insignificant/significant factors (Tables 10-12). The (Figures 8-10) illustrates the surface plot, which denotes the combined effects of independent variables on dependent variables. It was observed that the combine effect of MCC and Crospovidone concentration inversely proportional to DT, friability and wetting time (Figure 14-16).

Stability Study

The optimized formulations batch D4 stored at 40 ± 2°C/75 ± 5 % was found to be stable. After storage at 40 ± 2°C/75 ± 5 %, no shape deformation in the tablets was found. The cumulative percentage drug release was nearly similar before and after storage. Therefore, it is clear that drug was thermally stable at 40 ± 2°C as well as not affected by high humidity at 75 ± 5%. Considering the *in vitro* drug release behaviour of optimized formulation of cevimeline Hydrochloride initially and after 1 month, it was found that there was no much more variation in the *in vitro* drug release behaviour of tablets (Table 13).

CONCLUSION

The objective of this investigation has been achieved by preparing CEVH's MDT by using direct compression technology. The results of 2^3 factorial design revealed that concentration of disintegrating agent and superdisintegrants are significantly affect on the dependant variables which shows better disintegration, good mechanical strength and maximum *in vitro* drug release. It can be best alternative to liquid dosage form as well as orally administered solid dosage form, i.e. hard gelatine capsules for paediatric and geriatric patients who suffers from Sjogren syndrome.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies with human or animal subjected performed by any of the authors.

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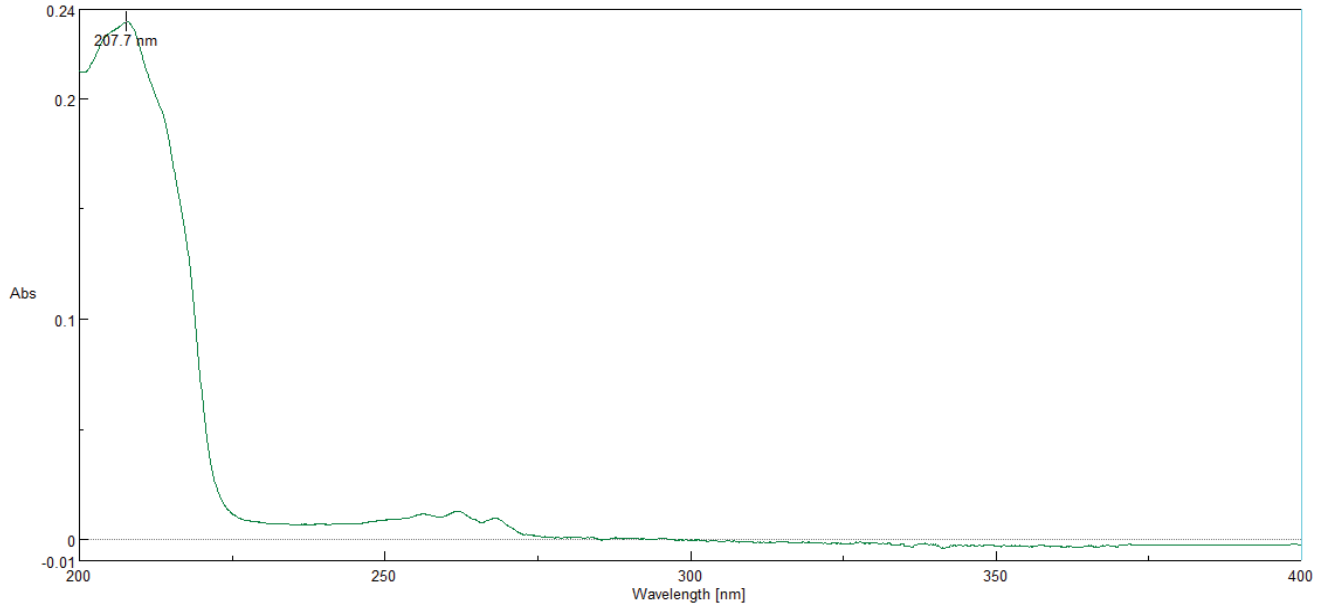


