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OPTIMIZATION OF ENTERIC-COATED TABLET OF DIVALPROEX SODIUM USING DESIGN EXPERT

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ABSTRACT

The present study deals with the formulation of an enteric-coated tablet of Divalproex sodium using the polymer Eudragit L 100-55. The core tablet was prepared by non-aqueous granulation technique and seal coated with Hydroxypropyl methylcellulose (HPMC) which acts as a moisture protectant. This seal coated tablet was further enteric coated with Eudragit L 100-55 to dissolve the drug in the intestinal fluid. Three factors and two levels (2^3) factorial design was applied using the design expert software to scrutinize the interaction effects of independent variables namely; quantity of Hydroxypropylcellulose EXF, Croscarmellose sodium, and Corn starch on the parameters like disintegration time and in vitro drug release. ANOVA analysis demonstrated that Hydroxypropylcellulose EXF level and, Croscarmellose sodium level had a significant effect ($P \leq 0.05$) on the dependent responses of the core tablet. Further, the optimized batch shows the in vitro result of the enteric-coated tablet is gastro-resistant in acidic media. The comparative study was conducted with the marketed formulation using the (f1) dissimilarity and (f2) similarity factor. A similarity factor (f2) of the optimized batch was higher than 50 and thus, the formulated enteric-coated tablet could be a promising alternative to the conventional dosage form.

Keywords – *Divalproex sodium, Enteric-coated tablet, Design of experiment, In-vitro release study.*

1. INTRODUCTION

Divalproex sodium is used as an Anticonvulsant agent and also used for the treatment of the manic episodes which are associated with bipolar disorder.[1] Divalproex sodium [bis(2 propylpentanoate)] is a stable compound that is made up of sodium valproate and valproic acid in ratio of a 1:1 molar relationship. Its molecular weight and the chemical formulae are 310.4 g/mol and $C_{16}H_{31}NaO_4$ respectively. Divalproex Sodium is classified under the BCS class I but unlike others, it has pH-dependent solubility. It is believed to act on GABA neurotransmitters by increasing its activity in the brain. Also, it inhibits GABA transaminase which prevents the breakdown of GABA.[2] Thus, these results in the calming effect of GABA and further it stabilizes the activity of electric

nerve to prevent episodic seizers. The side effects reported at the initial stages of therapy were nausea, vomiting, irritation, and indigestion. The other reported side effects are abdominal cramps, diarrhea, and constipation. The administration of the delayed-release divalproex sodium could result in the reduction of gastrointestinal side effects.[2]

Considerable endeavors have been utilized to enhance the quality attributes of the core tablets concerning its optimization between disintegration time and in vitro release of the drug. Among the different technologies, non-aqueous granulation technology was preferred because it is the most reliable and cost-effective technique for the manufacturing of such tablets. However, while manufacturing Divalproex Sodium core tablets, it was observed that the granules were sticking to the die during compression and also disintegration time and dissolution time was higher than expected.[3] Further to overcome these problems, the concentrations of the Anti-sticking agent, Disintegrant and binder needs to be optimized by applying the Design of Experiment (DoE) approach while retaining their Mechanical strength.

The Enteric-coated tablets act as a barrier that controls the site of drug release in the GI tract. The word "enteric" refers to the small intestine; as it prevents the drug release before reaching the small intestine. The polymers which are used as the enteric coating remain unionized and insoluble at acidic pH. But as pH becomes basic in the GIT, the acidic functional groups get ionized and results in swelling of polymer which further gets solubilized in the intestinal fluid of the small intestine. The materials used for enteric coating are CAP, CAT, HPMC, and Eudragit.[3,4]

The reasons for such coatings are:

- It protects the active pharmaceutical ingredients from the acidic environment of the stomach.
- To prevent gastric stress like nausea and vomiting from a drug due to irritation.
- To deliver the drugs that are mostly absorbed in the small intestine at their primary absorption site in the most concentrated form.
- To provide a delayed-release action repetitively.
- Need for minimizing the first-pass metabolism of drugs.

The selection of the polymer and the thickness percentage of the coated layer are critical for controlling the pH solubility profile of the enteric-coated dosage form.[5], [6]

2. MATERIALS AND METHODS

2.1 Materials

Divalproex sodium was obtained from Teva Pharmaceuticals Pvt. Ltd. Mumbai, India. Hydroxypropylcellulose (HPC EXF) was a gift sample received from Ashland India Pvt. Ltd., Mumbai, India. Eudragit L 100-55 and Hydroxypropyl methylcellulose (HPMC) were donated by Evonik India Pvt .Ltd., Mumbai, India and Colorcon Asia Pvt. Ltd., Mumbai, India. Magnesium stearate, Talc, Microcrystalline cellulose (MCC), Croscarmellose sodium (CCS) and Colloidal silicon dioxide 200 were procured from Teva Pharmaceuticals Pvt. Ltd., Mumbai, India. All other excipients used were of analytical grade.

