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AN UPDATED RISK ASSESSMENT AS PART OF THE QBD-BASED ORALLY DISINTEGRATING TABLET DESIGN AND DEVELOPMENT

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Keywords:

Brivaracetam, Orally disintegrating tablets, QbD Approach, QTPP, Risk assessment and critical quality attributes (CQA)

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ABSTRACT: In this paper, a Quality by Design-guided and Risk Assessment (RA)-based study was performed to determine the Critical Material Attributes and the Critical Process Parameters. Direct compression method was applied for the preparation of ODT containing Brivaracetam using 2^2 factorial designs with the quantity of drug, pharmabust 500 and crosspovidone as independent variables. Pharmabust 500 and crosspovidone were used as Superdisintegrants. Design Expert 11.0 described adequately impact of selected variables as dependent (pharmabust 500 and crosspovidone) at various levels for response under study (DT and Drug Release at 2 min). Further Optimization of formulation was done using Factorial design (2 factor 2 levels) and established control strategy and design space of the formulation. Design validation was done and final optimized batch P7 was chosen from the design space. The final formulation P7 was tested for Accelerated Stability Studies for 1 month and found stable. As per the results obtained from the experiments, it can be concluded that QbD is an effective and efficient approach for developing quality into ODT with the application of QTPP, risk assessment and critical quality attributes (CQA).

INTRODUCTION: Drinking water is mostly required for the oral administration of drugs, like tablets and capsules, in which some patients experience nuisance in swallowing bulky conventional dosage forms. Orodispersible tablets are introduced as a substitute in oral DDS, designed to disintegrate in the mouth without water to prevent dysphagia and improve patient compliance. So, they are useful in conditions where water is not available or prohibited as before the operation, in kinetosis, cough episodes due to neurological stimulation, or chest infections. These orodispersible tablets (ODT) can be administered to patients with difficulty swallowing. They are also recognized as mouth dissolvable, melt-inmouth, fast dissolving, rapi-melts or porous tablets [1].

Brivaracetam is a racetam derivative of levetiracetam used to treat partial-onset seizures. Brivaracetam binds SV2A with 20 times higher affinity than levetiracetam. Brivaracetam is a white to off-white crystalline powder. It is very soluble in water, buffer (pH 1.2, 4.5 and 7.4), ethanol, methanol and glacial acetic acid. It is freely soluble in acetonitrile and acetone and soluble in toluene. It is very slightly soluble in n-hexane. Brivaracetam

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is highly permeable and is rapidly and almost completely absorbed after oral administration. Brivaracetam is weakly bound to plasma proteins (≤20%). Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid metabolite and secondarily by hydroxylation on the propyl side chain to form the hydroxy metabolite. Half-Life is 9 h [2-5].

Quality by Design Pharmaceutical industry is alert on product Quality, Safety, and Efficacy. Implementing scientific tools such as QbD (Quality by Design) have increased product quality. Scientific approaches will provide the clear and sufficient knowledge from product development to manufacturing [6-8]. These QbD tools will minimize the risk by increasing the output and quality. The QbD is a holistic and systemic way of improvements, where the primary focus is on the profound preliminary target product design. Thus, the theoretical design phase is extended based on prior knowledge (from literature and previous research) and risk estimation [9-10]. This accurate design, especially implementing the Risk Assessment(s) (RA), helps set up practical experiments correctly. A QbD method-guided development has several steps specified in the abovementioned guidelines. The first step is the definition of the Quality Target Product Profile (QTPP), which contains the essential parameters of the formulation from the patient's point of view and the requirements from the clinical field. The QTPP selection is followed by the product's design and the manufacturing process according to the predefined quality profile, which means selecting those parameters that have a critical influence on the QTPP. These are the Critical Quality Attributes (CQAs), which are related to the safety and efficacy of the product. The CQAs are those physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit range or distribution to ensure the targeted product quality. The potential CQAs of the drug product are derived from the QTPPs, and prior knowledge guides the product and process development [11-12].

MATERIALS AND METHODS:

Materials: The brivaracetam gift sample is from Astron Research Centre. Ahmedabad. Crospovidone, Sodium Starch Glycolate, Croscarmellose Sodium, Sucralose, Talc, Pharmaburst 500, Ludiflash, Pearlitol are from Balaji Chemicals, Ahmedabad. Avicel pH 102 Diluent is from ACS Chemicals.