Figure 1. UV spectra of cevimeline hydrochloride

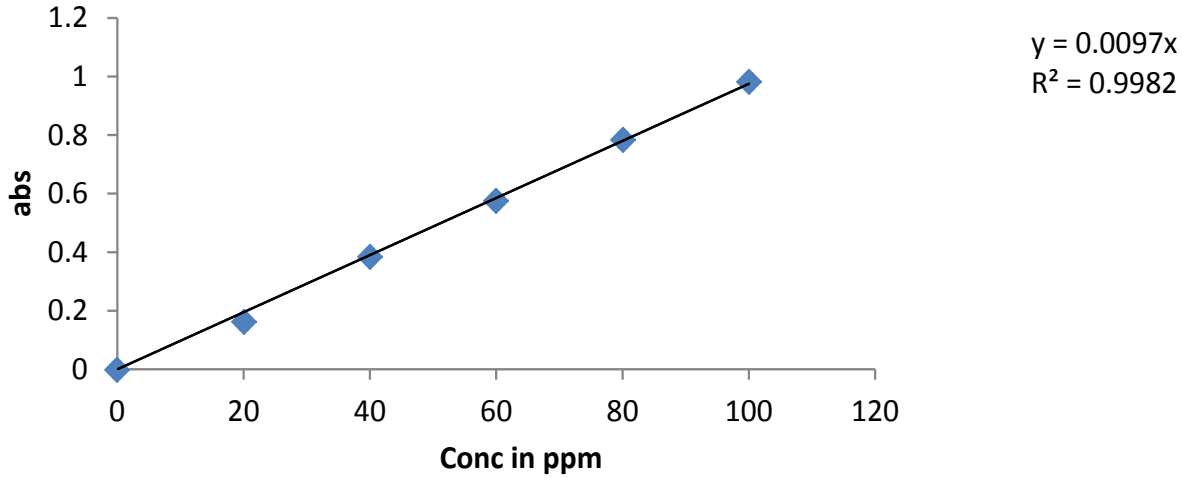


Figure 2. Calibration curve of cevimeline hydrochloride

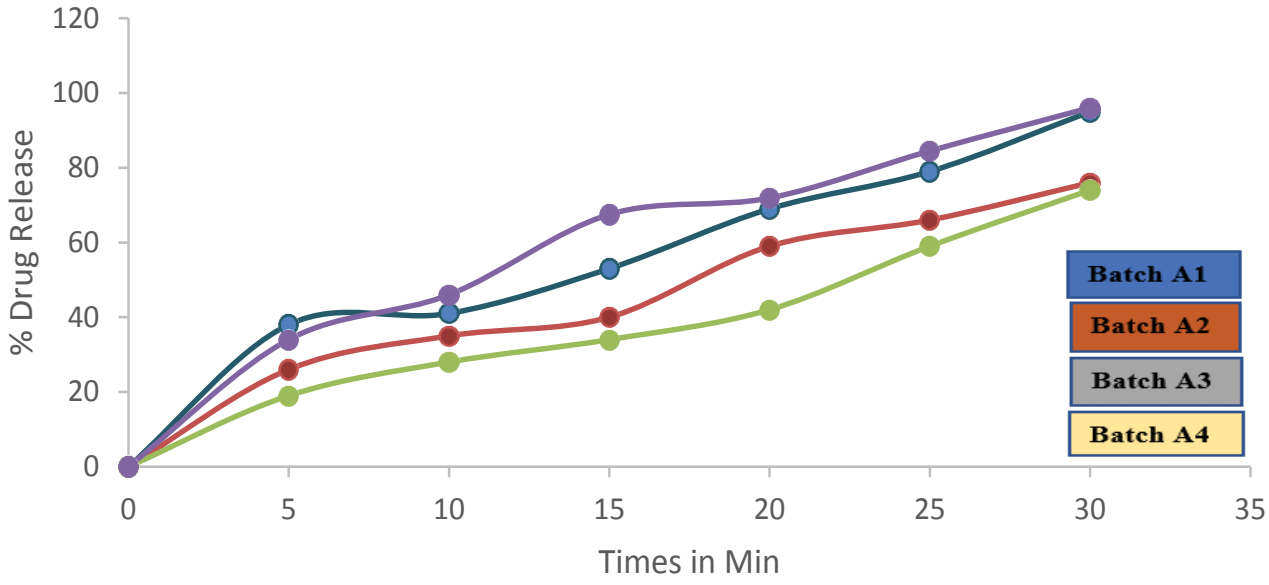


Figure 3. Dissolution profile of preliminary trial batches

