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FORMULATION DEVELOPMENT OF DONEPEZIL HYDROCHLORIDE ORAL DISINTEGRATING TABLETS USING QUALITY BY DESIGN APPROACH

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Key words:

QBD, Quality Risk Management, Factorial Design, Orodispersible Tablets.

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ABSTRACT: This study posed a challenge for the risk management to research and development projects in a highly regulated and volatile pharmaceutical industry, in which projects are extremely long, complex, costly and prone to failure. Project management in new product development, must be efficient and effective. This emphasizes the importance of risk management. Quality by design (QbD) refers to an advanced approach toward drug development. QbD is a vital part of the modern approach to pharmaceutical quality. There is much confusion among pharmaceutical scientists in generic drug industry about the appropriate element and terminology of QbD. The purpose of this research was to discuss the pharmaceutical QbD for formulation development with a case study of Orally Disintegrating Tablet (ODT) of Donepezil Hydrochloride (DPH). The study describes elements of the QbD for DPH ODT, include: Defining quality target product profile, identifying critical quality attributes, establishing design space, control strategy. ODT of DPH was prepared by direct compression method using Crospovidone, MCC and level of polymer was optimized, factorial design was used as part of risk analysis to optimize the level of other excipients. Thus, the work facilitates the adoption and implementation of QbD for formulation development using QbD and could increase efficiencies, provide regulatory support.

INTRODUCTION: Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk [1].

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Possible steps used to initiate and plan a quality risk management process might include: (a) Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk; (b) Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment; (c) Identify a leader and necessary resources; (d) Specify a timeline, deliverables and appropriate level of decision making for the risk management process [2, 3]. Quality risk management supports a scientific and practical approach to decision-making.

It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current

knowledge about assessing the probability, severity and sometimes detectability of the risk [4].

A risk assessment of the drug substance attributes was performed to evaluate the impact that each attribute could have on the drug product CQAs. The outcome of the assessment and the accompanying justification is provided as a summary in the pharmaceutical development report. The relative risk that each attribute presents was ranked as high, medium or low. The high risk attributes warranted further investigation whereas the low risk attributes required no further investigation. The medium risk is considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk [5-8]. The same relative risk ranking system was used throughout pharmaceutical development and is summarized in **Table 1**.

TABLE 1: OVERVIEW OF RELATIVE RISK RANKING SYSTEM

Low	Broadly acceptable risk. No further investigation is needed.
Medium	Risk is acceptable. Further investigation may be needed in order to reduce the risk
High	Risk is unacceptable. Further investigation is needed to reduce the risk.

The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies [9-11]. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight [12, 13].

Orally disintegrating dosage forms has to be placed in mouth and then get dispersed in saliva without the need of water. Orally disintegrating tablets are also called as or disperse, mouth dissolving, rapidly disintegrating, fast melt, and quick dissolve system. From past decade, there has been an increased demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing day by day [14, 15]. United States Food and Drug Administration (FDA) define orally disintegrating tablets as "A solid dosage form which contain a medicinal substance or active ingredient which disintegrates rapidly within a matter of seconds when placed upon a tongue".

The aim of the present work is to develop oral disintegrating tablets of donepezil hydrochloride using quality risk management tool of the Quality by Design (QbD) approach. Various process variables involved in the development of ODT was indentified and it was optimized for minimum risk level using design of experiments (DoE) tool for efficient reduction in the risk assessment. Risk assessment was done before applying DoE and it was again reassessed after applying DoE. This will reduce the risks involved in the development of ODTs and yields a good quality product. The Quality risk management assesses the risk involved in the development of oral disintegrating tablets and reducing this risk during development for the continuous improvement in the product development and to manufacture high quality product with reduced process variables and higher product quality.

MATERIALS AND METHODS:

Donepezil Hydrochloride was obtained as gift sample from Astron Research centre, Ahmedabad, India. all other excipients used in the development of ODTs was obtained as received from the supplier and were of analytical grade.

Methods:

Characterization of Donepezil Hydrochloride:

Purity of drug was identified and characterized using FT-IR and DSC Studies. These studies also

include the drug-excipients compatibility study during development of ODTs.

