Research Article

Formulation and evaluation of methylphenidate hydrochloride fast dissolving tablet by QbD approach

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Abstract

Objective: The aim of the proposed work was to apply quality by design (QbD) in the formulation and evaluation of methylphenidate HCl fast dissolving tablet using superdisintegrants for rapid dissolution of drug and absorption, which may produce rapid onset of action in the management of Attention deficit hyperactivity disorder (ADHD) with better patient compliance. **Method:** QbD assures pharmaceutical quality by understanding and controlling formulation and manufacturing variables ensuing as an advanced approach towards drug development. The study discusses elements of the QbD for development of methylphenidate HCl fast dissolving tablet via identifying quality target product profile, critical quality attributes, defining risk assessments, establishing design space, control strategy and product life cycle management &continuous improvement. FDT's were prepared by direct compression method using Avicel PH 102 and Indion 234 as superdisintegrants to enhance its disintegration. A 3^2 full factorial design was applied to inspect the effect of two independent variables i.e., concentration of Avicel PH 102 and concentration of Indion 234 on disintegration time (DT) and percentage drug release as dependent parameter. The compressed tablets were evaluated for hardness (kg/cm^2), thickness (mm), friability (%), weight variation (mg), drug content (%), wetting time (s), disintegration time (s), and in-vitro drug release (%). Furthermore, analysis of variance (ANOVA), multiple regression analysis, 3D response graph and Overlay plot were successfully implemented to understand significant effects of both the variables on the selected responses. **Result:** All the FDT's of all the formulation had drug content, weight variation, hardness and friability within USP limits. The optimized formulation showed percentage drug content of 98.88± 0.25%, wetting time of 23 ± 0.61 s, disintegration time of 14± 0.92 s and In-vitro drug release was found to be 98.14 ± 0.65 %. **Conclusion:** Thus, it can be conclude that formulation of Methylphenidate HCl FDT with increased dissolution rate and decreased disintegration time that dissolves rapidly in the mouth were prepared via implementation of QbD that could increase efficiencies and provide regulatory support.

Keywords: Methylphenidate HCl, quality by design (QbD), fast dissolving tablet (FDT), 3^2 factorial design, Attention deficit hyperactivity disorder (ADHD)

Introduction

The Center for Drug Evaluation and Research (CDER), US FDA defined Fast Dissolving Tablets (FDT) as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly, usually within a matter of seconds, when placed on the tongue." Fast dissolving tablet has achieved better patient compliance over other conventional dosage forms especially for geriatric, pediatric, bedridden patients, patients who have swallowing difficulties (dysphagia) and for patients who are busy, travelling or have no access to water. Furthermore FDT may increase the bioavailability of some drugs due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. As well as, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet (Khanna et al., 2016; Siddiqui et al., 2010; Kumar et al., 2014; Jain and Naruka, 2009).

Quality by design (QbD) was first outlined by well-known quality expert M. Juran. The elements of QbD are depicted in figure 1. The QbD is a systemic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure pre-

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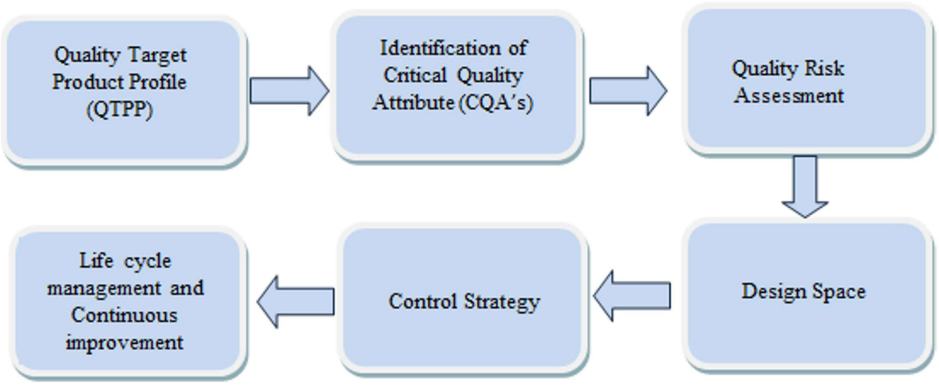

Figure 1. Elements of QbD

defined product quality. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provides scientific understanding to support the establishment of the design space, product and process specifications, and manufacturing controls along with quality risk management. This ultimately leads to understand the impact of raw materials i.e. Critical Material Attributes (CMA), Critical Process Parameters (CPP) on the Critical Quality Attributes (CQA's) (Chowdary et al., 2014; Wagh, 2015; Adepu and Bhogale, 2016).