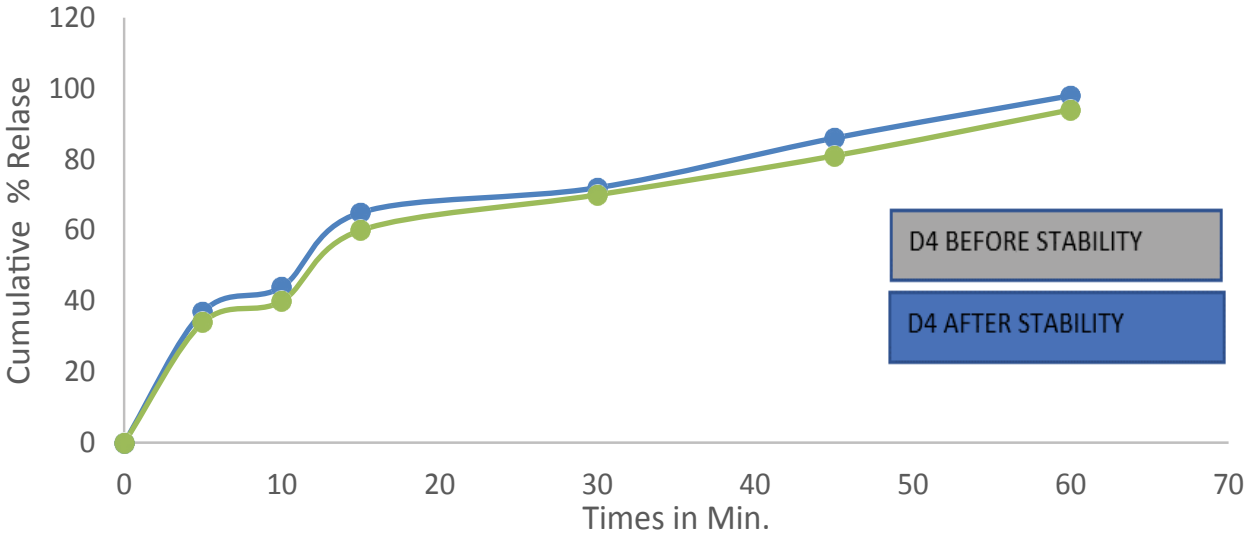


Figure 4. Dissolution profile of optimised formulation before & after stability

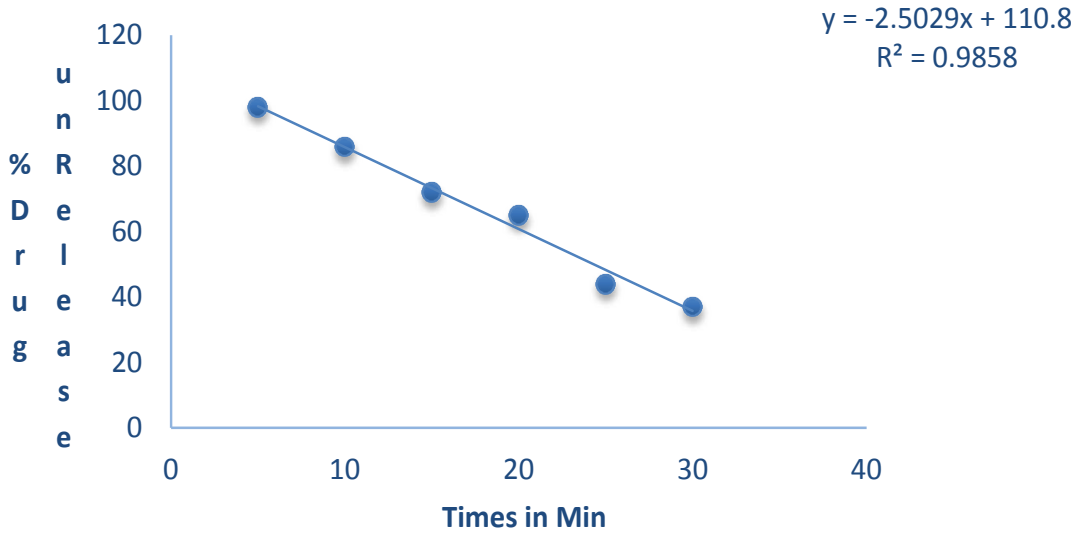


Figure 5. Zero order kinetics study

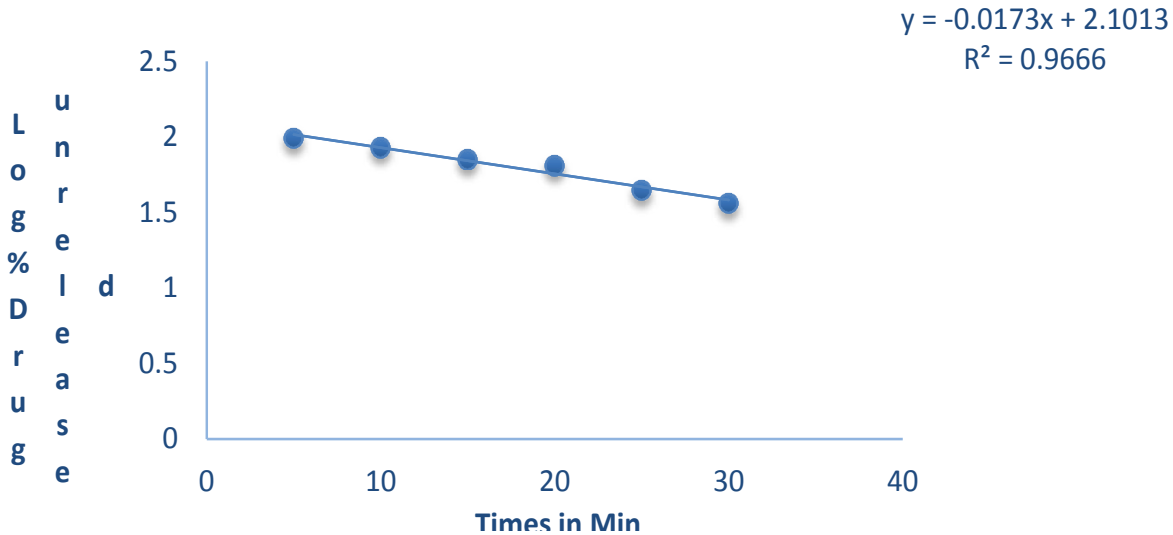


