Identification And Optimization Of Critical Process Parameters Of Ivermectin Tablet By Design Of Experiment Approach

Harshita Jain[1], Umesh K. Atneriya[2], Chintaman Kumawat[3], Dharmendra Solanki[4]

BM College of Pharmaceutical Education and Research Indore (MP) India 452020[1,4]

School of Pharmacy, Devi Ahilya Vishwavidyalaya, Indore (MP) India 452020[2]

Shri Bherulal Pharmacy Institute, Indore (MP) India 452020[3]

Abstract: -

All pharmaceutical products are formulated to specific dosage forms for drugs to be effectively delivered to patients. The major advantages of using design of experiments (DOE) are to develop and optimize manufacturing processes and control, increase the accuracy of performance and reduce the number of required tests. DOE takes into account all input variables simultaneously, systematically, and efficiently. Each single input variable and multi-variables interaction can be evaluated and their effect(s) on each response variables can be identified. The aim of this research is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The scientific approach may be used with identification of the desired dosage form a performance attributes through the target product profile. From this target product profile, an initial list of critical quality attributes was developed. A risk assessment was undertaken to identify the variables and unit operations which are most likely to impact the critical quality attributes. Once the significant parameters identification, they can be further studied (using design of experiments model) to achieve a higher level of process understanding. This was then used to focus development activities on potential high risk areas.

Keywords: -Design of experiment model, Critical Quality Attributes, Critical Process Parameters, Process parameters

1.0 Introduction

All pharmaceutical products are formulated to specific dosage forms for drugs to be effectively delivered to patients. Different dosage forms require different pharmaceutical technologies and usually present different technical challenges for formulation development. Because of the complex technical challenges scientists encounter during formulation development, it is important to use an effective methodology [1].

Design of experiments (DOE) and statistical analysis have been applied widely to formulation development and are useful in process optimization and process validation. The major advantage of using DOE to develop formulations for pharmaceutical products is that it allows all potential factors to be evaluated simultaneously, systematically and quickly. Using DOE, one can evaluate the effect of each formulation factor on each response and possibly the interaction effects between factors and identify the critical factors based on statistical analysis. [2-4].
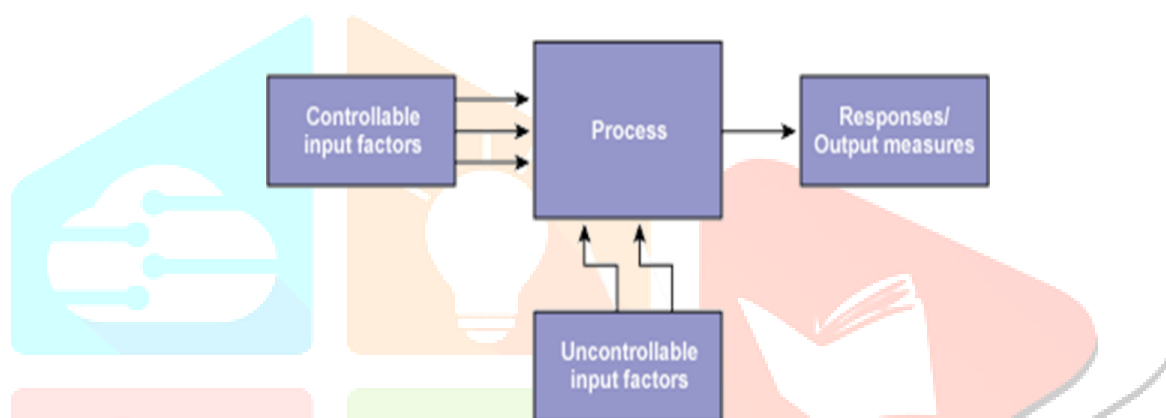

Figure 1 Process of design space

DOE is a structured, organized method for determining the relationships among factors affecting a process and its output. It has been suggested that DOE can offer returns that are four to eight times greater than the cost of running the experiments in a fraction of the time that it would take to run one-factor-at-a-time experiments.