2.2 Preparation of Core Tablets

The Core tablet was prepared by using the non-aqueous granulation technique.[7,8] The formulations were developed by using different amount of HPC EXF, Croscarmellose sodium, and corn starch as a binder, disintegrant and anti-sticking agent respectively to obtain the optimized batch. The other excipients like colloidal silicon dioxide, MCC and Talc and Magnesium stearate were used as a glidant, filler and lubricants respectively in a fixed quantity (Table 1). Rapid mixer granulator (RMG) was used for the

preparation of granules. The dry mix of Divalproex sodium, HPC EXF and colloidal silicon dioxide were mixed in RMG for 10 min. The blend of drug and excipients was further wet granulated with IPA at high speed of 250 RPM for 90 seconds and granules were dried in the rapid dryer for 60 min at airflow of 25 CFM. The residual moisture content of the granules was brought down to 1-2 % by continuous drying. The granules were then passed through a sieve 20 mesh to get uniform granules. Blender was used for mixing granules and presifted corn starch, Croscarmellose sodium, and MCC for 5 min at 9rpm. After completion of the blending, sifted talc and magnesium stearate were added in the blender and lubricated for 5 min at 9rpm. The lubricated granules then compressed into 320mg tablets to an average hardness of 5.5-7.5 Kp on a Cadmach rotary compression machine (Cadmach Machinery Co. Pvt. Ltd. Mumbai, India).

Table 1 – Formulation of core tablet

Ingredients	Quantity (mg)
Granulation	
Divalproex Sodium equivalent to 125 mg of Valproic Acid.	134.4
HPC EXF (Binder)	10 – 20
Colloidal silicon dioxide (Glidant)	6
IPA(Vehicle)	q.s
Extra-granular	
Corn starch (Disintegrant)	20 – 40
Croscarmellose sodium (Disintegrant)	0 – 20
Microcrystalline cellulose (Diluent)	103
Lubrication	
Talc	8 – 10
Magnesium stearate (Lubricant)	10 - 14

2.3 Experimental Design

A factorial design was employed as per the standard protocol. The amount of HPC EXF (X1), Croscarmellose sodium (X2) and corn starch (X3) were selected as the factors for study at 2 levels each. The central point was studied in triplicates. All other excipients and processing variables were kept undeviated throughout the study. Table 2 summarizes an account of the 11 experimental runs studied and their factor combinations. The following polynomial terms were developed to evaluate the responses.[9,10]

$$Y = \beta 0 + \beta 1X1 + \beta 2X2 + \beta 3X1X2 + \beta 4X12 + \beta 5X22 + \beta 6X12X2 + \beta 7X1X22$$

Here,

Y = dependent variable

β0 = arithmetic mean response of the 11 runs

β1 = estimated coefficient for the factor X1

X1 X2 = it is the average result of changing one factor at a time from its low to high value shows the main effects that represents

The interaction between X1X2 shows the change in response when 2 factors are changed simultaneously.

The statistical analysis of the factorial design was performed using the software Design-Expert. The statistical validity of the polynomials was established based on ANOVA provision in the Design expert Software. Disintegration time (Y1) and Dissolution at 15 min (Y2) were taken as the response variables.

Table 2 – Design of experiment

Formulation No.	Factor 1	Factor 2	Factor 3
	A:HPC EXF	B:corn starch	C:CCS
1	10	20	0
2	20	20	0
3	10	40	0
4	20	40	0
5	10	20	20
6	20	20	20
7	10	40	20
8	20	40	20
9	15	30	10
10	15	30	10
11	15	30	10

2.4 Preparation of Seal Coated Tablets

The Seal coating solution was prepared using purified water, HPMC, Triethyl citrate and Talc (Table 3). The purified water was stirred with propeller stirrer to form a vortex further to which HPMC, Triethyl citrate and Talc were added. The solution was continuously stirred in Vortex stirrer until the clear solution was obtained. The core tablets were taken in a Ganscoater coating machine for seal coating. The 5% of seal coat was applied over the tablet to prevent moisture penetration into the Core tablet and also to protect the drug interaction from the enteric coating.