Quality Target Product Profile (QTPP) element analysis of drug product:

The 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." The QTPP is an essential element of a QbD approach and forms the basis of design of the generic product [16, 17]. The QTPP is a quantitative substitute for aspects of clinical safety and efficacy. QTPP includes following elements:

Dosage form`	Tablet color	Tablet shape
Tablet weight	Mode of administration	Dosage straight
Pharmacokinetic	Physical attributes	Identification
Assay	Content uniformity	*In vitro*-dissolution
Friability	Disintegration time	Hardness

Study of Critical Quality Attributes (CQA) of Formulation and Process:

It was stated that the ICH working definition of CQA was: "A CQA is a quality attribute (a physical, chemical, biological or microbiological property or characteristic) that must be controlled (directly or indirectly) to ensure that the product meets its intended safety, efficacy, stability and performance."[18, 19] CQA includes following elements:

weight variation	Hardness	Identification
Assay	Content uniformity	Dissolution
Disintegration	Product degradation	Appearance

Initial Risk Assessment of Formulation Variable:

In this initial risk assessment for formulation development, the detailed manufacturing process has not been established. Thus, risks were rated assuming that for each formulation attribute that changed, an optimized manufacturing process would be established. For these studies, disintegrating agent level, diluents level and magnesium stearate levels are considered as formulation variables [20-23]. While hardness is considered as process variable and risk assessment had been discussed.

Preformulation Studies in Development of ODTs:

Angle of Repose:

Angle of repose is a measure of flowability of powders and granules. It was measured using procedure described in USP. A funnel was kept vertically in stand at a specified height above a paper placed on horizontal surface. The bottom was closed and 10 gm of sample powdered was filled in funnel. The funnel was opened to release the powered on paper to form a smooth conical heap. The height of heap was measured at four points. The average diameter was calculated and radius was found out form it. The angle of repose was calculated using following formula:

$$\mathbf{Tan\ \theta = h/r}$$

Where; h = height of the heap, r = radius of the heap

Bulk density:

The powdered to be tested was sized appropriately to break lumps during storage. A weighed quantity of this powered was then poured in to the measuring cylinder up to ¾ capacities. Bulk density of powder was calculated by using following equation:

$$Bulk\ density = \frac{mass\ (gm)}{volume\ (ml)}$$

Tapped density:

Cylinder was put in the holder of USP tapped density apparatus where it was tapped at an average rate of 100 times. After 100 taps volume of powder (v1) was noted and again tapped for another 100 taps. This gave a new volume (v2). If difference between v1 anmdv2 was more than 25%, another taps are given repeatedly until the difference reduces to less than 2%. Tapped density was calculated using following equation:

$$Tapped\ density = mass(gm)/volume\ (ml)$$

Compressibility index

The Compressibility Index of the blends is determined by compressibility index. Compressibility Index can be calculated by using following formula**:**

$$CI\% = [(TD - BD) \times 100]/TD$$

Hausner's ratio:
A similar index to indicate the flow properties can be defined by Hausner's ratio. Hausner's ratio can be calculated by using following formula:

$$H = 100 / (100 - C) \text{ and } HR = TD/BD$$

Where, TB= Tapped density, BD= Bulk density

Optimization of the formulation of ODTs using 3^2 Full Factorial Design:
Factorial design is suitable for exploring quadratic response surface and constructing second order polynomial models. The design consists of replicated center points and the set of point lying at the midpoint of the multidimensional cube that defines the region of interest [24, 25]. The nonlinear quadratic model generated by the design in the form;

$$Y = b_0\, b_1X_1 + b_2X_2 + b_{11}X_{12} + b_{22}X_{22} + b_{12}X_1X_2$$

Where; Y is response, b_0 is intercept, X_1 and $\mathbf{X_2}$ are coefficient of independent factors.

The coefficients with second order term (b_{11} and b_{22}) indicate the quadratic nature and b_{12} is the interaction term (combining effect of independent factors). This study investigated utility of a 2-factor, 3- level factorial design and optimization process for matrix tablet prepared by direct compression method. Amount of Crospovidone and Microcrystalline Cellulose were selected as the independent variables. **Table 2** indicated levels and experimental runs as per experimental design.

TABLE 2: LEVELS AND EXPERIMENTAL RUNS FOR FORMULATION OPTIMIZATION OF ODTS OF DONEPEZIL HYDROCHLORIDE (DPH)

Experimental Run	Coded value		Actual value	
	X_1	X_2	X_1	X_2
F1	-1	-1	2	60
F2	0	-1	4	60
F3	1	-1	6	60
F4	-1	0	2	100
F5	0	0	4	100
F6	1	0	6	100
F7	-1	1	2	140
F8	0	1	4	140
F9	1	1	6	140

Independent variable	Levels		
	Low (-1)	Middle (0)	High (+1)
Amount of CP(mg) (X_1)	2	6	10
Amount of MCC (mg) (X_2)	60	100	140

Evaluation of ODTs of Donepezil Hydrochloride
Thickness:
Thickness of the tablets was determined using a Micrometer screw gauge. Five tablets from each batch were used and average values were calculated. It is expressed in mm.