Figure 6. Firsts order kinetics study

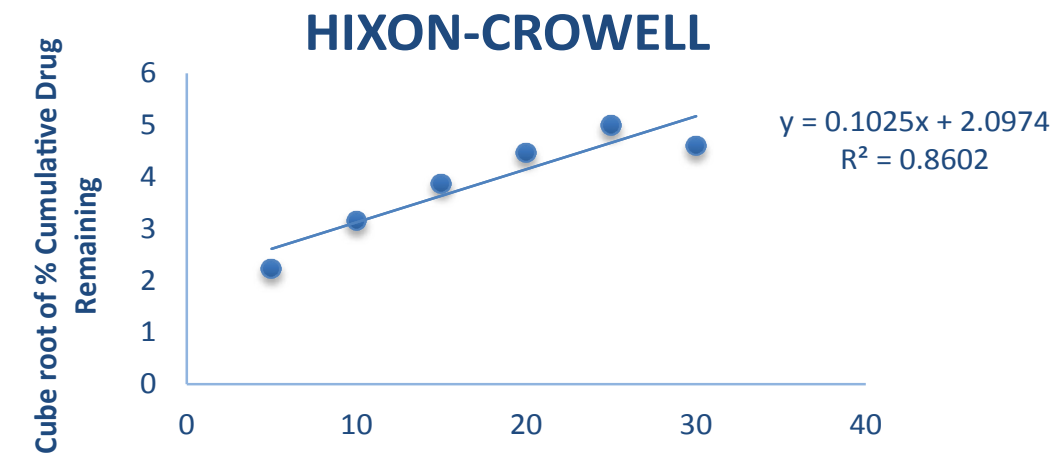


Figure 7. Hixon crowell model kinetics study

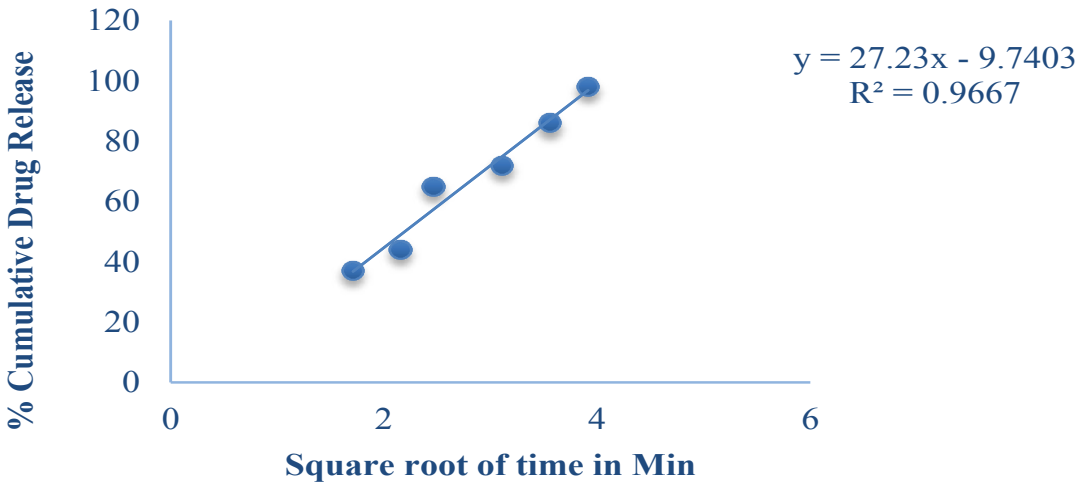


Figure 8. Higuchi model kinetics study