Table 3 – Formulation for seal coat

Seal coating (5%)	Quantity (%)
Hydroxypropyl methylcellulose (Hypromellose)	71.43
Triethylcitrate	7.12
Talc	21.38
Purified Water	q.s.

2.5 Preparation of Enteric Coated Tablets

The seal coated tablets were taken in the Ganscoater coating machine for enteric coating. The enteric coating was done at three different levels of 3%, 5% and 7% for dissolution studies. The enteric coating solution was prepared using IPA and purified water in the ratio of 95:5 respectively and stirred with propeller stirrer to form a vortex. The sufficient quantities of Eudragit L 100-55, Triethyl citrate and Talc were further added in vortex stirrer and stirred for 45 minutes (Table 4). [11]

Table 4 – Formulation of enteric coat

Enteric coating	Quantity (%)
Eudragit L 100 55	7%
Triethyl citrate	1.50%
Talc	1.50%
IPA	90% (95:5)
Purified Water	

2.6 Evaluation

2.6.1 Characterization of granules

The pre-compression parameters such as the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were evaluated for determining the micrometric properties of granules.

2.6.2 Evaluation of Tablet[12]

The formulated batches of core tablets were evaluated immediately for properties such as hardness, weight variation, thickness, friability and drug content. Weight variation of the tablets was carried out with 20 tablets using an electronic balance (Shimadzu). Friability was determined using 20 tablets in a Roche friabilator (Pharma Lab) for 4 minutes at 25 RPM. The hardness of 10 tablets was evaluated using a Dr. Schleuniger hardness tester. The thickness of 10 tablets was measured with a Vernier Caliper.

2.6.3 Drug content studies

The drug content was determined by using the UV spectroscopy method. The 20 tablets were collected and crushed using mortar & pestle from which the equivalent sample of 125 mg Divalproex sodium was weighed and dissolved in Methanolic HCL. The solution was further diluted and then absorbance was taken at 214 nm on HPLC (Shimadzu Corp., Japan).

2.6.4 Disintegration time

The disintegration apparatus USP of make Electrolab was used to determine disintegration time. The tablet samples were observed in 0 .1 N HCl for 2 h and then in phosphate buffer pH 7.5 for 1 hour maintaining the temperature at 37±2°C.

2.6.5 *In-vitro* Dissolution studies

In vitro drug release profile was evaluated, using a dissolution test apparatus. The USP Type II (Paddle type) apparatus (Electrolab, Mumbai, India.) was selected to perform the dissolution profile of Divalproexsodium enteric-coated tablets. The dissolution was performed into 250 ml 0.08 N HCl for 1 hour and then continued in the 900 ml of phosphate buffer pH 7.5 for 1 hour at the constant temperature of 37±0.5°C. The paddle rotation speed was kept constant at 50 rpm. Sample aliquots of 5 ml were withdrawn at regular intervals and filtered using a 0.45µ Millipore Millex-HV filter. The samples were further analyzed by HPLC (Shimadzu Corp., Japan).

3. RESULTS AND DISCUSSION

3.1 Characterization of Granules

The flow properties of the granules were determined by evaluating its pre-compression parameters such as the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The results in Table no. 5 show that the granules are free flowing.

Table 5 – Evaluation of pre-compression parameters of granules

Formulation No.	Pre-Compression Parameters				
	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's Ratio	Angle of Repose
F1	0.375	0.48	21.87	1.28	30.2
F2	0.352	0.461	23.64	1.3	29.8
F3	0.342	0.484	29.33	1.41	31.28
F4	0.4	0.521	23.22	1.3	27.4
F5	0.387	0.468	17.3	1.2	22.23
F6	0.363	0.444	18.24	1.22	21.8
F7	0.333	0.428	22.19	1.28	25.6
F8	0.324	0.413	21.54	1.27	26.78
F9	0.354	0.45	21.33	1.27	27.32
F10	0.39	0.496	21.37	1.28	26.54
F11	0.381	0.488	21.92	1.28	28.2

3.2 Evaluation of Core Tablets

The core tablets were evaluated for its post-compression parameters such as hardness, weight variation, thickness, friability and drug content. The results are shown in table no. 6. The average weight of the tablets was 320 mg. The thickness was around 4.5mm and hardness was between 5.5Kp – 7.5Kp. The friability was below limit i.e. 1%.