Hardness:
The resistance of tablets to shipping, breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For batch formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted.

Friability:
Roche Friabilator was used for testing the friability. Friabilator was rotated at speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed 20 tablets was placed in Roche Friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight in generally considered acceptable. % Friability (% F) was calculated using following equation.

$$\% F = \frac{Initial\ weight - Final\ weight}{Final\ weight} \times 100$$

Weight Variation Study:
In weight variation test, 20 tablets from each batch formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find deviation in weight.

Wetting Time Determination:
A piece of tissue paper folded twice containing amaranth powder on the upper surface was placed in a small Petri dish (ID =6.5 cm) containing 6 ml of phosphate buffer pH6.8, a tablet was put on the paper and the time required for formation of pink color on the surface of tablet was measured as wetting time. (n=3).

Content Uniformity:
Accurately weighed amount of drug-excipients blend was dissolved in small amount in a 100 ml volumetric flask volume of solution was made up using distilled water. This solution was filtered and absorption was measured using UV-spectrophotometer at 271 nm.

Determination of Disintegration Time:
The disintegration time for or dispersible tablets was measured using the conventional test for tablets as described in the Pharmacopoeia. Tablets were placed in the disintegration tubes and time required for complete disintegration, that is without leaving any residues on the screen was recorded as disintegration time.

***In-vitro* Dissolution Study:**
In vitro dissolution test of tablets was carried out in USP apparatus II (paddle apparatus). Paddle was rotated at 50 rpm & 900 ml phosphate buffer solution pH 6.8 was selected as dissolution medium. Apparatus temperature was at 37±1˚C. after an interval of 10 second 10ml aliquot was withdrawn & at same time fresh 10ml dissolution medium was replaced to maintained sink condition. Aliquot was analyzed for drug content using UV-Spectrophotometer at 271 nm λ_{max}. *In-vitro* dissolution test was performed until almost drug released from the dosage form.

Comparison of optimized formulation with marketed formulation using model independent method:
Model independent approach (similarity factor F_2) was used for comparison of in-vitro dissolution profiles of optimized batch and marketed formulation. Equivalent similarity factor (F_2) value between 50 to100. F_2 value was formed by following equation.

$$F_2 = 50log\left[\left\{1 + \frac{1}{n}\sum_{i=0}^{n} W_t(W_t - T_t)\right\}^{-0.5} \times 100\right]$$

Where F_2 is similarity factor, n is the number of observations, W_t is optional weight, R_t is percentage drug dissolved from marketed formulation as reference, and T_t is percentage drug dissolved from test formulation.

RESULTS AND DISCUSSION:
Characterization of DPH:
DPH and excipients were characterized using FT-IR and DSC studies. FT-IR spectra was analyzed and it indicated that drug is pure as received. FT-IR spectra of drug-excipient complex were also indicated there was no any in compatibility between drug and excipients. FT-IR spectra were presented in **Fig. 1**.

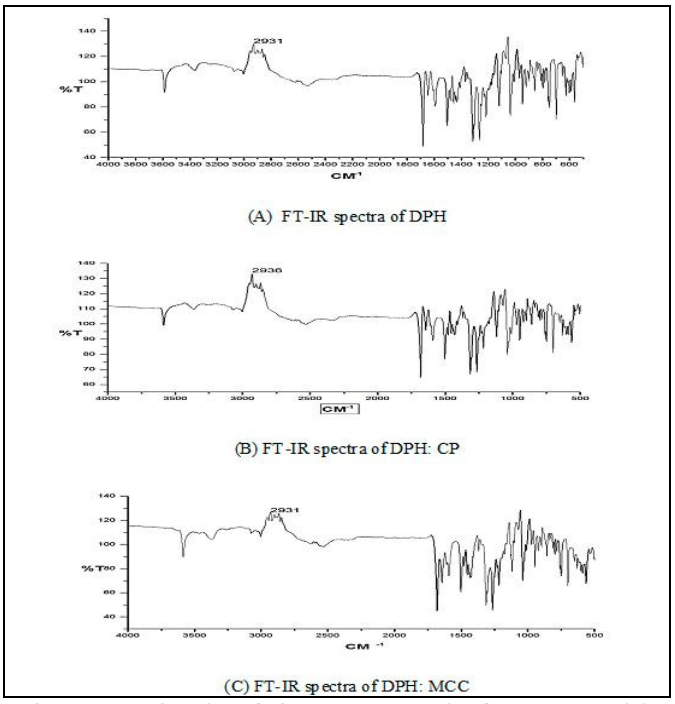

FIG. 1: FT-IR SPECTRA OF DPH, DPH: CP AND DPH:MCC

Fig. 2 showed DSC spectra of drug and excipients. It indicated no shifting of endothermic peak in complex. It indicated absence of sharp endothermic peak of DPH at 226.66ºC this might be due to complex formation of DPH with MCC and CP.