The drug selected for preparation of FDT is Methylphenidate HCl which is a CNS stimulant used to treat medical conditions such as Attention Deficit Hyperactivity Disorder (ADHD) and narcolepsy. It inhibits the reuptake of dopamine and norepinephrine and therefore increased dopaminergic and noradrenergic activity in the prefrontal cortex which explain its efficacy in ADHD. Methylphenidate HCl is having oral bioavailability of 11-52% with half life of 4hours and possess first pass metabolism. Fast dissolving tablet of drugs avoids first pass metabolism which may improve the bioavailability as compared to conventional oral dosage forms along with quick onset of action (Tripathi, 2001).

Hence, the rationale was to formulate and evaluate fast dissolving tablets of Methylphenidate HCl by QbD approach using superdisintegrants for rapid dissolution of drug and absorption, in the treatment of ADHD with better patient compliance.

Material and methods

Methylphenidate HCl was received as gift samples from Ipca laboratories limited, Sejavta, M.P India. All the other excipients for FDT preparation were of analytical grade.

Identifying a Quality Target Product Profile (QTPP)

The quality target product profile (QTPP) as defined in ICH Q8 (R1) is "a summary of the quality characteristics or attributes of a drug product that ideally will be achieved and thereby ensure the safety and efficacy of a drug product."

Critical Quality Attributes (CQA's)

CQA's as defined by ICH Q8 (R2) 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. CQA's are generally associated with raw materials & process parameter. This parameter directly affects the quality of final product.

Quality risk assessment

It is one of the tools that help in identifying, scientifically evaluating, and controlling potential risks to quality. It also helps in continual improvement in the product and process performance throughout the product life cycle.

The main objective of risk assessment in pharmaceutical development is to identify which material attributes and process parameters affect the drug product CQA's, that is, to understand and predict sources of variability in the manufacturing process so that an appropriate control strategy can be implemented to ensure that the CQA's are within the desired requirements.

Formulation of Methylphenidate HCl FDT using 3^2 full factorial design

A 3^2 full factorial design was constructed where avicel PH 102 and indion 234 concentrations were selected as the independent variables. All formulation batches and a 3^2 full factorial experimental design summary are given in Table 1 and 2 respectively. The tablets were prepared by direct compression technique. The ingredients were weighed accurately as per the formula given in the Table 1. The ingredients methylphenidate HCl, pearlitol SD 200, avicel PH 102 and indion 234 were passed through sieve # 40. All the above ingredients were mixed properly in polybag for 30 minutes. Aerosil and magnesium stearate were passed through sieve # 80, mixed properly and blended with initial mixture for 15 minutes. The powder blend was compressed into a tablet at an average weight of 100 mg using 6 mm

Table 1. Formulation of factorial batches

Sr. No.	Ingredients	Factorial batches								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Methylphenidate HCl	5	5	5	5	5	5	5	5	5
2	Avicel PH 102	2	7	2	5	7	5	2	5	7
3	Indion 234	2.5	4.5	4.5	3	3	2.5	3	4.5	2.5
4	Aerosil	2	2	2	2	2	2	2	2	2
5	Aspartame	3	3	3	3	3	3	3	3	3
6	SLS	3	3	3	3	3	3	3	3	3
7	Magnesium stearate	2	2	2	2	2	2	2	2	2
8	Pearlitol SD 200	80.5	73.5	78.5	77	75	77.5	80	75.5	75.5
	Total weight	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Table 2. Design summary

Factor	Independent variable	Units	Actual values		Coded values	
			Low	High	Low	High
X_1	Avicel PH 102	mg	2	7	-1	+1
X_2	Indion 234	mg	2.5	4.5	-1	+1

concave punches in 12 station Karnavati rotary tablet machine (Borde et al., 2016; Bhusnure et al., 2015; Kshirsagar, 2014).