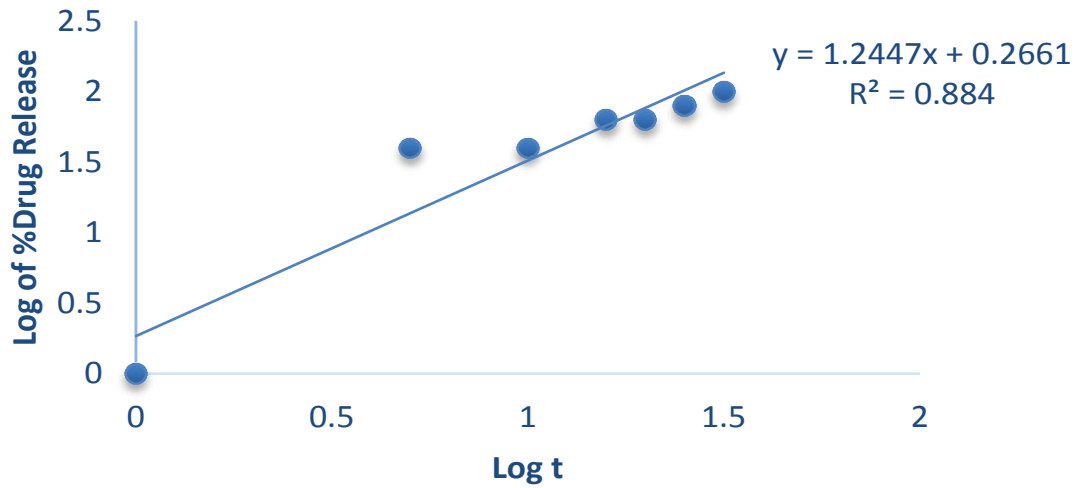


Figure 9. Korsemeyer peppa's model kinetics study

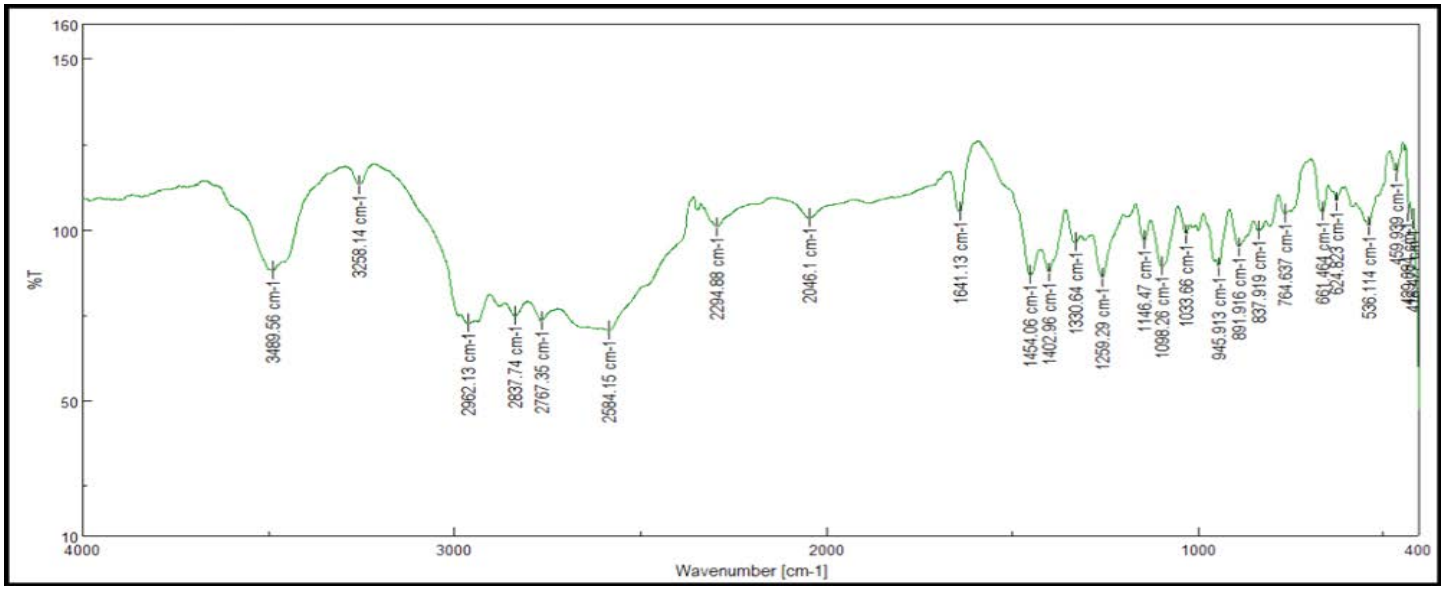


Figure 10. FTIR spectra of cevimeline hydrochloride

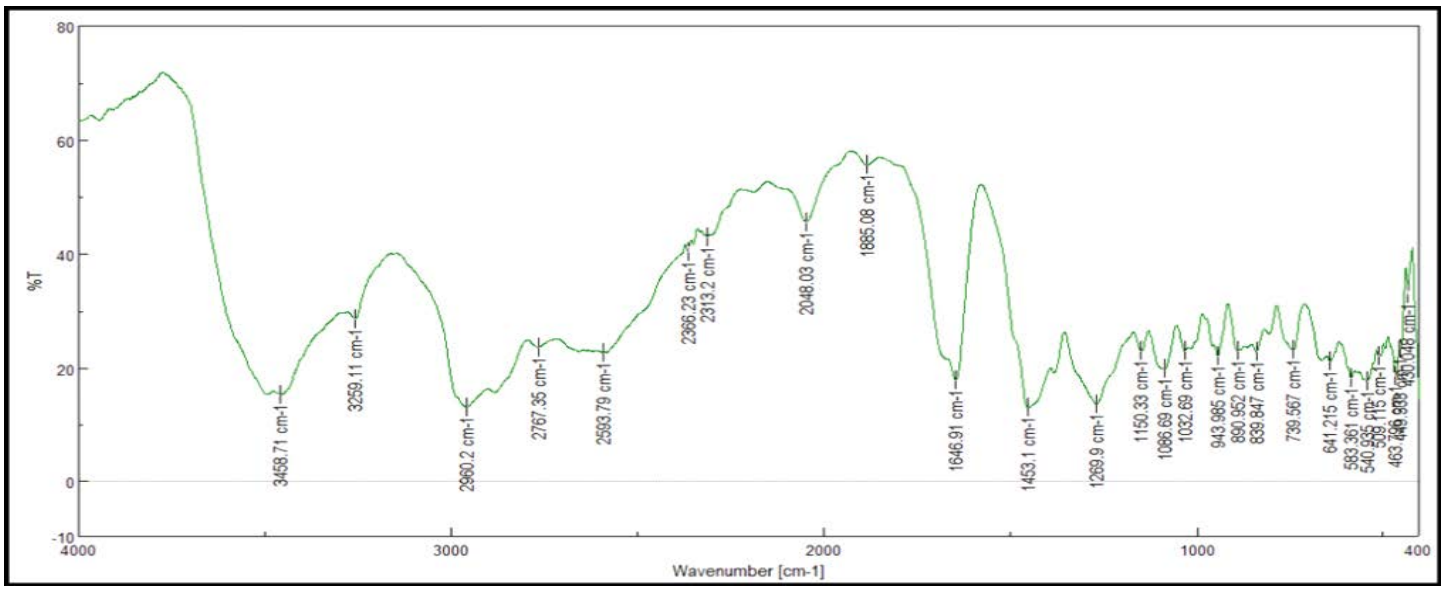