Application of DOE

- ❖ Gain maximum information from a minimum number of experiments
- ❖ Study effects individually by varying all operating parameters simultaneously
- ❖ Take account of variability in experiments, operators, raw materials or processes themselves
- ❖ Identify interactions among process parameters, unlike with one-factor-at-a-time experiments characterize acceptable ranges of key and critical process parameters contributing to identification of a design space, which helps to provide an "assurance of quality".

A design space may be constructed for a single unit operation, multiple unit operations, or for the entire process. [31].

Traditionally, process development experimentation focuses on changing one factor at a time. This approach is based on varying one independent factor while keeping other independent factors constant. This approach intrinsically cannot detect interactions between factors. But design space used for process development to

overcome a traditionally process problem. It is a multidimensional combination of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. The design space involves full understanding of the statistical relationships between the input variables (e.g. raw material and active pharmaceutical ingredient attributes), manufacturing process parameters and output response variables represented by critical quality attributes (CQAs) of finished drug product.

Risk-assessment tools can be used to identify and rank potential parameters deemed to have an impact on product quality based on prior knowledge and initial experimental data. The initial list of all possible parameters can be quite extensive, but is likely to be narrowed, as process understanding is increased, to a smaller list of potential parameters. Narrowing the list has the advantage of reducing the number of experiments necessary in the modeling of a design space.

The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, risk assessment, product specifications, and manufacturing controls.

02 Methods and Material

2.1 Material

Ivermectin were purched from IPCA Laboratory, Indore. Colloidal anhydrous silica, Crosscarmalose sodium, Anhydrous lactose, Microcrystalline cellulose, Zinc stearate,Talc were purchase from local market.

2.2 Methods

2.2.1 Preformulation Study

Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form.

2.2.1.1 Physical Appearance

A white to yellowish white, nonhygroscopic, crystalline powder.

2.2.1.2 Melting Point

The melting point of model drug was found to be within the range of 155-157^{0}C.

2.2.1.3 IR Spectroscopy

Identification of drug was carried out by its IR spectra, obtained by using Shimadzu IR Spectroscopy. Characteristic peak obtained at reported wave numbers are given in table 1.
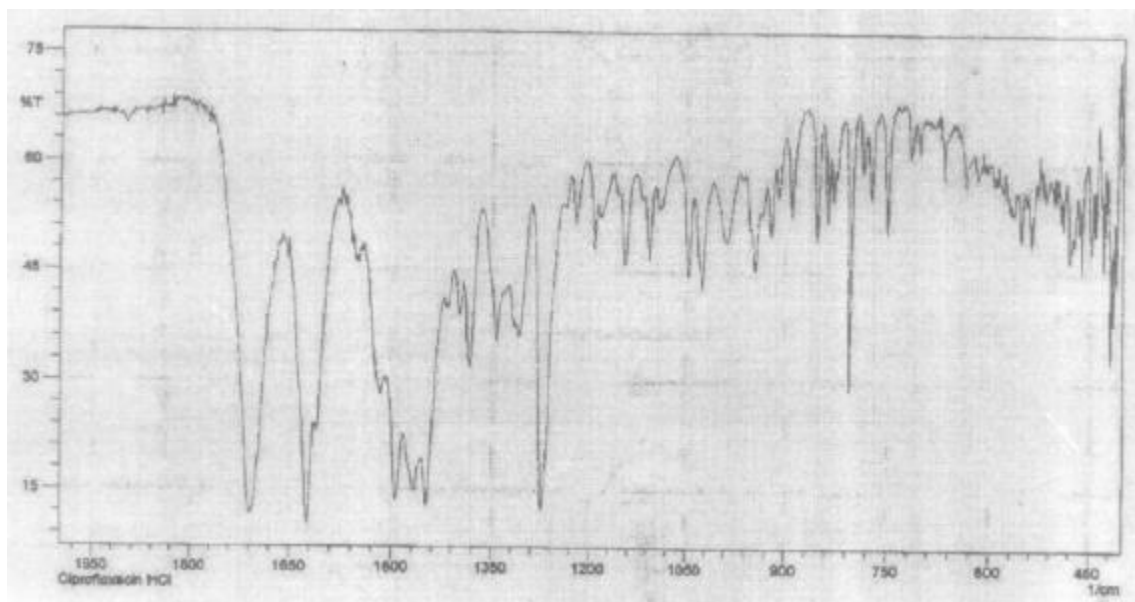
Fig 2 IR spectra of Ivermectin