Methods:

Quality by Design:

Quality Target Product Profile: The quality target product profile (QTPP) is "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product" **Table 1.**

A Critical Quality Attribute (CQA): CQA is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." Identifying a CQA from the QTPP is based on the severity of harm to a patient should the product fall outside the acceptable range for that attribute **Table 2.**

TABLE 1: QTPP OF THE PRODUCT

QTPP Elements	Target	Justification
Dosage Form	ODT	Patient Compliance
Dosage Design	Immediate Release tablet without scoring	For suitable replacementof marketed product
Route of Administration	Oral	Same route ofadministration
Dosage Strength	Similar to marketedproduct	
Pharmacokinetics	Similar to marketedproduct	
Stability	Similar to marketedproduct	PharmaceuticalEquivalence
Drug Product Quality Attributes	Physical Attribute	
	Identification	Pharmaceutically Equivalent to Marketed Product
	Assay	
	DisintegrationTime	
	Content Uniformity	
	Dissolution	

Administration/Concurrencewith labelling	Similar food effect	To achieve similarPharmacokinetics
Alternative methods of administration	None	None

TABLE 2: CQA OF THE PRODUCT

Quality Attributes of the Drug Product		Target	Is this a CQA?	Justification
Physical Attributes	Appearance	Acceptable to patient.No visual defects observed	No	Color, Shape and Appearance are not directly linked to safety and efficacy. Therefore not critical. The target is set to ensure patient acceptability.
	Odour	No unpleasant Odour	No	
	Taste	Acceptable taste.	Yes*	A bitter or unacceptable taste may alter the dosage regimen as the patient will be reluctant to take bitter taste formulation. Safety and efficacy is directly linked.
	Size	Acceptable to patient.	No	Shape and Appearance are not directly linked to safety and efficacy. Therefore not critical. The target is set to ensure patient acceptability.
	Friability	NMT 1.0%w/w	No	Friability is a routine test per Compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints.
Identification		Positive for Brivaracetam	Yes*	Identification is critical for safety and efficacy of the patient. But, since formulation and process variables do not impact identity, this CQA will not be addressed.
Assay		100%w/w of label claim	Yes	Drug content in the tablet will affect safety and efficacy as process variables affect the assay of the drug product. Hence itwill be evaluated throughout development
Content Uniformity		Conforms to Pharmacopoeial Standards	Yes	Drug content uniformity in the tablet will affect safety and efficacy as process variables affect the assay of the drug product. Hence it will be evaluated throughout development
Disintegration Time		Conforms to Pharmacopoeial Standards	Yes	For ODT disintegration time is the most important CQA. Any changes in disintegration time changes the dissolution rate of the drug. Hence it is critical.
Dissolution		NLT 90% in 10 minutes in 900 ml of 0.1N HCl using USP Apparatus 2 at 50 RPM	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affectthe dissolution profile.

Pre-Compression Parameters: Angle of repose (θ) (n=3) bulk density (g/ml) (n=3) tapped density (g/ml) (n=3) hausner's ratio (n=3) carr's consolidation index (%) (n=3) were performed.

Post Compression Parameters: Weight variation (mg) (n=20) thickness (mm) (n=3) hardness (kg/cm^2) (n=3) friability (%), disintegration time (sec) (n=6) water absorption ratio (%) (n=3) wetting time (sec) (n=3) assay (%) (n=3), dissolution (within 30 min) were performed.

Formulation Variables

Initial Risk Assessment of the Formulation Variables:

TABLE 3: INITIAL RISK ASSESSMENT OF FORMULATION VARIABLES

Drug Product CQA	Drug Substance PSD	Diluent Type	Disintegrant Type	Disintegran t Level	Colloidal Silicon dioxide	Talc	Magnesium Stearate
Assay	Low	Low	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Low	Low	Low
Disintegration Time	Low	High	High	High	Low	Low	Low
Dissolution	Medium	High	High	High	Low	Low	Medium

Justification for the Initial Risk Assessment of the Formulation Variables: From the Initial Risk Assessment of the formulation variables, it was concluded that the variables that could play an important role in achieving the product CQAs will be