Figure 11. FTIR of cevimeline hydrochloride with excipients

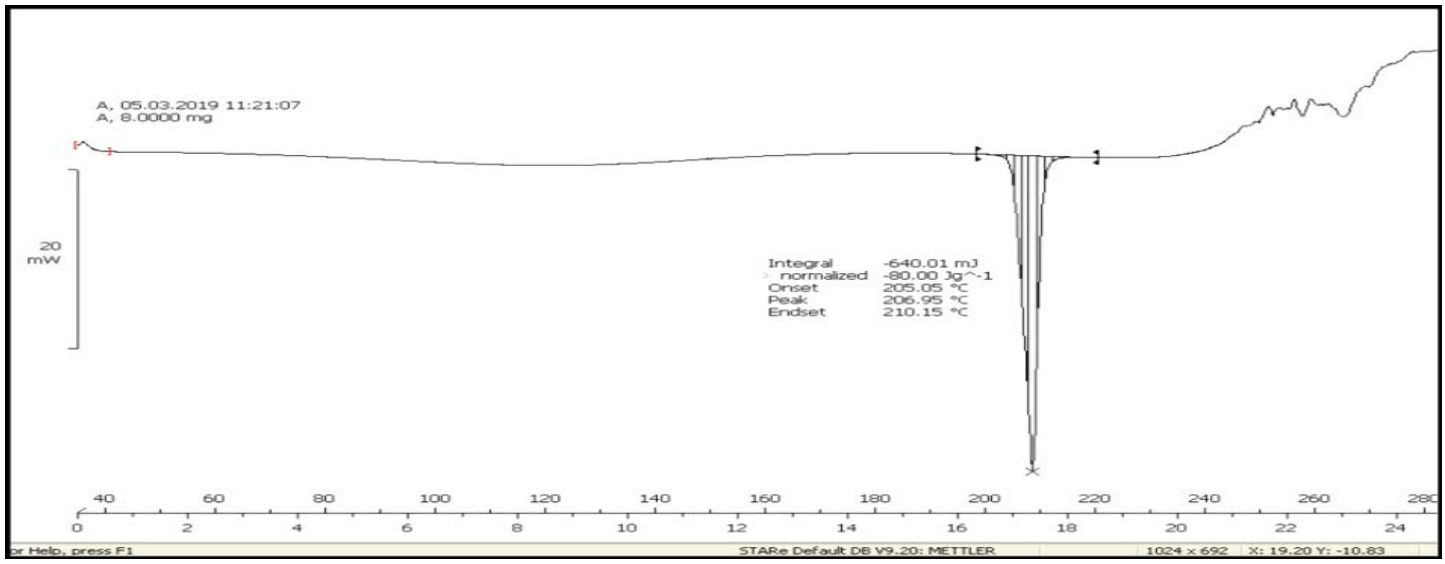


Figure 12. DSC spectra of CVEH

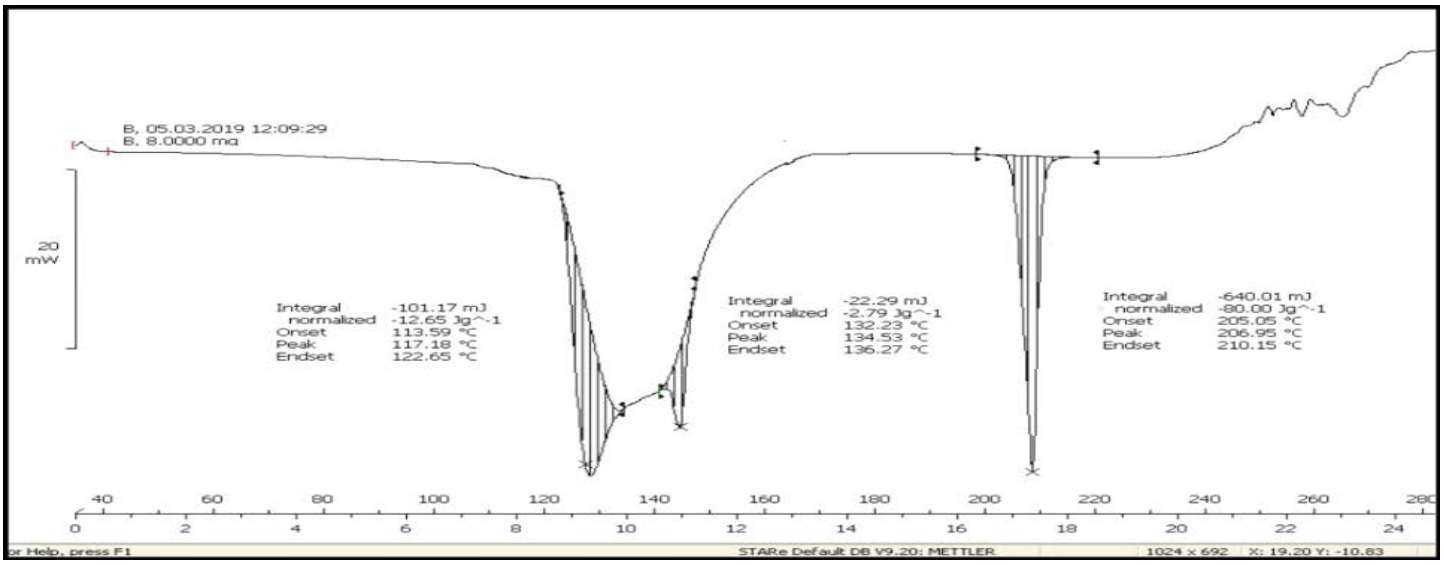
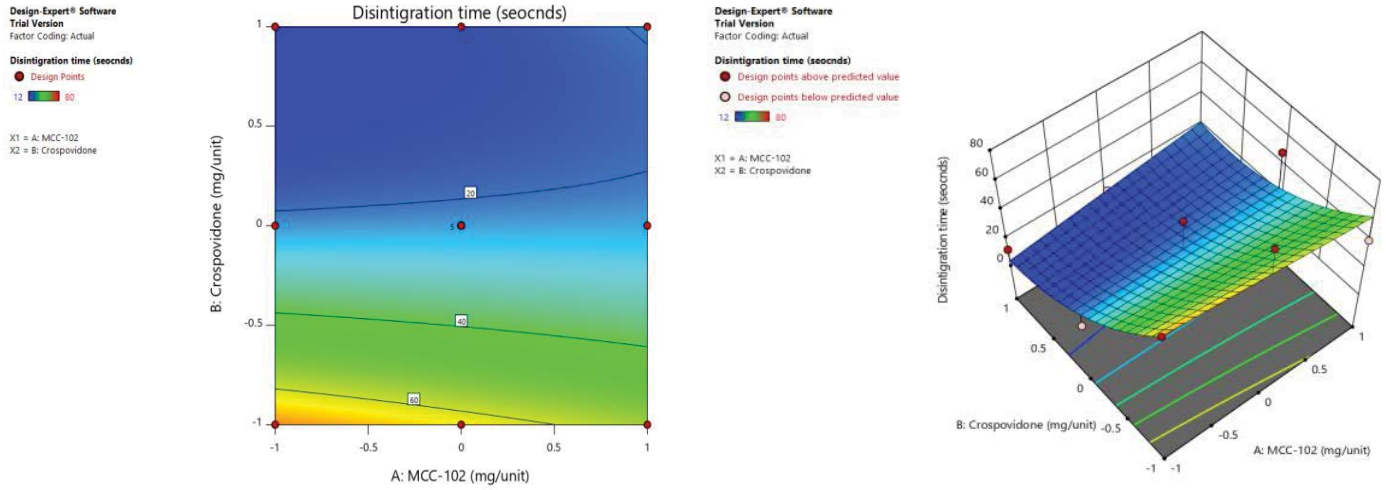
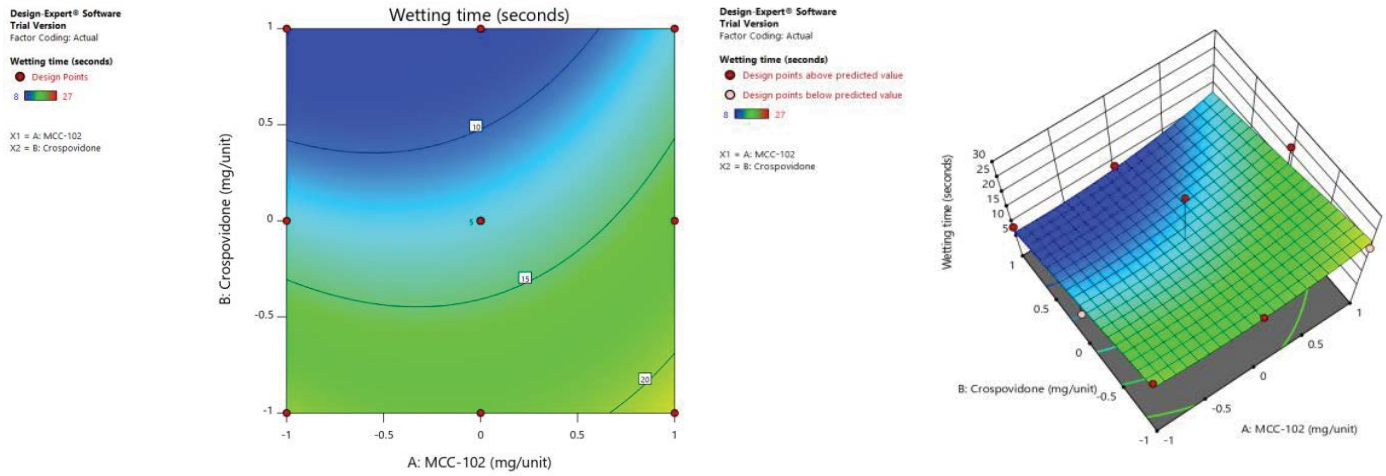