Evaluation of FDT

The prepared tablets were evaluated for various parameters as follows:

Appearance and shape

The general appearance of the tablet includes the morphological characteristics like size, shape, color etc. Also tablets may have lines, break-marks and may bear a symbol or other markings.

Uniformity of thickness and diameter

The uniformity of the diameter and thickness was measured using vernier caliper. The average diameter and thickness of the tablets were calculated.

Hardness

Monsanto hardness tester was used to check the hardness of the tablet. The FDT was placed vertically between the jaws of the tester. The two jaws placed under tension by spring and screw gauge. By turning the screw, the load was increased and collapsed; the applied pressure from the spring was measured in kg/cm^2.

Weight variation

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.

Friability

Friability was determined using Roche friabilator. A sample of pre-weighed 20 tablets was placed in Roche Friabilator, rotated at 25 rpm which was then operated for 100 revolutions. The tablets were then reweighed. A loss of less than 1 % in weight is generally considered acceptable.

Drug content

Twenty tablets were weighed and crushed to a fine powder. An accurately weighed sample equivalent to 5mg of methylphenidate HCl was taken in a volumetric flask. The content was dissolved in 100 ml pH 6.8 phosphate buffer. This solution was filtered through Whattman filter paper and respective dilution was done. The drug content was calculated by measuring the absorbance of the solution at 207.8 nm.

Wetting time

Wetting time of dosage form is related with the contact angle. Wetting time of the fast dissolving tablet is another important parameter, which needs to be assessed to give an insight into capillarity and subsequently the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet.

A piece of tissue paper folded double was placed in a petri plate (internal diameter is 10 cm) containing 10 ml of 6.8 pH phosphate buffer. The tablet was placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded in seconds.

Disintegration time

The disintegration time for fast disintegrating tablet was determined in USP conventional disintegration test apparatus. The apparatus consist of 6 glass tubes that are 3 inches long, open at one end and held against 10 mesh screen at the bottom end of basket rack assembly. To test for disintegration time, one tablet were placed in each disintegration tubes and the basket arch is positioned in one liter beaker of water at $37 \pm 2^{o}C$.

In-vitro dissolution study

The release rate of methylphenidate HCl from FDT (n=3) was determined using USP Apparatus 2 (Paddle). The dissolution test was performed using 900 ml of pH 6.8 phosphate buffer for 15 minutes at 50 rpm. The temperature of the medium was maintained at $37 \pm 0.5^{o}C$. Aliquot of 5 ml were withdrawn at an interval of 3, 6, 9, 12 and 15 minutes. The withdrawn samples were replaced with fresh dissolution medium. The samples were filtered through Whattman filter paper and analyzed spectrophotometrically at 207.8 nm (Bala, 2012; Lachman et al., 1991; Martin and Chun, 1994; Kumar et al., 2014; Patel et al., 2016).

Results and discussion

Table 3. QTPP for fast dissolving tablet formulation development

Profile component	QTPP target	Justification/ Remark/Rationale	In house Performed
Physical Attributes			
Active ingredient	Same	Pharmaceutical equivalence requirement	No
Dosage form	Tablet	Pharmaceutical equivalence requirement: same dosage form	Yes
Route of administration	Oral	Pharmaceutical equivalence requirement: Same route of administration	Yes
Dosage design	Fast dissolving tablet which releases drug substance by disintegration	Fast dissolving tablet formulated for immediate drug release, to avoid gastric instability & first pass metabolism	Yes
Dosage strength	5 mg	Pharmaceutical equivalence requirement: Same strength	Yes
Tablet weight	100 mg	Manufacturability and patient acceptability	Yes
Stability	At least 24-month shelf-life at room temperature	For global regulatory filing and determining shelf life.	Yes
Appearance	Tablet confirming to description shape and size	Needed for patient acceptability	Yes
Drug product quality attributes	Physical attributes	Pharmaceutical equivalence requirement	Yes
	Colour	Patient compliance	Yes
	Odour	No unpleasant odour	Yes
	Drug content	98-102%	Yes
	Content uniformity	Within ± 15% and NMT ± 25%	Yes
	Friability	NMT 1.0%	Yes
	Disintegration	Within 30 seconds	Yes
	Dissolution	Drug release NLT 90 % at 15 minutes in phosphate buffer pH 6.8.	Yes
Container closure system	Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life & to ensure tablet integrity during shipping	No
Administration	The tablet can be taken without regard to food.	Food has no effect on absorption	No
Storage condition	Preserve in tight containers and store at room temperature.	Needed for stability	Yes
Chemical attributes			
Identification	FTIR analysis	Needed for clinical effectiveness and safety	Yes
	UV analysis	Needed for clinical effectiveness and safety	Yes
Assay for API	Not less than 98.0% & NMT 102.0%	Needed for clinical effectiveness	Yes
Biological attributes			
Intended use	In treatment of Attention deficit hyperactivity disorder (ADHD) and narcolepsy.	It is a dopamine reuptake inhibitor in the CNS.	No