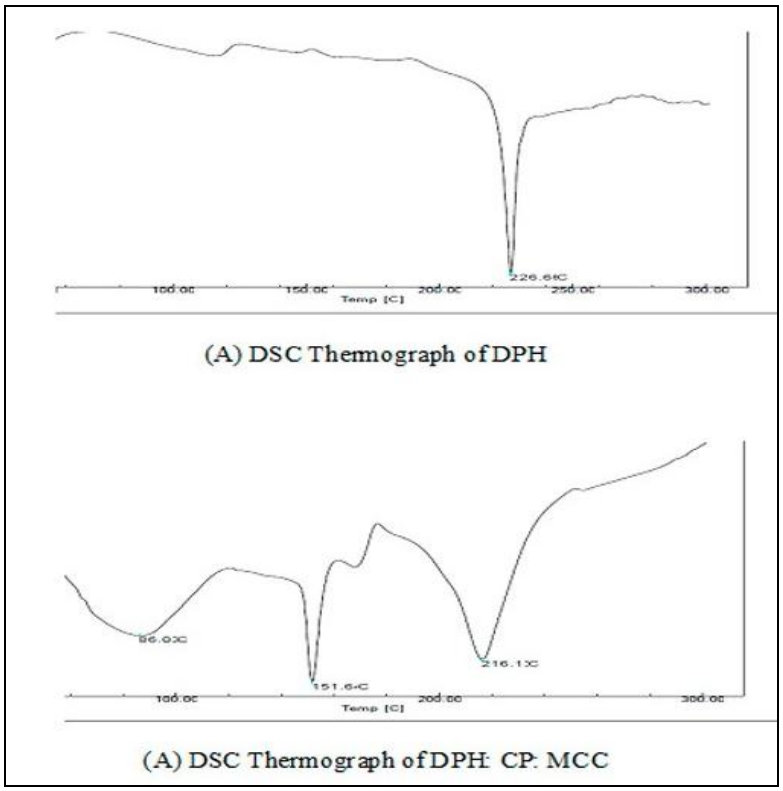

FIG.2: DSC THERMOGRAPHS OF DPH AND COMPLEX OF DPH: CP: MCC

Quality Target Product Profile (QTPP) and CQA element analysis of drug product:

QTPP profile for the development of DPH oral disintegration tablets were indicated in **Table 3**. Table 4 showed CQA for the Oral Disintegrating Tablets of DPH. CQA of ODT for DPH indicated which attributes were classified as drug product critical quality attributes for this product assay, weight variation, identification of drug, content uniformity, in-vitro dissolution and in-vitro disintegration time were initiated as the CQA that have potential to be impacted on product development and it would be investigated for product development.

TABLE 3: QTPP ANALYSIS FOR DPH ORAL DISINTEGRATION TABLETS

Quality Target Product Profile (QTPP)	Target	Requirement
Dosage form	Tablet	Pharmaceutical equivalence requirement: Same dosage form
Dosage design	Oral disintegrating Tablet	Same as RLD
Route of administration	Oral	Pharmaceutical equivalence requirement: Same route of administration
Dosage strength	10 mg	Pharmaceutical equivalence requirement: Same strength
Color	White	White
Pharmacokinetics	Absorbed throughout oral cavity Bioequivalence	Requirement needed to ensure rapid onset and efficacy
Drug product quality attributes	Physical attributes	Pharmaceutical equivalence requirement: Must meet the same compendia or other applicable (quality) standards (i.e., identity, assay, purity)
	Identification	IR
	Assay	Pharmaceutical equivalence requirement: 90 % to 110 % as per IP

	CU	More than 90% as per IP
In vitro availability	Mean dissolution 100 % Dissolved in 60 second	Orally disintegrate but complete drug release can be displayed in phosphate buffer solution. (pH 6.8)
Friability	Not more than 1.00 %	Pharmaceutical equivalence requirement: as per USP
Disintegration time	< 30 sec	As per the FDA guideline for ODT. (equivalent to RLD)
Hardness	3.5 to 5 Kg/cm^2	Pharmaceutical equivalence : as per USP