Figure 13. DSC spectra of CVEH with excipients



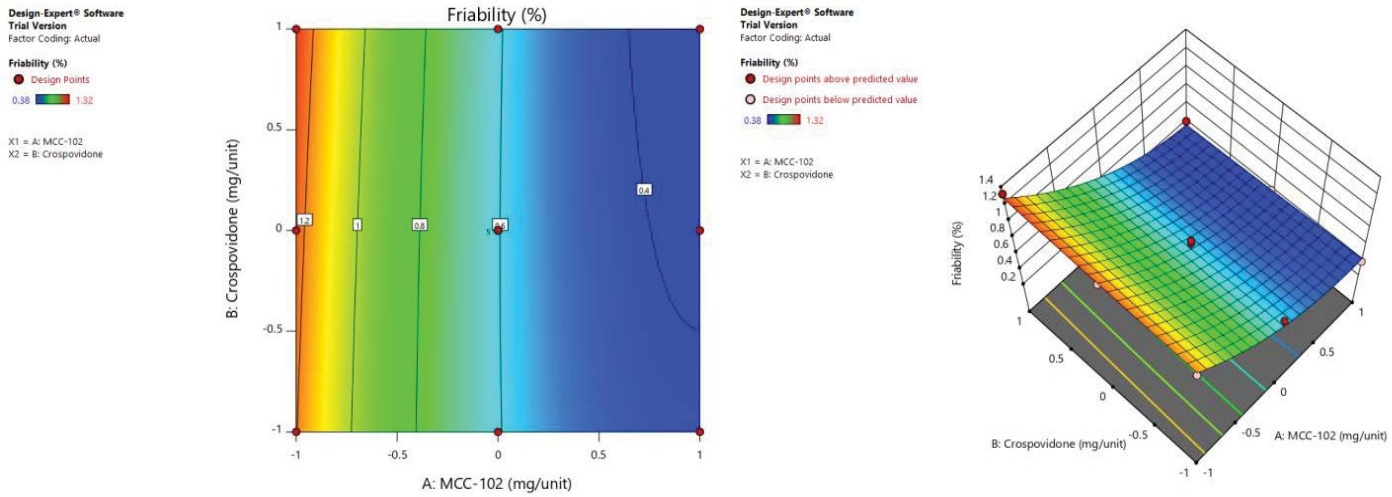
(A) (B)

Figure 14. Disintegration time. (A) Contour plot, (B) 3d Surface responses.



(A) (B)

Figure 15. Wetting time (A) Contour Plot (B) 3D Surface Responses



(A) (B)

Figure 16. Friability (A) Contour Plot (B) 3D Surface Responses

Table 1: Selection of excipients based on IIG limit.

Sr. No	Ingredient	Role	IIG Limit (mg)
1	Mannitol	Diluent	140
2	MCC-102	Diluent	340
3	Crospovidone	Superdisintigrant	25.5
4	SSG	Superdisintigrant	24.3
5	Croscarmellose	Superdisintigrant	26.8
6	Talc	Lubricant	2.5
7	Mag. Stearate	Lubricant	16
8	Orange	Flavor	-

Table 2: Solubility study in different solvents.

Sr. No	Solvents	Solubility (gm/mL)
1	Water	1 gm/mL
2	0.1 N HCl	1 gm/mL
3	0.01 N HCl	1 gm/mL
4	0.001 N HCl	1 gm/mL
5	pH 4.5 Phosphate buffer	1 gm/mL
6	pH 4.5 Phosphate buffer	1 gm/mL
7	pH 4.5 Phosphate buffer	1 gm/mL

Table 3: Preliminary trail batch CVEH tablets.

Ingredient	mg/tab			
	Batch A1 mg/tab	Batch A2 mg/tab	Batch A3 mg/tab	Batch A4 mg/tab
API	30	30	30	30
Mannitol	110	110	110	100
MCC-102	-	-	-	10
Crospovidone	8	-	-	8
SSG	-	8	-	-
croscarmellose cellulose	-	-	8	-
Flavor	QS	QS	QS	QS
Talc	0.75	0.75	0.75	1
Magnesium stearate	0.75	0.75	0.75	1
Total	150	150	150	150

Table 4: Evaluation of preliminary trial batches.

Batches	Avg. Weight (mg) ± SD (n=3)	Thickness (mm) ± SD (n=3)	Hardness (kpa) ± SD (n=3)	Dt (sec) ± SD (n=6)	Wetting time (sec) ± SD (n=3)	friability (%) ± SD (n=3)
A1	145 ± 2	2.1 ± 4	4.5 ± 1.5	15 ± 10	13 ± 5	1.78 ± 0.10
A2	152 ± 2	2.1 ± 4	4.5 ± 1.5	80 ± 20	37 ± 5	1.2 ± 0.10
A3	148 ± 2	2.1 ± 4	4.5 ± 1.5	120 ± 20	46 ± 5	1.32 ± 0.10
A4	143 ± 2	2.1 ± 4	4.5 ± 1.5	15 ± 5	11 ± 5	0.72 ± 0.10

Table 5: % Drug release of preliminary trial batches.

Times in min	Batch A1	Batch A2	Batch A3	Batch A4
5	38	26	19	34
10	41	35	28	46
15	53	40	34	67.5
20	69	59	42	71.9
25	79	66	59	84.5
30	95	76	74	96.07

Table 6: Optimization of A4 batch by using factorial design.

Sr no	Ingredient (mg/tab)	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13
1	API	30	30	30	30	30	30	30	30	30	30	30	30	30
2	Mannitol	106	98	98	98	106	98	106	90	98	98	90	98	90
3	MCC-102	8	16	8	12	8	8	8	16	8	16	16	16	16
4	Crospovidone	4	4	12	8	4	12	4	12	12	4	12	4	12
5	Orange Flavor	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
6	Talc	1	1	1	1	1	1	1	1	1	1	1	1	1
7	Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1	1
8	Total	150	150	150	150	150	150	150	150	150	150	150	150	150

Table 7: Absolute values of level of variables.