Identifying a Quality Target Product Profile (QTPP)

The target product profile describes the use, safety and efficacy of the product that initiates the development strategy.

The QTPP for Methylphenidate fast dissolving tablet is as given in table 3.

Critical quality attributes (CQA)

The initial CQA's were defined from QTPP to identify satisfactory quality of the product. CQA is a physical,

Table 4. Critical Quality Attributes (CQA's) for fast dissolving tablet formulation development

Drug product	Target	CQA's	Justification	In house performed
Physical attributes				
Dosage form	Fast dissolving tablet	No	Not linked to safety and efficacy	Yes
Route of administration	Oral	No	Only related to patient compliance and acceptability	Yes
Strength	5 mg	No	Related to pharmaceutical equivalence requirement	Yes
Dosing frequency	Thrice a day	No	Only related to patient compliance and acceptability	Yes
Stability	Comply with ICH Q2R1	Yes	Related to efficacy of the product as shelf life hamper the product quality	Yes
Drug product quality attribute				
Appearance	Color and shape acceptable to the patient. No visual tablet defects observed	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical	Yes
Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy	Yes
Weight variation	NMT 2 tablets should out of the range of ± 7.5% of 100 mg	Yes	It is carried out when the tablet has 90-95% of active ingredient	Yes
Friability	NMT 1.0% w/w	No	This target friability will not impact patient safety or efficacy	Yes
Identification	Positive for methylphenidate HCl	Yes	Identification is critical for safety and efficacy	Yes
Assay	98-102% w/w	Yes	Assay variability results in dose fluctuation and hampers safety and efficacy	Yes
Content uniformity	Within ± 15% and NMT ± 25%	Yes	Ensure consistency of dose deliver to the patient, hence impact on safety and efficacy	Yes
Hardness	Low	No	Critical for dissolution profile	Yes
Disintegration	Within 30 seconds	Yes	Failure to meet the disintegration time can impact on efficacy	Yes
Dissolution	Immediate but complete drug release phosphate buffer (pH 6.8)	Yes	Dissolution can impact on bioavailability and ultimately efficacy	Yes

chemical, biological or microbiological property. Table 4, summarizes the CQA's for methylphenidate HCl fast dissolving tablet formulation development. The assay, content uniformity, disintegration, dissolution and stability are identified as potential CQAs for formulation development that have an impact on formulation or process variables hence related to safety and efficacy. Therefore, these CQA's were investigated and discussed in subsequent formulation development studies.

Quality Risk assessment

To estimate the impact of CQA in product development a risk assessment of the drug substance was carried out. Initial risk assessment for formulation component & Operation variables was determined in table 5. Justification for assigned risk was summarized in table 6.

Design of experiment for formulation of methylphenidate HCl FDT using 3^2 full factorial design

A 3^2 full factorial design was used to optimize fast dissolving tablets of methylphenidate HCl using an experimental design program Design Expert 7 via direct compression method. Avicel PH 102 concentration (X_1) and indion 234

Table 5. Initial risk assessment for formulation component & operation variables

Drug Product CQAs	Formulation Variables		Operation Variables		
	API Particle size	MCC particle size	Blending & lubrication	Compression	Press speed
Assay	Medium	Low	Medium	High	Low
Content uniformity	High	Medium	High	High	High
Disintegration Time	High	High	Medium	High	High
Drug release	High	High	Medium	High	High