TABLE 4: CQA ANALYSIS FOR DEVELOPMENT OF ODTS OF DPH

Drug product	Target	Is this a CQA?	Justification
Physical attributes	Appearance	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set. To ensure patient acceptability.
	Size & Odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability.
	Weight variation	Yes	It is carried out when the Tablet has 90-95% of active ingredient.
	Friability	No	Friability is a routine test per compendia 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 DPH	Yes	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system. Formulation and process variables do not impact identity.
Assay	Pharmaceutical equivalence requirement: 90 % to 110 % as per IP	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
CU	More than 95%	Yes	Variability in CU will affect safety and efficacy. Both formulation and process variables impact CU, so this CQA will be evaluated throughout product and process development.
Disintegration	Complete disintegration Within 30 sec	Yes	OTD Tablet should be easily disintegrated so that API will be available for absorption.
Dissolution	Complete drug release can be displayed in phosphate buffer solution. (pH 6.8)	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.

Initial Risk Assessment of Formulation Variables for Development of ODTs of DPH:

A risk assessment of the drug substance was performed to evaluate the impact of CQA in product development. The relative risk assessment ranking system was used during development and it was summarized in **Table 5**. Justification for assigned level of risk was presented in **Table 6**.

Optimization of Formulation Variables for Development of DPH Oral Disintegrating Tablets using 3^2 Factorial Design:

A 3^2 full factorial experimental design was implemented to prepare ODT Tablet of DPH by using direct compression method. Experimental design was used to optimize formulation parameter as well as process parameter of ODT. Two independent factors were selected among them one was amount of Crospovidone (X_1) and another was amount of microcrystalline cellulose (X_2).

Disintegration time and D_{60} (% drug dissolved in 60 sec) was selected as dependent variable. This dependent variable was selected on the basis of level for initial risk assessment of CQA to development ODT indicated in **Table 5.**

Evaluation of Preformulation Parameters for Development of DPH oral disintegrating Tablets: Results of various preformulation parameters were showed in **Table 7**. It indicated all parameters met the requirements for the development of ODTs for DPH.

TABLE 5: INITIAL RISK ASSESSMENT OF THE FORMULATION VARIABLE

Drug product CQA	Identification of Risk				
	DPH	Disintegrating Agent	MCC	Lactose	Magnesium Stearate
Identification	High	Low	Low	Low	Low
Disintegration Time	Low	High	Medium	Low	Low
Assay	High	Low	Low	Low	Low
Content Uniformity	High	Medium	Medium	Low	Low
Dissolution	High	High	Medium	Medium	Medium

TABLE 6: JUSTIFICATION OF RISK ASSESSMENT OF CQA FOR DEVELOPMENT OF ODTS

Formulation variables	CQA's	Justification
Disintegrating agent	Disintegration time	Pharmaceutical equivalence requirement: Same dosage form
	Assay	Polymer can impact the flow properties of the blend. This, in turn, can impact Tablet CU. The risk is high. Occasionally, poor CU can also adversely impact assay. The risk is medium CU.
	Dissolution	Release of drug from Tablet depends on the amount of polymer in formulation so the risk is high
MCC	Disintegration time	MCC as diluents so that effect on Tablet disintegration time
	Assay	Polymer can impact the flow properties of the blend. This, in turn, can impact Tablet CU. The risk is high. Occasionally, poor CU can also adversely impact assay. The risk is medium CU.
	Dissolution	Release of drug from Tablet partially depends on the amount of polymer in formulation so the risk is medium.

TABLE 7: RESULTS OF PREFORMULATION STUDIES FOR DEVELOPMENT OF ODTS

Batch	Bulk Density(g/ml)	Tapped Density(g/ml)	Carr's Index	Hausner Ratio	Angle of Repose(θ)
F1	0.5	0.7	28.57	1.4	39
F2	0.54	0.73	26.02	1.35	38
F3	0.41	0.66	37.87	1.60	43
F4	0.42	0.64	34.37	1.49	45
F5	0.42	0.6	30.00	1.42	39
F6	0.32	0.5	36.00	1.50	36
F7	0.47	0.73	35.61	1.55	42
F8	0.69	0.69	39.13	1.64	41
F9	0.46	0.66	30.30	1.42	35

Evaluation of Oral Disintegrating Tablets for DPH:

Prepared tablets were evaluated for different parameters like thickness, hardness, content uniformity, weight variation, % friability, and disintegration time and *in-vitro* dissolution studies. **Table 8** showed results of different evaluation parameters like thickness, hardness, content uniformity, weight variation, % friability, a disintegration time. Results indicated by applying DoE one can optimize the different formulation parameters. All the formulation showed the results in the desired range. For selection of more optimized batch from all 9 formulations multiple regression analysis was done.