Sr no	Variables	Level			
	Independent Variables	**Coded**	**-1**	**0**	**1**
1	MCC-102 (mg/tab)	X1	8	12	16
2	Crospovidone (mg/tab)	X2	4	8	12
	Dependent Variables		**Acceptable Ranges**		
3	Disintegration Time	Y1	NMT 60 Seconds		
4	% Friability	Y2	NMT 1%		
5	Wetting Time	Y3	NMT 10 Seconds		

Table 8: Evaluations of optimization formulation.

Batches No	Avg. Weight (mg)SD (n=3)	Thickness (mm) SD (n=3)	Hardness (kpa) ± SD (n=3)	Dt (sec) SD (n=6)	Wetting time (sec) SD (n=3)	Friability (%) SD (n=3)
D1	145 ± 2	2.1 ± 0.4	4.5 ± 1.5	48 ± 5	11 ± 3	0.52 ± 0.10
D2	143 ± 2	2.1 ± 0.4	4.5 ± 1.5	43 ± 5	20 ± 3	0.38 ± 0.10
D3	146 ± 2	2.1 ± 0.4	4.5 ± 1.5	13 ± 5	13 ± 3	0.54 ± 0.10
D4	152 ± 2	2.1 ± 0.4	4.5 ± 1.5	12 ± 5	09 ± 3	0.83 ± 0.10
D5	141 ± 2	2.1 ± 0.4	4.5 ± 1.5	42 ± 5	09 ± 3	0.42 ± 0.10
D6	148 ± 2	2.1 ± 0.4	4.5 ± 1.5	12 ± 5	10 ± 3	0.52 ± 0.10
D7	146 ± 2	2.1 ± 0.4	4.5 ± 1.5	48 ± 5	12 ± 3	0.39 ± 0.10
D8	143 ± 2	2.1 ± 0.4	4.5 ± 1.5	12 ± 5	18 ± 3	0.34 ± 0.10
D9	145 ± 2	2.1 ± 0.4	4.5 ± 1.5	12 ± 5	09 ± 3	0.59 ± 0.10
D10	152 ± 2	2.1 ± 0.4	4.5 ± 1.5	50 ± 5	09 ± 3	0.43 ± 0.10
D11	147 ± 2	2.1 ± 0.4	4.5 ± 1.5	11 ± 5	20 ± 3	0.39 ± 0.10
D12	146 ± 2	2.1 ± 0.4	4.5 ± 1.5	46 ± 5	19 ± 3	0.27 ± 0.10
D13	146 ± 2	2.1 ± 0.4	4.5 ± 1.5	10 ± 5	22 ± 3	0.22 ± 0.10

Table 9: Evaluations of optimized batch (d4) after stability.

Batch No	Avg. Weight (mg)± SD (n=3)	Thickness (mm) ± SD (n=3)	Hardness (kpa) ± SD (n=3)	Dt (sec) ± SD (n=6) ± SD	Wetting time (sec) ± SD (n=3)	Friability (%) ± SD (n=3)
D4	152 ± 2	2.1 ± 4	4.5 ± 1.5	15 ± 2	10 ± 5	0.62

Table 10: ANOVA model response 1: disintigration time.

Cor Total	Sum of Squares	df	Mean Square	F-value	p-value	
Model	4924.51	5	984.9	3.37	0.0722	not significant
A-MCC-102	2.67	1	2.67	0.0091	0.9266	-
B-Crospovidone	3952.67	1	3952.67	13.53	0.0079	-
AB	256	1	256	0.8761	0.3804	-
A^2	0.0296	1	0.0296	0.0001	0.9923	-
B^2	612.89	1	612.89	2.1	0.1908	-
Residual	2045.49	7	292.21	-	-	-
Lack of Fit	1373.49	3	457.83	2.73	0.1786	not significant
Pure Error	672	4	168	-	-	-
Cor Total	6970	12	-	-	-	-

Table 11: ANOVA model response 2: wetting time.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
	239.91	5	47.98	1.01	0.4765	not significant
Model	239.91	5	47.98	1.01	0.4765	not significant
A-MCC-102	24	1	24	0.5054	0.5001	-
B-Crospovidone	192.67	1	192.67	4.06	0.0838	-
AB	6.25	1	6.25	0.1316	0.7275	-
A^2	13.45	1	13.45	0.2833	0.611	-
B^2	0.1182	1	0.1182	0.0025	0.9616	-
Residual	332.39	7	47.48	-	-	-
Lack of Fit	63.19	3	21.06	0.313	0.8164	not significant
Pure Error	269.2	4	67.3	-	-	-
Cor Total	**572.31**	**12**	-	-	-	-

Table 12: ANOVA model response 3: friability.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
	1.23	5	0.245	33.49	<0.0001	Significant
A-MCC-102	1.08	1	1.08	148.13	<0.0001	-
B-Crospovidone	0	1	0	0.0023	0.9633	-
AB	0.0042	1	0.0042	0.5775	0.4721	-
A^2	0.1153	1	0.1153	15.76	0.0054	-
B^2	0.0001	1	0.0001	0.007	0.9356	-
Residual	0.0512	7	0.0073	-	-	-
Lack of Fit	0.0205	3	0.0068	0.8923	0.518	not significant
Pure Error	0.0307	4	0.0077	-	-	-
Cor Total	1.28	12	-	-	-	-

Table 13: Release mechanism of optimized formulation.

Release kinetics	R^2 value	Regression equation
Zero-order kinetics	0.9858	y=2.5029x+110.8
First-order kinetics	0.9666	y=0.0173x+2.1013
Hixon-Crowell	0.9858	y=0.1025x+2.0974
Higuchi Model	0.9667	y=27.23x-9.7403
Korsemeyer Peppa's	0.909	y=0.3743x+1.3072