TABLE 4: JUSTIFICATION FOR THE INITIAL RISK ASSESSMENT OF THE FORMULATION VARIABLES

FormulationVariables	Drug Product CQAs	Justification
Drug SubstancePSD	Assay Content Uniformity Disintegration Time	Drug Substance PSD will not affect the Assay, CU and DT of the tablet. Hence risk is rankedlow.
	Dissolution	Drug Substance PSD will directly affect the Dissolution rate of the drug. But since the drug isfreely soluble BCS Class I drug, Drug Substance PSD is unlikely to have any impact on the dissolution rate.
Diluent Type	Assay Content Uniformity	Diluent type will not affect the Assay and CU the tablet. Hence risk is ranked low.
	Disintegration Time Dissolution	Diluents constitute major portion of the formulation. Hence are very likely to impact the DT and Dissolution of the tablet. Proper selection of Diluent is of utmost importance. Hence risk isranked high.
Disintegrant Type	Assay Content Uniformity	Disintegrant type will not affect the Assay and CU the tablet. Hence risk is ranked low.
	Disintegration Time Dissolution	Disintegrant directly affect the wetting behaviour of the tablet and lead to disintegration. Faster disintegration would promote a faster dissolution rate. Hence proper disintegrant selection isvery important. And, the risk is ranked high.
Disintegrant Level	Assay Content Uniformity	Disintegrant level will not affect the Assay and CU the tablet. Hence risk is ranked low.
	Disintegration Time	Disintegrant concentration affects the disintegration of the tablet and in turn affects the dissolution of the drug. Hence proper selection disintegrant level is very important. And, the risk is ranked high.
Sucrose	Dissolution Assay Content Uniformity Disintegration Time Dissolution	Sweetener will only impact the taste of ODTs. It will not affect any other CQAs of the tablet.Hence the risk is ranked to low.
Colloidal Silicon dioxide	Assay Content Uniformity Disintegration Time Dissolution	Colloidal Silicon Dioxide will not affect the Assay and CU the tablet. Hence risk is ranked low.
Talc	Assay Content Uniformity Disintegration Time	Talc will not affect the Assay and CU the tablet. Hence risk is ranked low.
MagnesiumStearate	Dissolution Assay Content Uniformity Disintegration Time Dissolution	Magnesium Stearate will not affect the Assay and CU the tablet. Hence risk is ranked low. Since magnesium stearate is hydrophobic in nature, it can retard the rate of dissolution by forming a fine layer around the drug particles. But since the drug is freely water soluble, it will not be a concern. Hence the risk is ranked medium.

Diluent Type: For the current study, a range of novel ODT platforms were selected and evaluated on same concentrations.

The choice of platforms was Pharmaburst 500 from SPI Pharma, Ludiflash from BASF and Pearlitol from Roquette. All these novel excipients are Compendial after screening trials, one will be shortlisted and used for further development.

Disintegrant Type: For an ODT selection of proper disintegrant type is the most important step as it governs the disintegration pattern and time of the tablet. Three disintegrant *i.e.,* Crospovidone,

Croscarmellose Sodium and Sodium Starch Glycolate to be evaluated and the best disintegrant will further be evaluated.

Disintegrant Level: After selection of disintegrant type, level of disintegrant will be the next important step in formulation development. The short listed disintegrant should be evaluated at 4 levels to obtain the best possible disintegration time at the lowest possible concentration. Keeping in mind the above 3 variables, the formulation strategy is defined.

Preparation of Formulation: Direct Compression Method was adopted as it is the simplest of approach for ODT tablet fabrication. It involves least number of unit operations and is cost-effective when it comes to commercialization of the product. Detailed formula mentioned in table below. Dispensing and Sifting a) Dispensed quantity of Drug, Pharmaburst 500 / Ludiflash / Pearlitol, Crospovidone / Croscarmellose Sodium / Sodium Starch Glycolate, Avicel pH 102, Sucralose and Colloidal Silicon dioxide were sifted through #40 mesh. b) Talc and Magnesium Stearate were sifted through #60 mesh. 2. Blending and Lubrication: a) Material of Step 1.a was transferred to a Double Cone blender, and the material was blended together for 15 minutes at 20 RPM. b) to the above-blended material, sifted Magnesium Stearate was added and the blend was lubricated for 5 minutes at 20 RPM.