Table 6. Justification for risk assessment of CQA for FDT development

Process steps	Drug product CQAs	Assigned Risk	Justification
Blending and lubrication	Assay	Medium	Blending and lubrication may cause variable flowability of the blend affecting assay.
	Content uniformity	High	The PSD and cohesiveness of the drug substance adversely impact its flowability. If not blended properly with excipients, it may affect CU.
	Disintegration time	Medium	Blending process variables may impact the distribution of CCS in the blend which could impact disintegration of the granules.
	Drug release	Medium	Blending process variables may impact the distribution of CCS in the blend which could impact disintegration of the granules and ultimately, dissolution of the tablets.
Compression force	Assay	High	Assay is dominated by BU and flowability.
	Content uniformity	High	CU is dominated by BU and flowability and is unrelated to main compression force
	Disintegration time	High	Suboptimal compression force may affect tablet hardness and friability and, ultimately, disintegration.
	Drug release	High	Suboptimal compression force may affect tablet hardness and friability, disintegration and, ultimately, dissolution
Press speed	Assay	Low	A faster than optimal press speed may cause inconsistent die filling and weight variability which may then impact CU, disintegration and dissolution.
	Content uniformity	High	
	Disintegration Time	High	For efficiency, the press speed will be set as fast as practically possible without adversely impacting tablet quality.
	Drug release	High	
	Degradation Products	Medium	

concentration (X_2) were selected as the independent factors and disintegration time (DT) and % drug release as a response i.e., dependent variable and experimental trials were performed for all nine possible combinations.. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the experimental design.

Evaluation of FDT for methylphenidate HCl

The prepared fast dissolving tablets were evaluated for various parameters like weight variation, hardness, friability, thickness, wetting time, disintegration time (DT), assay and readings were recorded. All the formulation batches showed the results in the desired range as given in table 7.

In- vitro dissolution study

FDT showing lower disintegration time will be evidence for high drug release. Drug release of formulation F1-F9 was depicted in table 8. For factorial batches F1 to F9 the drug release was in the range of 80.12 to 98.14%.

In-vitro dissolution profile (Figure 2) revealed, F7 batch

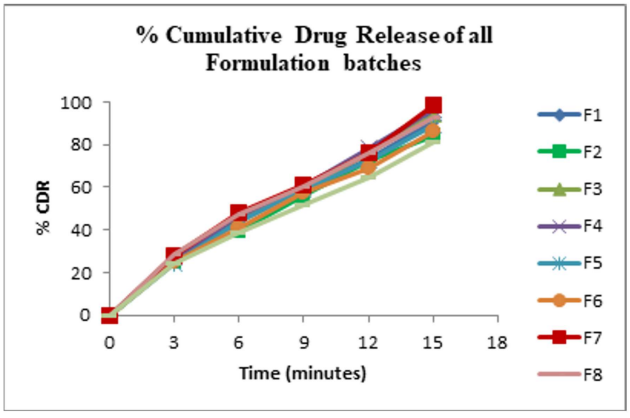

Figure 2. Percentage Cumulative drug release of all formulation batches (F1-F9)

Table 7. Evaluation of FDT for methylphenidate HCl

Batches	Weight variation (mg± SD)*	Hardness (Kg / cm^2) ± SD*	Friability (%)*	Thickness (mm ± SD)*	Wetting time (s)*	DT (s)*	Assay (%)*
F1	99.89±0.47	3.5 ± 0.17	0.34±0.08	2.47 ± 0.06	30 ± 0.21	26 ± 0.71	98.87± 0.21
F2	98.11±0.53	3.7 ± 0.21	0.44±0.02	2.50 ± 0.05	51 ±0.10	47 ± 0.52	98.60± 0.09
F3	101 ± 1.06	3.4 ± 0.80	0.36±0.05	2.54 ± 0.05	27 ± 0.31	23 ± 0.67	101.1± 0.40
F4	98.18±0.85	3.4 ± 0.49	0.29±0.08	2.44 ± 0.08	25 ± 0.72	21 ± 0.78	98.67± 0.31
F5	100 ± 0.78	3.5 ± 0.52	0.41±0.05	2.45 ± 0.09	35 ± 1.04	31 ± 0.57	98.54± 1.01
F6	100 ± 0.55	3.6 ± 0.23	0.35±0.90	2.58 ± 0.02	40 ± 0.22	36 ± 0.82	100± 0.07
F7	99.93±0.83	3.4 ± 0.61	0.37±0.07	2.50 ± 0.09	23 ± 0.61	14 ± 0.92	98.40± 0.19
F8	101 ± 0.77	3.7 ± 0.84	0.42±0.01	2.43 ± 0.05	31 ± 0.81	24 ± 0.89	98.43± 0.11
F9	98.07±1.33	3.8 ± 0.49	0.38±0.07	2.55 ± 0.10	61 ±0.43	57 ± 0.49	98.37± 0.38