Table 6 – Evaluation of core tablets

Formulation No.	Weight Variation (mg)	Hardness (Kp)	Thickness(mm)	Friability (%)
F1	318-324	5.8-6.5	4.51-4.53	0.09
F2	316-322	6.1-7	4.49-4.52	0.1
F3	319-323	6.2-7.5	4.47-4.50	0.11
F4	320-322	5.6-6.9	4.48-4.51	0.13
F5	317-324	5.5-7	4.49-4.51	0.08
F6	319-325	6.2-7.2	4.49-4.52	0.16
F7	320-322	6.5-7.5	4.48-4.53	0.18
F8	318-321	5-6.5	4.52-4.54	0.12
F9	315-321	5.7-6.8	4.50-4.53	0.2
F10	318-326	6.6-7.4	4.52-4.55	0.19
F11	316-323	5.7-7.4	4.49-4.53	0.15

3.3 Drug Release Studies of Core tablets[13]

The dissolution studies were carried out as per the USP which is demonstrated in table no.7. The formulation F5 and F7 show the desirable disintegration time at 546 seconds and 506 seconds respectively with their complete dissolution at 15 minutes. The central points of the design i.e. formulation F9, F10 and F11 Show more disintegration time with relatively less dissolution as compared to formulation F5 and F7. The drug release profile of Divalproex sodium contains a different binder and disintegrant ratios of HPC EXF, Croscarmellose sodium, and corn starch as shown in Fig. 1. The change made in the concentration of binder and disintegrant leads to different disintegration time as shown in Fig. 2.

Table 7 –Disintegration time and *in vitro* drug release data of factorial design batches

Formulation No.	Disintegration time (sec)	% Drug dissolution at 15min	% Drug dissolution at 30 min
1	650	85	100
2	830	76	99
3	630	86	99
4	745	80	101
5	546	100	100
6	615	88	99
7	506	100	100
8	656	84	100
9	612	87	100
10	620	90	100
11	600	85	100