TABLE 8: RESULTS OF EVALUATION OF ODTsFOR DONEPEZIL HYDROCHLORIDE

Batch	% Friability	Weight Variation (mg ± SD)	Hardness (Kg/Cm^2 ± SD)	Diameter (mm ± SD)	Thickness (mm ± SD)	Disintegration Time (Sec ± SD)	Content Uniformity (% ± SD)
F1	1.0	200.12±0.84	4.34±0.01	8.1±0.007	3.0±0.012	28.4±0.01	100.1±0.03
F2	0.84	200.26±0.99	4.37±0.03	8.0±0.013	3.2±0.020	22.8±0.01	98.70±0.02
F3	0.83	200.13±0.92	4.01±0.39	7.9±0.010	2.9±0.019	28.1±0.02	101.23±0.01
F4	0.5	200.13±0.82	4.02±0.06	8.1±0.036	3.0±0.027	19.0±0.01	104.21±0.01
F5	1.0	199.49±1.56	4.01±0.56	8.0±0.036	3.2±0.080	15.1±0.03	97.03±0.01
F6	0.84	200.05±0.84	4.00±0.03	8.0±0.006	2.9±0.021	16.5±0.01	99.81±0.01
F7	0.83	200.13±1.03	4.12±0.05	8.2±0.027	3.1±0.012	11.4±0.01	102.03±0.02
F8	0.5	200.14±0.86	4.16±0.08	8.0±0.027	3.0±0.011	11.5±0.01	99.25±0.02
F9	0.67	200.05±0.47	4.01±0.02	8.1±0.001	3.1±0.081	9.3±0.013	99.95±0.01

In-vitro Dissolution Study:

Results of *in-vitro* dissolution study showed that almost all drug was released within 100 seconds. Batch F1 to F3 showed in100% drug release within 100 seconds. Batch F4 to F5 showed almost 100% drug release within 70 seconds. While batch F7 to F8 showed almost all drug release within 60 seconds. This must be due to increased amount of CP and MCC in batch F1 to F9 among all batches F9 showed almost drug release within 50 second. Hence, it may be a good formulation for further studies. **Fig. 3** showed *in-vitro* drug release profile curve of F1 to F9.

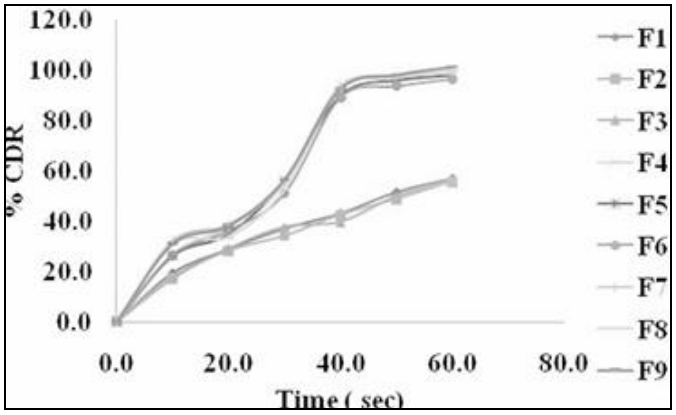

FIG.3: *IN-VITRO* DRUG RELEASE PROFILE CURVE FOR BATCH F1 TO F9

Optimization of Formulation:

Experimental runs and response for optimization of ODT formulation was resulted in **Table 9**. Responses surface curvature was examined when the two variables were investigated at three levels. The design was provided the following empirical second order equation (Full Model).

$$Y=b_0++b_1X_1+b_2X_2+b_{12}X_{11}+b_{22}X_{22}+b_1b_2X_{12}$$

Where Y was represented response, b_0 was intercept, b_1 and b_2 are the coefficient of main effects, b_{12} was the coefficient for the interaction term and b_{11} and b_{22} were the coefficients for the second order quadratic terms. Non-significant estimated coefficients were dropped from the full model by adopting a significance test for the regression coefficient. Design expert (version 9.0.4) was used to identify non-significant terms. A coefficient was significant if <0.05. The refined model was used for calculation of residuals or for drawing contour plots and 3D response surface plots.