*mean ±standard deviation (SD), n=3

Table 8. In-vitro dissolution drug release of formulation F1-F9*

Time (min)/ Batches	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	25.67±0.35	24.8±1.22	27.97±0.67	26.78±0.33	24.4±1.86	25.19±0.44	27.57±1.98	28.76±0.35	24±2.45
6	49.69±1.22	39.73±1.77	46.9±0.56	46.89±1.03	43.69±1.45	40.52±0.87	48.13±1.35	47.7±0.76	38.93±0.65
9	58.84±1.44	56±1.02	59.67±1.45	60.05±0.87	59.21±0.46	57.59±0.17	61.42±1.87	60.08±0.98	52.01±0.44
12	73.31±0.89	72.46±1.65	76.53±1.32	78.5±0.56	72.49±0.98	69.27±1.64	76.55±0.76	76.55±0.99	64.43±1.54
15	91.1±0.99	83.89±1.44	94.11±1.22	96.11±1.45	89.11±1.65	86.26±1.22	98.14±0.65	93.09±0.89	80.12±1.22

*mean ±standard deviation (SD), n=3

Table 9. Evaluation of optimized batch

Batch	Weight variation (mg ± SD)*	Hardness (Kg / cm^2) ± SD*	Friability (%)*	Thickness (mm ± SD)*	Wetting time (s)*	Assay (%)*
Optimized batch	100 ± 0.53	3.4 ± 0.75	0.33±0.09	2.49 ± 0.07	23 ± 0.61	98.88± 0.25

*mean ±standard deviation (SD), n=3

containing 3% indion 234 and 2% avicel PH102 gave maximum drug release i.e., 98.14% amongst factorial batches. Hence it was evident that increase in concentration of avicel PH 102 the drug release from tablet was found to be decreased but in case of indion 234 at middle concentration gave highest drug release.

Analysis of data by design expert software

ANOVA study

The analysis of variance (ANOVA) and multiple regression analysis were done using Stat-Ease Design Expert 7.1.4 software. The statistical treatment and interpretation of data were essential steps where the p-value indicated main effects on optimization of formulation. P values of co-efficient of X1 and X_2 indicated the model significant, since the p value was found to be less than 0.05 i.e., (*p<0.05). Therefore, established the significant effect of both the variables on the selected responses considering both the variables caused significant change in the responses.

Validation of the experimental design

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i(b_1,b_2,,b_{12},b_{11} and b_{22}) is the estimated coefficient for the corresponding factor X_i (X_1,X_2,X_{12},X_{11}, and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

The fitted regression equations relating the responses DT and Drug release are shown in the following equations, respectively.

DT = + 277.40958 – 6.42348* Avicel PH 102 – 147.6839 *

Indion 234 - 0.41296 * Avicel PH 102 * Indion 234 + 1.40000 * Avicel PH 102^2 + 20.77778 * Indion 234^2

($R^2 = 0.9497$)

The first variable X_1 (Avicel PH 102 concentration) and the second variable X_2 (Indion 234 concentration) showed negative sign indicating negative effect on DT. R^2 value 0.9497 for disintegration time indicated the adequate fitting of the quadratic model.

% Drug release = -31.13662 + 2.91419 * Avicel PH 102 + 71.9959 * Indion 234 +0.0627 * Avicel PH 102 * Indion 234 - 0.57100* Avicel PH 1022 – 10.00333 * Indion 2342

($R^2 = 0.9829$)

The first variable X_1 (Avicel PH 102 concentration) and the second variable X_2 (Indion 234 concentration) both showed positive sign indicating positive effect on drug release. R^2 value 0.9829 for drug release indicated the adequate fitting of the quadratic model.

Response surface plot

The relationship between the response and independent variables can be directly visualized from the response surface plots. A 3D response surface plot was generated in which the responses were represented by curvature surface as a function of independent variables to study the effects of independent variables on response DT and drug release. The 3D response surface plot of factorial variable on disintegration time and Drug release are as shown in figure 3(A) and 3(B) respectively.