Table 1 IR spectral analysis of Ivermectin (pure drug)

S.No.	IR signal (cm^{-1})	Remark
1	3490	C-H Stretching
2	3320	O-H Stretching
3	2930	C=O Stretching
4	1605	C=C Stretching
5	1435	C-O Stretching

2.2.1.4 Solubility Profile of Ivermectin

Solubility may be defined as the spontaneous interaction of two or more substance to form a homogeneous molecular dispersion. The solubility of Ivermectin was tested in a various common solvent and the solubility profile of drug is given in Table 2

Table 2 Solubility Profile of Ivermectin

S.No.	Solvent	Remark
1	Distilled water	Insoluble
2	Methanol	Soluble
3	Ethanol	Soluble
4	Methyl ethyl ketone	Soluble
5	Cyclohexane	Insoluble
6	Acetone	Soluble
7	Chloroform	Insoluble
8	Acetonitrile	Soluble
9	Ethyl Acetate	Soluble

2.2.1.5 Partition Coefficient

The partition coefficient value of model drug was found to be 6.0 and 8.8

2.2.1.6 Quantitative Estimation of Ivermectin

UV spectrophotometric method was used to estimate the drug concentration in 0.1 N HCl and phosphate buffer pH 6.8.

2.2.1.7 Preparation of Phosphate Buffer pH 6.8

Placed 50 ml of 0.2M potassium dihydrogen phosphate in 200 ml volumetric flask, added 37.1 ml of 0.2M sodium hydroxide and added sufficient water to make volume upto the mark.

2.2.1.8 Determination of Absorption Maximum (λ_{max})

In 0.1 N HCl

Absorption maximum was determined by dissolving 10 mg of model drug in 10 ml 0.1N HCL. From this stock solution, 0.3ml solution was added to the 10 ml volumetric flask and volume was made upto 10ml with 0.1 N HCl. The solution was scanned in the range of 200 - 400 nm in the UV-visible spectrophotometer (Shimadzu UV-1700). The λ_{max}, was found to be 248 nm.