TABLE 9: RESULTS OF RESPONSE OF DEPENDANT VARIABLES FOR OPTIMIZATION OF FORMULATION

Batch	Factors		Response	
	X_1	X_2	Disintegration Time (Sec)	D_{60} (%)
F1	-1	-1	22.8	57.09
F2	0	-1	28.1	55.60
F3	1	-1	28.4	55.62
F4	-1	0	11.4	85.31
F5	0	0	15.1	89.21
F6	1	0	19	90.18
F7	-1	1	16.5	98.25
F8	0	1	11.5	98.64
F9	1	1	9.3	98.64

Disintegration time:

ANOVA of disintegration time indicated the model F-value of 34.36 implies the model is significant. Where the p value < 0.05, p value greater than 0.05 was omitted from the model & refined model was developed. P value of co-efficient of X_1 is greater than 0.05 but it indicates main effects so not omitted in refined model. In this model coefficient of X_2 has p –value less than 0.05, that means it was considered has significant term in optimization of formulation. The polynomial equation generated by using regression analysis was described below.

$$\text{Disintegration Time} = +18.01 - 0.82X_1 - 7.85X_2$$

Positive value of B_0 indicated positive effect of variables on disintegration time. Negative value of coefficient X_1 (-0.82) indicated negative effect on disintegration time increased in value of X_1 range in value of disintegration time. Figure 4 presented the 3D response surface plot showing effect of X_1 and X_2 on disintegration time respectively. It indicated that amount of MCC increased disintegration time was increased.

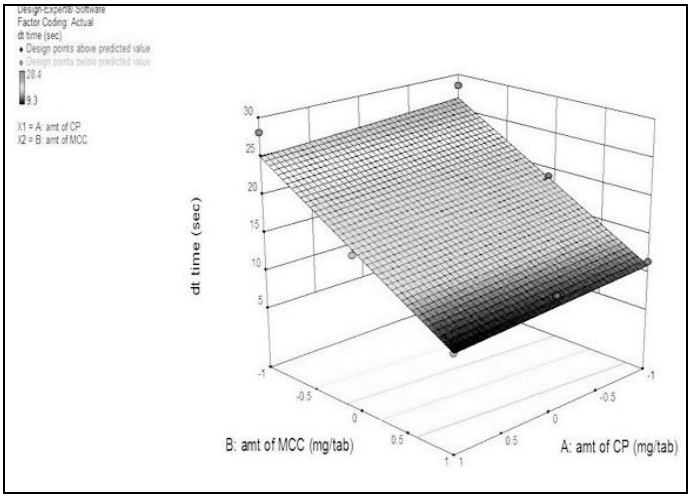

FIG.4: 3D RESPONSE SURFACE PLOT SHOWING EFFECT OF X_1 AND X_2 ON DISINTEGRATION TIME

D_{60} (%):

ANOVA of D_{60} indicated the model F-value of 193.75 implies the model is significant. Where the p value < 0.05, p value greater than 0.05 was omitted from the model & again regression analysis was done. P value of co-efficient of X1 is greater than 0.05 but it indicates main effects so not omitted in reduced model. In this model coefficient of B has p –value less than 0.05, that means it was considered has significant term. The polynomial equation generated by busing regression analysis was described below.

$$\text{Disintegration Time} = +88.27 + 0.85X_1 + 21.3X_2 + 0.8X_1X_2 - 0.87X_{11} - 10.68X_{22}$$

Positive value of B_0 indicated positive effect of variables on D_{60}. Positive coefficient value of X_1 (0.85) was showed positive effect of X_1 on D_{60}. Amount of X_1 changed the value of D_{60} significantly. Partial value of coefficient of X_2 (21.43) showed positive effect on D_{60}. This indicated change in amount of X_2 does not change the value of D_{60} from desired value. **Fig. 5** indicated response surface plot showing effect of amount of CP and MCC on D_{60} of ODTs.

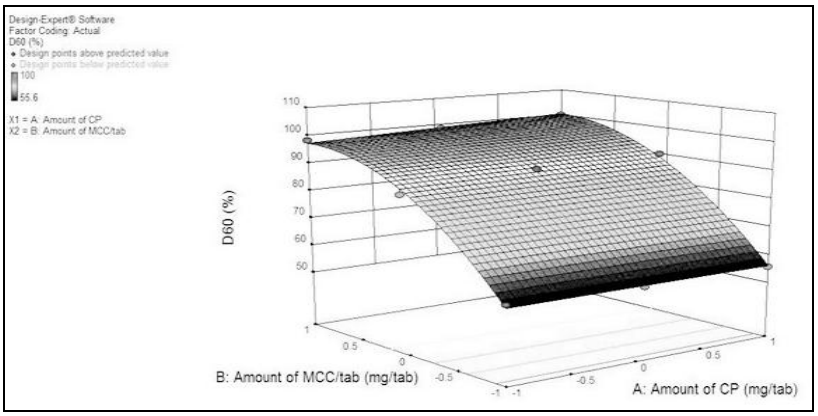

FIG. 5: 3D RESPONSE SURFACE PLOT SHOWING EFFECT OF X_1 AND X_2 ON D_{60}

Comparison of Optimized Batch (F9) and Marketed Formulation:

Fig.6 showed comparison in-vitro dissolution profile of batch F9 and marketed preparation. Model independent approach (similarity factor F2) was used for comparison of in-vitro dissolution profiles. Similarity factor (F2) value was 91 that were in range 50 to 100 indicated there was no significant difference in the in-vitro release profiles between F9 and marketed formulation.