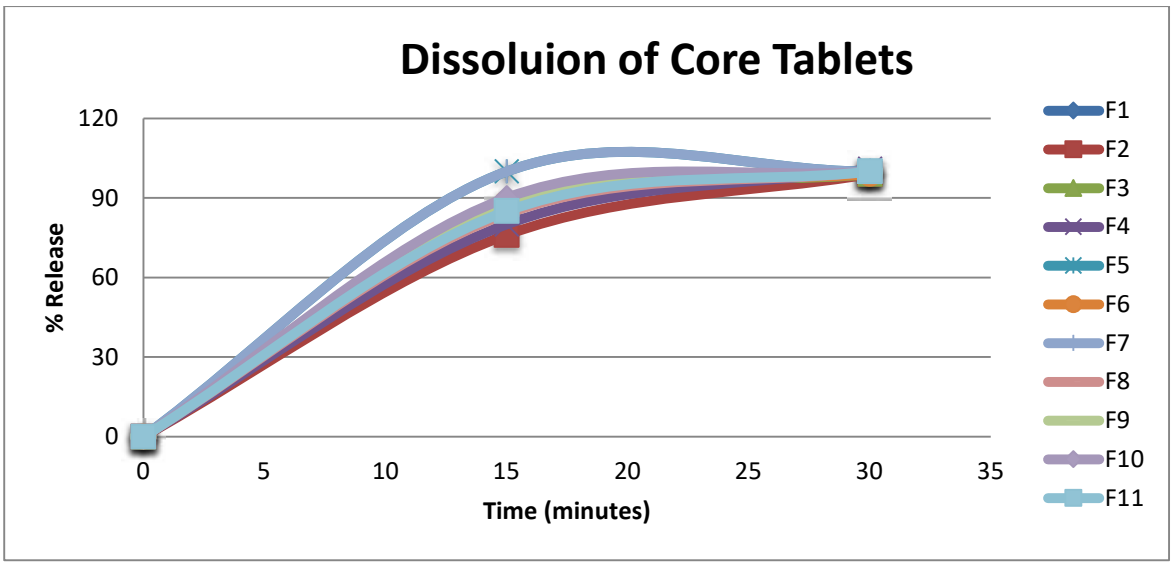

Fig. 1: Percent drug release of core tablets

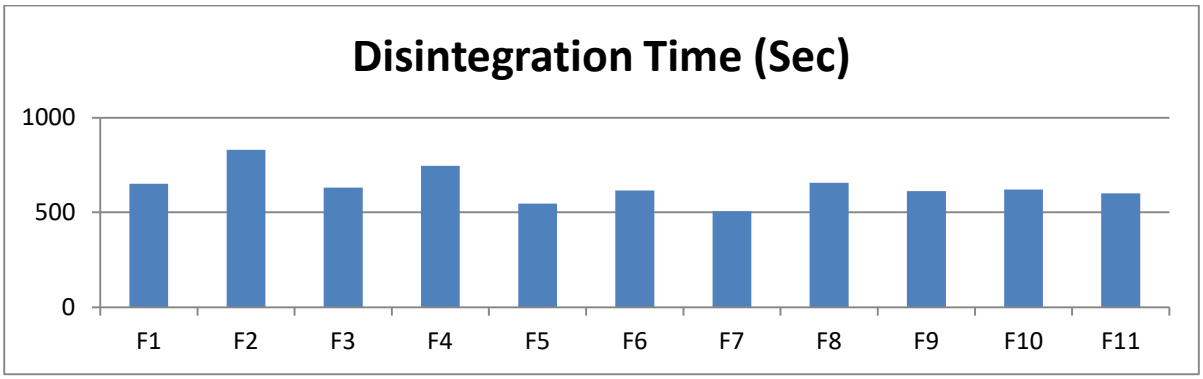

Fig. 2: Disintegration time of core tablet formulation

3.4 Experimental Design

Factorial design: The statistical analysis of the mathematical equations was performed by using the design expert. Equation of Disintegration time (Y1) and Dissolution at 15 min (Y2) were taken as the response variables.

Disintegration time (Y1) = 637.27 + 64.25A – 66.50C

Dissolution at 15 min (Y2) = +87.36 – 5.37A + 5.63C

where A is HPC EXF C: CCS

The equation in terms of coded factors can be used to make predictions about the responses for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels of the factors are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients. The analysis of variance (ANOVA) was employed as per the provision of Design-Expert Software (Table 8). The ANOVA summary explains p-value and f-value which should be significant i.e. ($p < 0.05$). Summary of all the responses conducted and interactions state that model was significant.

Table 8 –Analysis of variance (ANOVA) for all responses

ANOVA	Disintegration time Y1		Dissolution time at 15 min Y2	
Factor	F-value	p-value	F-value	p-value
Model	29.43	0.0002	38.51	< 0.0001
Intercept	637.27		87.36	
A-HPC exf	64.25	0.0007	-5.37	0.0003
C-CCS	-66.5	0.0006	5.63	0.0002