Table 10. Comparison of predicted and obtained values of optimized formulation

Responses	Optimized formulation	
	Predicted	**Experimental (Optimized)***
DT (s)	12	14 ± 0.92
Drug release (%)	98.14	98.14 ± 0.65

*mean ±standard deviation (SD), n=3

Validation of optimized formulation

To validate the model, a formulation from design space with 2.2 mg Avicel PH 102 and 3 mg Indion 234 were selected. The optimized formulation selected was prepared to obtain the predicted and experimental values of all the response variables i.e., disintegration time and percentage drug release. The tablet properties were evaluated and found within limits (Table 9). The predicted and observed experimental values of responses were obtained which showed close resemblance depicting the validity of the chosen formulation and attaining desired QTPP for fast dissolving tablet of methylphenidate HCl (Table 10).

Design space

ICH Q8 (R2) defines design space as the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality. Concentration of avicel PH 102 and indion 234 was found to be critical on responses DT and % cumulative drug release. Based on the requirement of product quality the criteria considered for responses was DT not more than 30 seconds and drug release not less than 90% at 15 minutes. This study leads to the design space from multidimensional combination of Avicel PH 102 and Indion 234 to the acceptable operating ranges for formulating fast dissolving tablet with respect to target product profile. When critical variables operated within the established design space compliance to CQAs would be assured. Design space (Overlay plot) shown in figure 4 had shaded region with yellow color indicates that region of successful operating ranges.

Control strategy

Control strategy is defined as “a planned set of controls, derived from current product and process understanding that assures process performance and product quality”. It

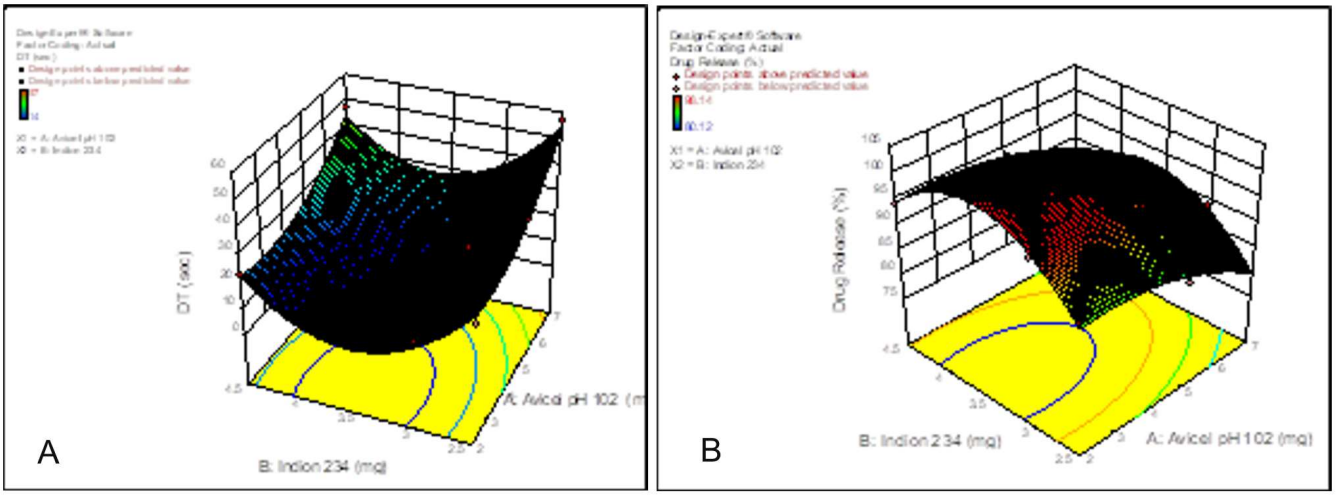

Figure 3. 3D Response surface plot of factorial variable on disintegration time (A), Drug release (B)