Fig 3 U.V spectra of Ivermectin in 0.1 N HCL

In phosphate buffer pH 6.8

Absorption maximum was determined by dissolving 10mg of Ivermectin in 10ml of phosphate buffer pH 6.8. From this stock solution, 0.3ml solution was added to the 10ml volumetric flask and volume was made upto 10ml with phosphate buffer. The solution was scanned in the range of 200-400 nm in the UV-visible spectrophotometer (Shimadzu UV-1700). The λ_{max}, was found to be 245 nm.
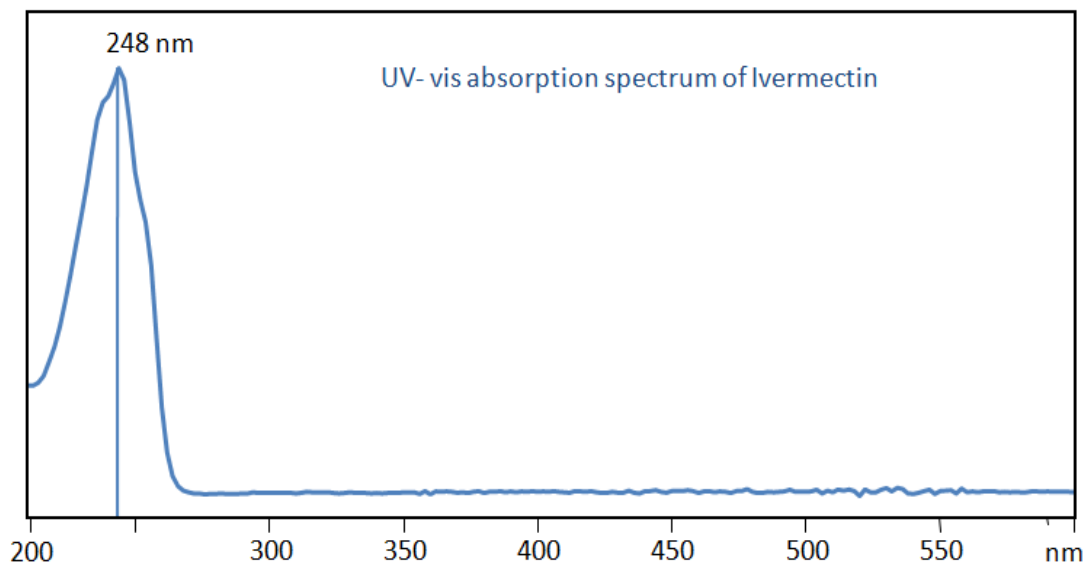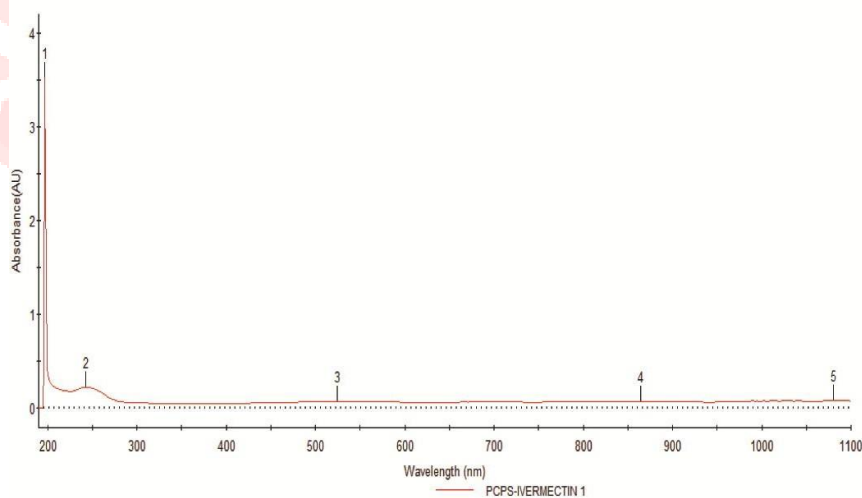

Fig 4: U.V spectra of ivermectin in phosphate buffer (pH 6.8)

2.2.1.9 Preparation of Calibration Curve in 0.1 N HCl

Accurately weighed 10 mg of Ivermectin was added to 10 ml volumetric flask and volume was made upto 10 ml with 0.1 N HCL. From this stock solution different dilutions were prepared in the concentration range of 10, 20, 30, 40 and 50µg/ml in 10 ml volumetric flask and absorbance was taken at 248 nm. Calibration curve was prepared by observations recorded in Table.