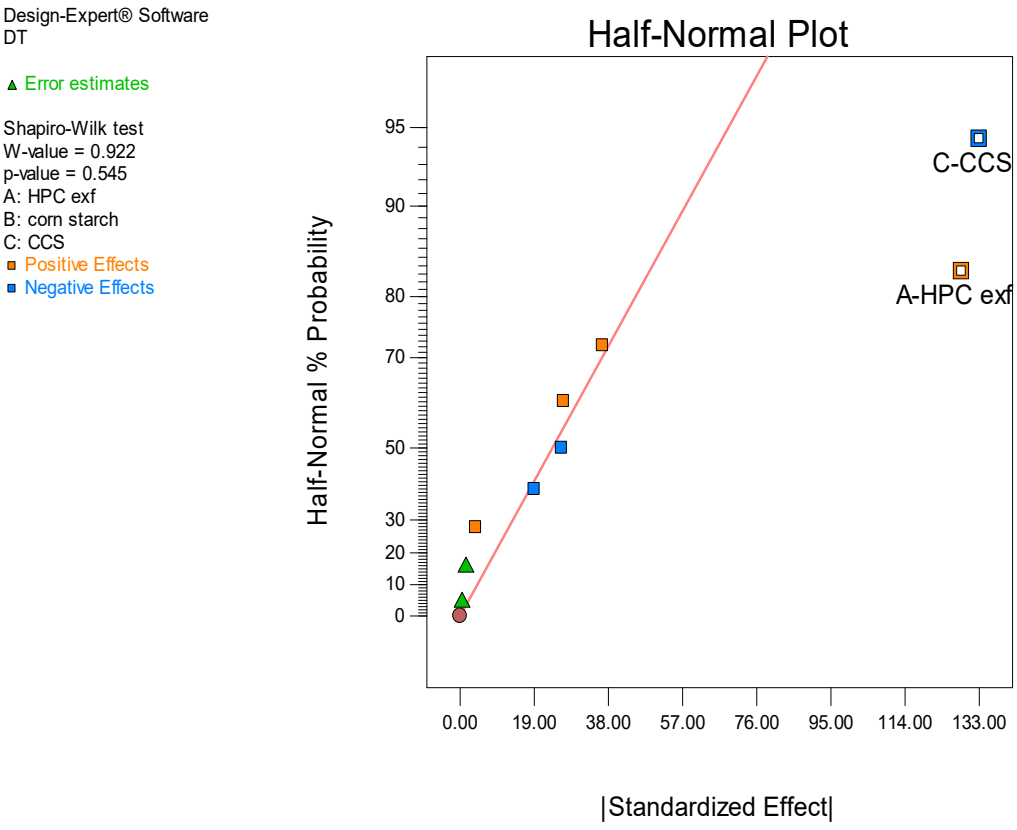

Fig. 3: Half-Normal plot of disintegration time (Y1)

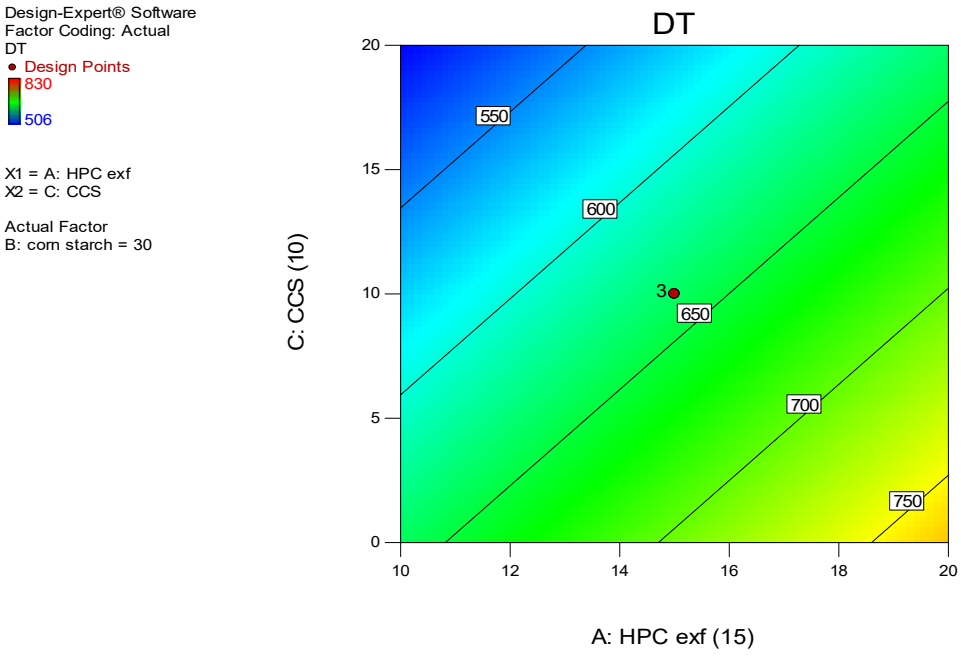

Fig 4: Two-dimensional contour plot expressed effect of Disintegration time (Y1)