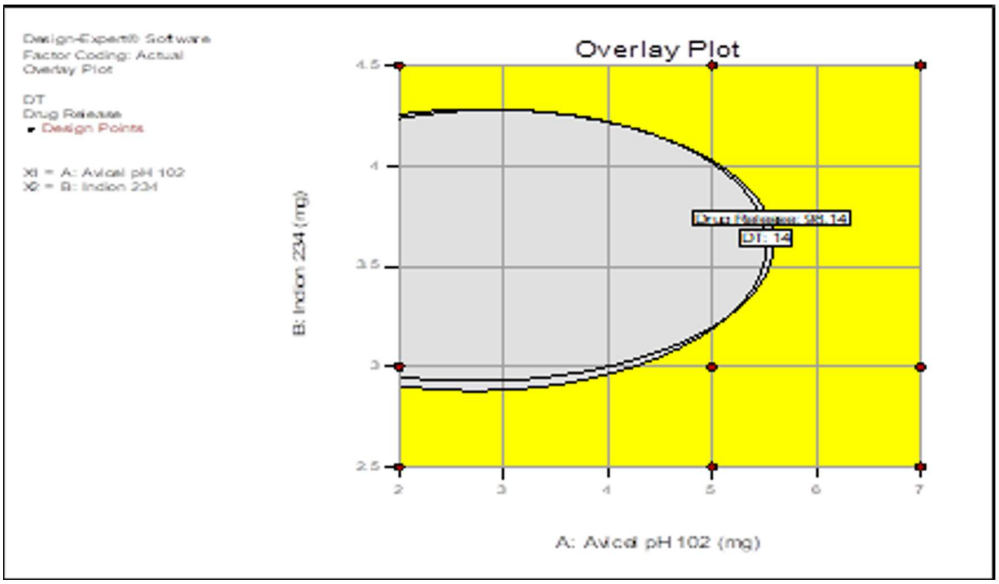

Figure 4. Overlay plot

helps in avoiding defect & maintaining desired quality. These studies investigated the material attributes and process parameters that were deemed high risk to the CQAs of the drug product during the initial risk assessment. The control strategy of methylphenidate HCl FDT for process parameters included assay, concentration of Avicel PH 102 and Indion 234, weight variation, hardness and thickness for which the acceptable operating ranges were established.

Product life cycle management &continuous improvement

Continuous improvement is a vital element in a modern quality system that aims at increase efficiency by optimizing a process and eliminating wasted efforts in production. Upon approval, the manufacturing process for methylphenidate HCl fast dissolving tablets will be validated using the lifecycle approach that employs risk-based decision making throughout the drug product lifecycle as defined in the FDA process validation guidance. Throughout the product lifecycle, the manufacturing process performance will be monitored to ensure desired quality attributes are achieved. If any unexpected process variability is detected, appropriate actions will be taken to correct, anticipate, and prevent future problems so that the process remains in control.

Conclusion

From the findings, it may be concluded that, fast dissolving tablet of methylphenidate HCl by QbD approach can be successfully prepared by direct compression techniques using selected superdisintegrants for the better patient compliance and effective therapy. Implementing QbD concept provided a systematic approach in FDT development emphasizing on product and process understanding and process control to ensure predefined product quality objectives. In the present study initial risk assessment was done and QTTP, CQA for fast dissolving tablet was identified. Concentration of Avicel PH 102 and Indion 234 was identified as critical parameters to achieve desired QTPP. Also disintegration time and in vitro dissolution was found to be a CQA for the development of FDT.

And thus, this CQA was optimized using 3^2 full factorial design. The selected independent variable exhibits significant effect on dependent variables like drug release and DT. Polynomial equations, ANOVA, different statistical values were utilized to interpret significance of formulation parameters on responses and design space was proposed with desired QTPP. The validation of optimized formulation showed close resemblance depicting the validity of the chosen formulation and attaining desired QTPP for fast dissolving tablet of methylphenidate HCl Graphical presentation of the data using response surface plot helps to show the relationship between the response and the independent variables. The information given by graph was similar to that of mathematical equations obtained from statistical analysis.

From the experiments, it can be concluded that if formulation parameters were operated within the proposed design space, high risk can be converted to low level of risk. The formulation prepared within design space resulted in formulation with acceptable disintegration time and percentage drug release. Hence, finally it can be concluded that formulation of fast dissolving tablets of methylphenidate HCl which disintegrates and disperses in saliva within 30 seconds and showed more than 90 % cumulative drug release is a promising approach for the treatment of Attention deficit hyperactivity disorder (ADHD).

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Conflict of interests

Declared none

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