The blend was then evaluated for pre-compaction parameters. 3. Compression: The blend from step 2.b was compressed using a Multipunch Tablet compression machine from Cadmach machinery using a 5.5 mm round tip punch sets. The tablets were then evaluated for post-compression parameters of ODT.

TABLE 5: FORMULATION OF ODT BRIVARACETAM

		Screening of Diluent			Screening of Super Disintegrants			Optimization of Super Disintegrant		
Sr. no.	**Ingredients**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	Brivaracetam	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
2	Pharmaburst 500	50.0	-	-	50.0	50.0	50.0	50.0	50.0	50.0
3	Ludiflash	-	50.0	-	-	-	-	-	-	-
4	Pearlitol	-	-	50.0	-	-	-	-	-	-
5	Crospovidone	-	-	-	7.5	-	-	5.0	7.5	10.0
6	Croscarmellose Sodium	-	-	-	-	7.5	-	-	-	-
7	Sodium Starch Glycolate	-	-	-	-	-	7.5	-	-	-
8	Avicel pH 102	76.0	76.0	76.0	68.5	68.5	68.5	66.5	68.5	76.5
9	Sucralose	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
10	Colloidal Silicon Dioxide	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
11	Talc	2.0	2.00	2.0	2.0	2.0	2.0	2.0	2.0	2.0
12	Magnesium Stearate	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
	Total	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0

Quality by Design: Based on the trial batch results, statistical design was applied for optimization of final formulation. It was observed that the amount of superdisintegrant and the directly compressible excipient is critical and the physicochemical parameters were depend on the both factors. Hence, factorial design was applied by taking crospovidone and Pharmaburst 500 as an independent variable **Table 6**. 2 factor 2 level factorial design was applied as per below; Evaluation of factorial batches **Table 7** was done as per trial batches and the results were recorded in results and discussion.

TABLE 6: FACTORIAL DESIGN TABLE

Independent Variable	Low	Center Point	High
Crospovidone	5.0	7.5	10
Pharmaburst 500	40	50	60
Dependant Variable			
Y1=Disintegration Time			
Y2=Drug Release at 2 min			

TABLE 7: FORMULATION TABLE FOR FACTORIAL BATCHES

Sr. no.	Ingredients (mg)	P1	P2	P3	P4
1	Brivaracetam	10.0	10.0	10.0	10.0
2	Pharmaburst 500®	40.00	40.00	60.00	60.00
3	Crospovidone	5.0	10.0	5.0	10.0
4	Avicel pH 102	81	76	61	56
5	Sucralose	4.0	4.00	4.00	4.00
6	Colloidal Silicon Dioxide	4.0	4.00	4.00	4.00
7	Talc	2.0	2.00	2.00	2.00
8	Magnesium Stearate	4.0	4.00	4.00	4.00
	Total	150.0	150.0	150.0	150.0

RESULT:

Design Expert:

Factorial Batches Table 7: Factorial batches P1-P4 were evaluated for various parameters and the results were tabulated below. From the below results of factorial batches P1-P4, it was found that all four batches were passed the weight variation limit.

The results are well within an acceptable range. Thickness was found to be uniform in all formulations. Hardness was good enough to pass the friability test. The friability of all four formulations was below 1 hence, found satisfactory. Further, the disintegration time was observed 42 sec in P1 batch and 8 sec in P4 batch. The Assay results are also found to be well within an acceptable range. The dissolution study was performed for all 4 batches given below, along with the graph. The drug release describes the effect of the disintegrant and directly compressible grade Pharmaburst effect.

Higher amounts release more drugs for both factors. The ANOVA table for Disintegration time shows that the Crospovidone and Pharmaburst 500 have a significant impact on Disintegration time **Table 11**. ANOVA table for Drug release at 2 min shows that the Crospovidone and Pharmaburst 500 both have a significant impact **Table 12.**