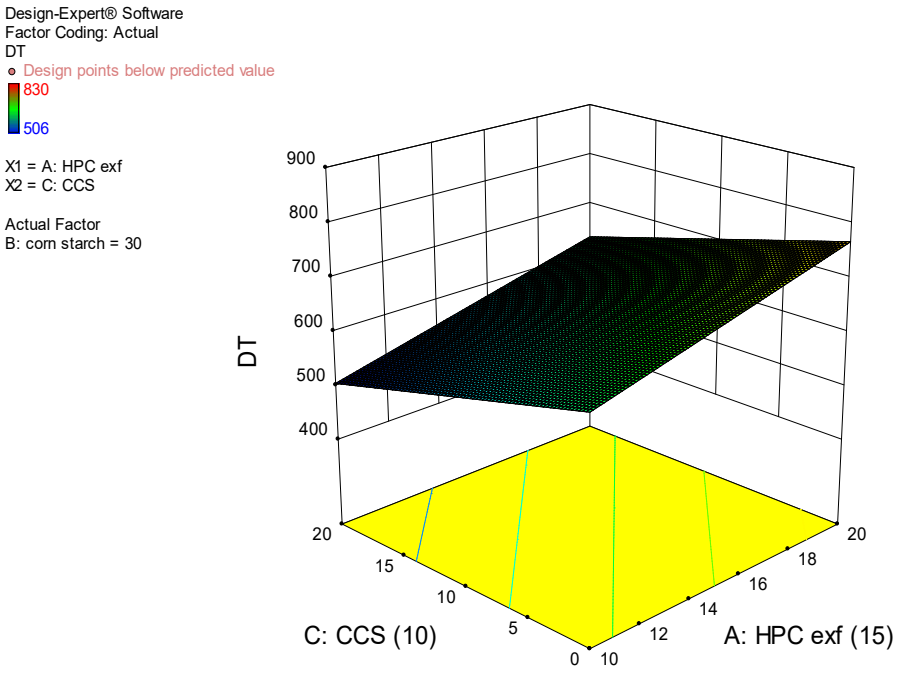

Fig. 5: Three-dimensional (3D) response surface plots for disintegration time Y1

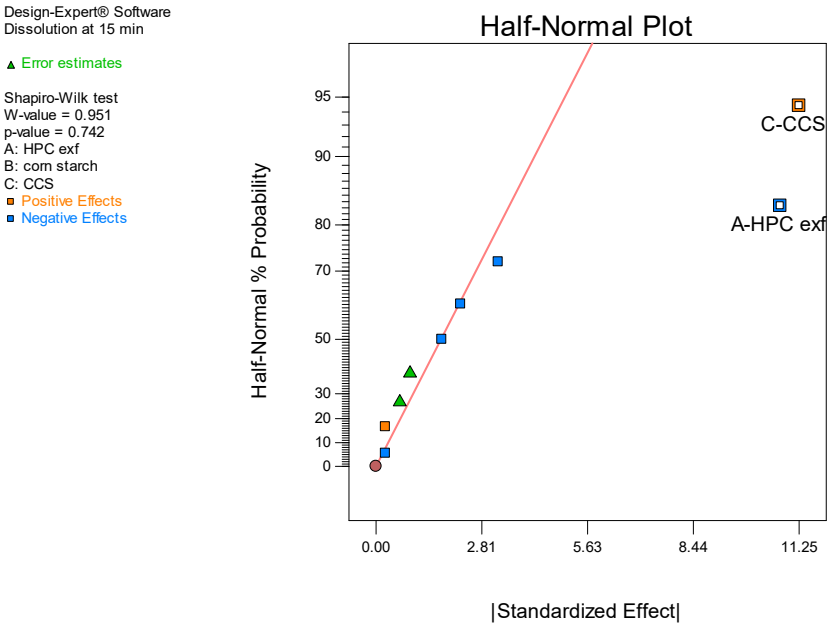

Fig. 6: Half-normal plot of dissolution at 15 min (Y2)

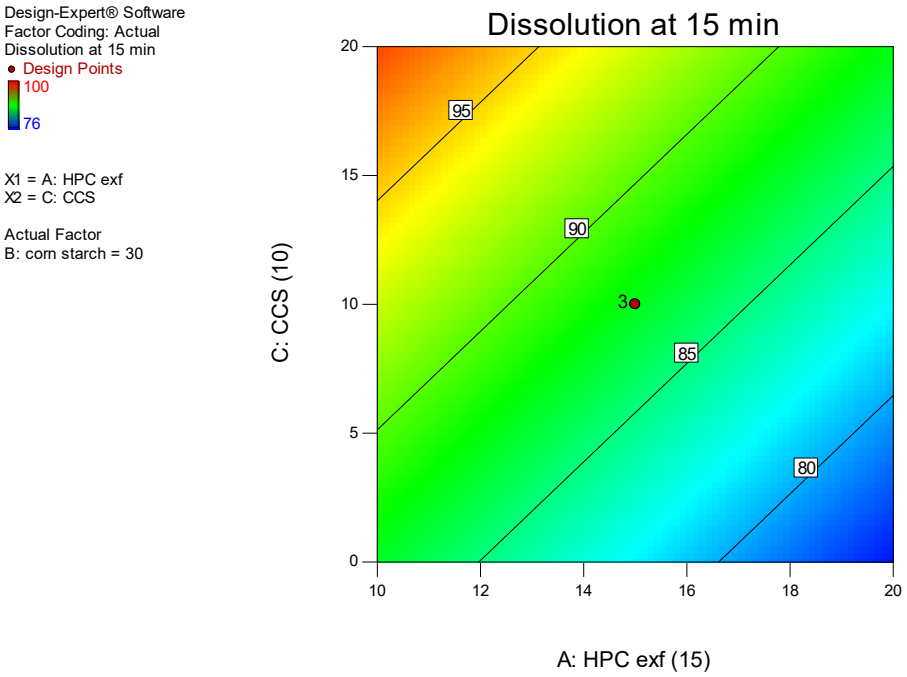

Fig. 7: Two-dimensional contour plot expressed effect of dissolution at 15 min (Y2)