Updated Risk Assessment for Formulation Variables:

After optimization of the formulation variables using experimental design tool, risk assessment of the variables was done. It showed that variables which were in high risk at initial level of the development were now at low level of f the development. Updated risk assessment of the formulation variable and justification for the same was summarized in **Table 10** and **Table 11** respectively.

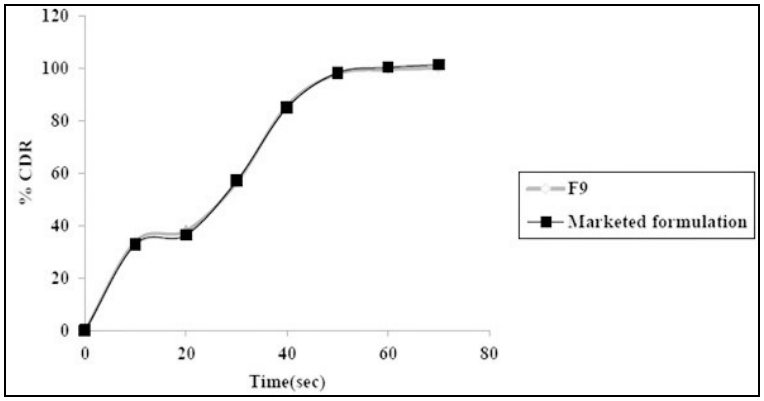

FIG.6: COMPARISON OF *IN-VITRO* RELEASE PROFILE OF F9 AND MARKETED FORMULATION

TABLE 10: UPDATED RISK ASSESSMENT OF THE FORMULATION VARIABLE

Drug product CQA	Identification of Risk				
	DPH	Disintegrating Agent	MCC	Lactose	Magnesium Stearate
Identification	Low	Low	Low	Low	Low
Disintegration Time	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Medium	Low	Low
Dissolution	Low	Low	Medium	Medium	Medium

TABLE 11: JUSTIFICATION FOR THE REDUCED RISK OF THE FORMULATION VARIABLES

Formulation Variables	Drug Product CQAs	Justification
Drug Substance	Identification	Polymer can interaction with drug substance, so performed FT-IR studied & result showed no any interaction between drug and polymer. The risk was reduced from high to low level.
	Assay	All tablets showed acceptable assay. The risk is reduced from high to low.
	Content Uniformity	The poor flow properties of the drug substance by increasing mixing time. The risk was reduced high to low level.
	Dissolution	The risk was reduced from high to low level by controlling disintegrate agent and hardness of ODT.
CP/MCC Ratio	Content Uniformity	The risk is reduced from medium to low level by optimizing the CP/MCC ratio and increasing mixing time.
	Disintegration Time	The risk was reduced from high to low by controlling CP and MCC ratio.
	Dissolution	The risk was reduced from high to low level because filler ratio yielded tablets with acceptable friability within a wide range of tablet hardness (3 to 6 kg/cm2). CP was increasing disintegration time.

CONCLUSION: In the present study initial risk assessment was done and QTTP, CQA for oral disintegration tablet was identified. According to this study disintegration time and in vitro dissolution was found to be a CQA for the development of ODT. Hence, this CQA was optimized using 3^2 full factorial design. Design expert (version 9.0.4) was used for statistical evaluation of the optimization. Amount of disintegrating agent and amount of directly compressible diluents was selected as independent variable on the basis of initial risk assessment study. All prepared batches F1 to F9 was showed disintegration time in between 28.4 sec to 9.3 sec. and had almost 100% drug release within 100secs. From the optimization study F9 batch was selected as optimized batch.

From the findings obtained so far, it can be concluded that, development of formulation using Quality by Design approach DPH ODT can successfully similar to the marketed preparation. QbD is very important approach for pilot scale up. Production of generic as well as branded product. Ensures better design of products with fewer problems in manufacturing. It is a cost effective method to develop generic drug production The product can be consistently produced without batch to batch variations. From the findings obtained so far, it can be concluded that, prepared ODT of DPH was similar as marketed product in terms of product quality.

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