TABLE 8: RESULTS OF FACTORIAL BATCHES

EvaluationParameters	P1	P2	P3	P4
Weight Variation(mg) (n=20)	149 ± 3.1	151 ± 2.8	150 ± 3.2	151 ± 1.9
Thickness (mm)(n=3)	4.12 ± 0.20	4.10 ± 0.13	4.08 ± 0.09	4.15 ± 0.08
Hardness (kg/cm^2) (n=3)	5.4 ± 0.1	5.3 ± 0.2	5.2 ± 0.1	5.3 ± 0.1
Friability (%)	0.56	0.48	0.21	0.34
Disintegration Time (sec) (n=6)	42 ± 2.3	29 ± 3.5	19 ± 2.7	8 ± 1.7
Wetting Time (sec)(n=3)	58 ± 3.5	32 ± 4.2	45 ± 3.0	17 ± 2.9
Water AbsorptionRatio (%) (n=3)	37.9 ± 4.5	40.8 ± 3.6	60.1 ± 1.3	66.9 ± 2.5
Assay (%)(n=3)	99.8 ± 1.0	98.9 ± 1.5	98.5 ± 2.4	99.7 ± 1.2

TABLE 9: DISSOLUTION RESULTS OF FACTORIAL BATCHES

Batch	0 min	2 min	4 min	6 min	8 min	10 min
P1	0	25.8 ± 4.5	62.5 ± 2.7	79.8 ± 1.7	88.9 ± 1.7	97.9 ± 0.9
P2	0	40.9 ± 3.5	85.6 ± 2.1	94.8 ± 3.2	98.9 ± 1.7	99.6 ± 1.2
P3	0	33.4 ± 2.9	69.7 ± 4.3	87.5 ± 1.7	97.2 ± 3.4	98.9 ± 1.7
P4	0	49.1 ± 3.8	97.5 ± 1.9	98.7 ± 2.0	99.9 ± 1.4	99.9 ± 0.9

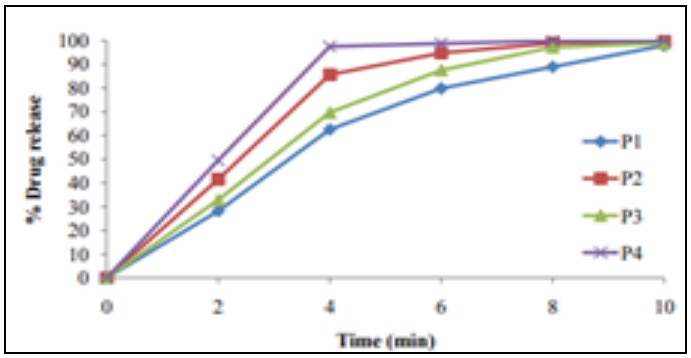

FIG. 1: DISSOLUTION P1-P4

TABLE 10: FACTORIAL DESIGN TABLE

Run order	Center Pt	Blocks	Crospovidone	Pharmaburst 500	Disintegration Time (sec)	Dissolutionat 2 min
1	1	1	5	60	19	33.4
2	1	1	5	40	42	25.8
3	1	1	10	60	8	49.1
4	1	1	10	40	29	40.9

TABLE 11: ANALYSIS OF VARIANCE FOR DISINTEGRATION TIME

Source	DF	Seq SS	Adj SS	F value	P value	Remarks
Main Effects	2	628.0	628.0	314.0	0.040	Significant
Crospovidone	1	144.0	144.0	144.0	0.053	Significant
Pharmaburst 500	1	484.0	484.0	484.0	0.029	Significant
Residual Error	1	1.0	1.0	-	-	-
Total	3	629.0	-	-	-	-

Regression Equation: Disintegration time = 97.500-2.40 Crospovidone- 1.10 Pharmaburst.