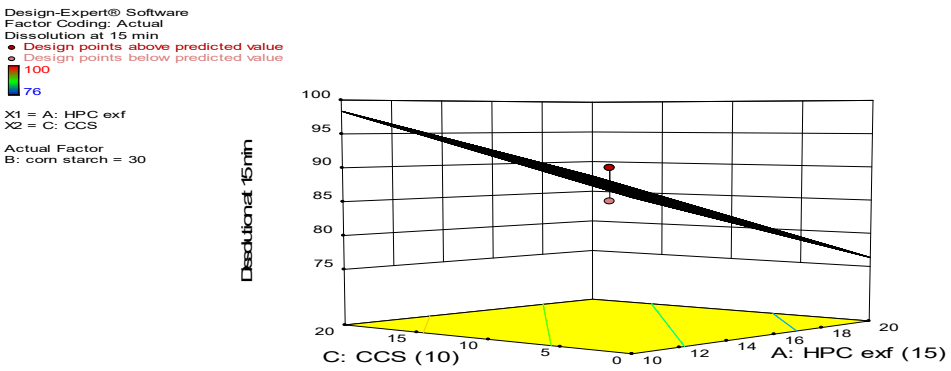

Fig. 8: Three-dimensional (3D) response surface plots for dissolution at 15 minY2

3.4.1 Optimized Batch determination

Suggested batches were determined from the software- 'Design Expert' as shown in Table 10. All the batches were formulated and evaluated for DT and drug release profile. The Disintegration time and % drug release of the F1 trail was found to be matched with the value shown by the software. Thus, the F1 trail was selected for further process and evaluations.

Table 9 – Goal for optimum formulation.

Name	Goal	Lower Limit	Upper Limit
A:HPC exf	is in range	10	20
B:corn starch	is equal to 30	20	40
C:CCS	is in range	0	20
DT	minimize	506	830
Dissolution at 15 min	maximize	85	100
Dissolution at 30 min	none	99	101

Table 10 –– Suggested batches by software- 'Design Expert'

Solutions given by the Software as Optimized Batch.								
Number	**HPC exf**	**corn starch**	**CCS**	**DT**	**Dissolution at 15 min**	**Dissolution at 30 min**	**Desirability**	
1	10.000	30.000	20.000	506.523	98.364	99.818	0.943	Selected
2	10.000	30.000	19.924	507.027	98.321	99.818	0.941	
3	10.054	30.000	20.000	507.221	98.305	99.818	0.940	
4	10.220	30.000	20.000	509.352	98.127	99.818	0.931	
5	10.256	30.000	20.000	509.815	98.088	99.818	0.929	
6	10.000	30.000	18.802	514.488	97.690	99.818	0.908	
7	10.000	30.000	18.500	516.498	97.520	99.818	0.899	
8	10.000	30.000	17.320	524.347	96.856	99.818	0.864	

3.4.2 Enteric Coating

The enteric coating of F1 trail was carried out at 3 different levels of coating i.e. 3%, 5% and 7%. The Dissolution profile of obtained batches was compared with the Marketed formulation using (f1) dissimilarity and (f2) similarity factor. The results are discussed in Table 11.

Table 11–Comparative study data with marketed formulations

Dissolution	Time	Marketed	T-1	T-2	T-3	T-4	T-5	T-6
Dissolution in 0.08 N HCl	**60**	**0**	**8**	**0**	**0**	**7**	**0**	**0**
Dissolution in pH 7.5 phosphate buffer USP II apparatus	10	9	45	10	0	48	11	0
	15	21	92	19	12	90	22	15
	20	51	99	40	30	98	52	32
	30	90	99	69	57	99	90	60
	45	94	100	95	82	100	99	89
Assay			99	100	99	101	100	102
F1 Value			25	6	19	25	2	15
F2 Value			19	49	36	19	79	39

4. CONCLUSION

The factorial design experiment was applied to study the interaction between HPC EXF and CCS has shown a significant effect on a dependent variable like disintegration time and drug release. According to ANOVA analysis, the design was concluded to be significant based on the obtained response. Trail (T-5) having a desirable drug release of an optimized batch was selected for

comparative studies with marketed formulation using (f1) dissimilarity and (f2) similarity factor in which it 2 and 79 respectively. Thus, the formulated enteric-coated tablet could be a promising alternative to the conventional dosage form.

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