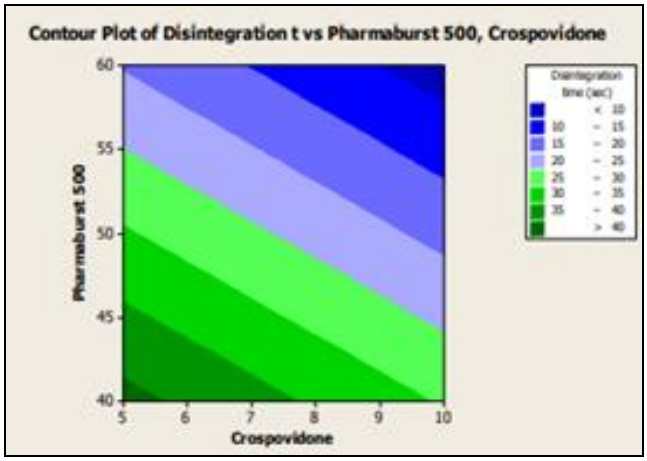

FIG. 2: CONTOUR PLOT OF DT

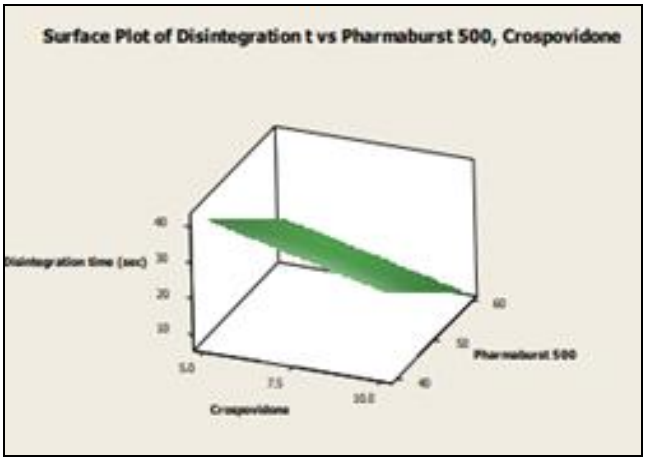

FIG. 3: SURFACE PLOT OF DT

TABLE 12: ANALYSIS OF VARIANCE FOR DRUG RELEASE AT 2 MIN

Source	DF	Seq SS	Adj SS	F value	P value	Remarks
Main Effects	2	299.570	299.570	1664.28	0.017	Significant
Crospovidone	1	237.160	237.160	2635.11	0.012	Significant
Pharmaburst 500	1	62.410	62.410	693.44	0.024	Significant
Residual Error	1	0.090	0.090	-	-	-
Total	3	299.660	-	-	-	-

Regression Equation: Drug release at 2 min = -108.800+1.86 Crospovidone+0.465 Pharmaburst.

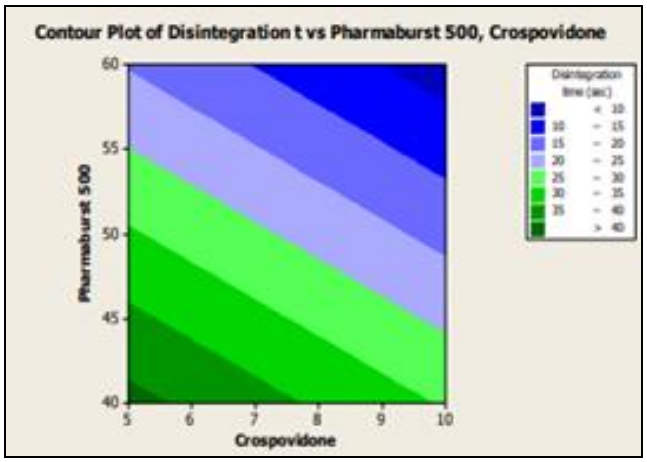

FIG. 4: CONTOUR PLOT OF DRUG RELEASE

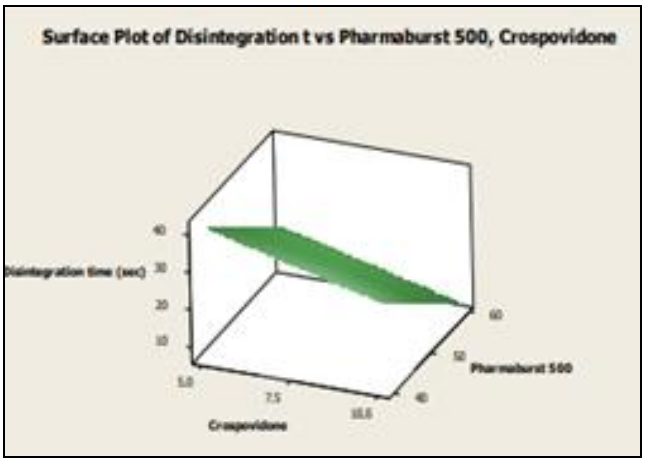

FIG. 5: SURFACE PLOT OF DRUG RELEASE

Optimized Batch:

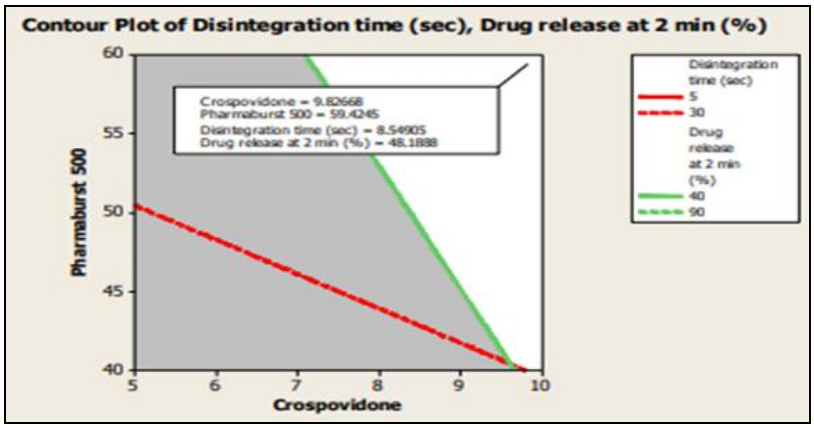

FIG. 6: OVERLAY CONTOUR PLOT FOR OPTIMIZED BATCH P7

DISCUSSION: Precompression parameters of all the blends (F1 to F9) and it was observed that there was no significant difference amongst all the blends in terms of flow ability and compressibility. Weight Variation of all the Formulations was found well within the prescribed Pharmacopoeial limits of not more than 7.5 %. All the formulations were compacted to achieve a target hardness of 4.5 kg/cm$^{2.}$ All the formulations showed a similar thickness profile. Target Hardness was optimized to 4.5 kg/cm^2 keeping in mind the tablet weight and dimensions. All the formulations showed a very good compressibility which could be due to choice of ODT platform used in the formulation. Friability for all the formulation was well below the Pharmacopoeial limit of not more than 1.0%. Proper selection of hardness and a good compactability of the blend resulted in a satisfactory friability result.

The most important attribute of an ODT is Disintegration Time. For an Orodispersible tablet the Pharmacopoeial limit is not more than 3 minutes. All the formulations passed this limit. However, for a tablet to be claimed as Orally Disintegrating Tablet, as per USP, the limit is not more than 30 sec. Formulations F8 and F9 matched these criteria. Hence the level of super disintegrant was finalized as per trial F8. Wetting Time results were comparable to the Disintegration Time showing good correlation to the grade and level of super disintegrants. Formulation F9 with highest level of Crospovidone XL 10 showed least amount of Wetting Time. Since Crospovidone XL 10 absorbs a great amount of water by wicking mechanism, its Water Absorption Ratio is also the highest. Dissolution was rapid for all the formulations as all the formulations had a disintegration time below 2 minutes. All formulations showed comparable dissolution, with F8 showing >90% of drug release at 10 minutes with the least disintegrant level. From the above results of factorial batches P1-P4 (TABLE 8), it was found that all four batches passed the weight variation limit. The results are well within an acceptable range. Thickness was found to be uniform in all formulations. Hardness was good enough to pass the friability test. The friability of all four formulations was below 1 hence, found satisfactory. Further, the disintegration time was observed 42 sec in P1 batch and 8 sec in P4 batch. The Assay results are also found well within acceptable range. The dissolution study was performed for all 4 batches which were given below along with the graph. The drug release describes the effect of disintegrant and directly compressible grade Pharmaburst effect. Higher amount, release more drug for both factors. Design Type: Full Factorial Design Factors: 2 Runs: 4 Center pts (total): 0 after fitting of data in Minitab 16, regression analysis was done and the analysis outcome showed Above in **Tables 11** & **12.**

CONCLUSION: Orodispersible tablets of Brivaracetam were successfully formulated by the Direct Compression method. Preformulation studies of the drug were performed; the infrared spectral analysis studies revealed that no chemical interaction with excipients was compatible with drugs. Risk Assessment of Formulation Variables showed that Diluent selection and type and level of

Disintegrants were most likely to affect the CQAs of the ODT.

Hence, were ranked high. Based on Weight variation, Hardness, friability, Disintegration Time and Dissolution, all the formulation was satisfactory as per Pharmacopoeial Standards. Disintegration Time was 90% of drug release at 10 minutes with least disintegrant level.

Further formulation optimization was done using Factorial design (2 factor 2 levels) and established the formulation's control strategy and design space. Design validation was done and final optimized batch P7 was chosen from the design space.

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CONFLICTS OF INTEREST: The authors have no conflict of interest to declare.

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