Table 3 Calibration curve of Ivermectin in 0.1 N HCl at 248 nm

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	10	0.388
3	20	0.740
4	30	1.115
5	40	1.536
6	50	1.912
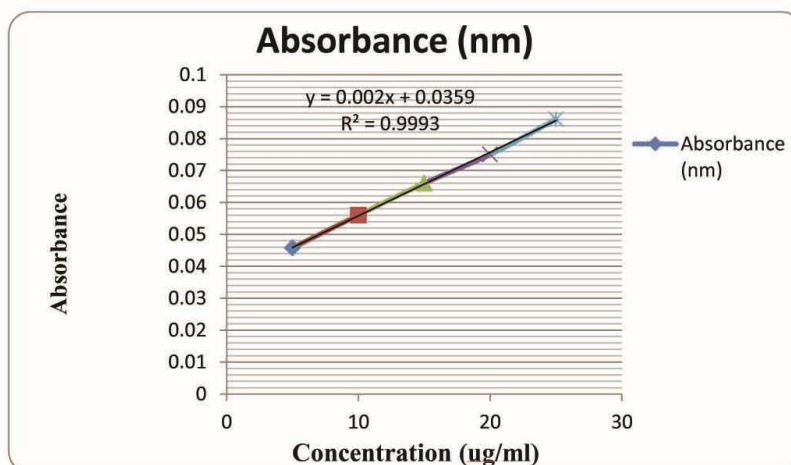
Fig 5 : Calibration curve of Ivermectin in 0.1 N HCL at 248 nm

2.2.1.10 Preparation of Calibration Curve in Phosphate buffer pH 6.8

Accurately weighed 10 mg of Ivermectin was added to 10 ml volumetric flask and volume was made upto 10 ml with Phosphate buffer pH 6.8. From this stock solution different dilutions were prepared in the concentration range of 10, 20, 30, 40 and 50 µg/ml in 10 ml volumetric flask and absorbance was taken at 245 nm.

Table 4 Calibration curve of model drug in Phosphate Buffer pH 6.8 at 245 nm

S.No.	Concentration (µg/ml)	Absorbance
1	10	0.024
2	20	0.044
3	30	0.061
4	40	0.078
5	50	0.093
6	60	0.11

$y = 0.0337x + 0.0218$
$R^2 = 0.9993$

Fig: 6 Calibration curve of Ivermectin in Phosphate Buffer pH 6.8 at 245 nm

2.3 Process for tablet manufacturing

2.3.1 DOE model for optimization of tablet manufacturing process
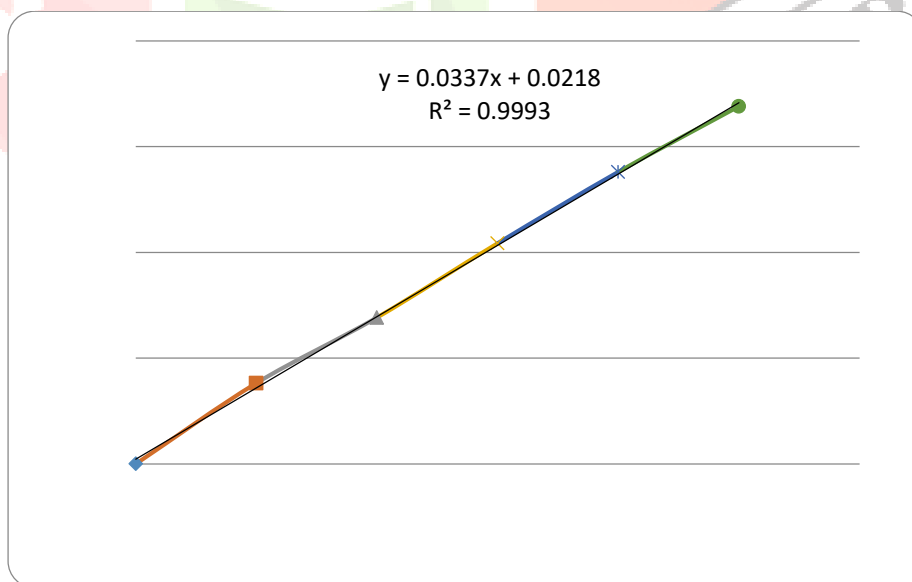
The strategic approach was used for optimization of manufacturing process by using DOE and Risk assessment. This approach was described in following steps;

2.3.1.1 Quality target profile

The pharmaceutical target profile for model drug was a safe efficacious convenient dosage form, preferably a tablet, which will facilitate patient compliance. The tablet should be of an appropriate size, with a single tablet per dose.

2.3.1.2 Cause and effect analysis

Cause and effect diagram was prepared for tablet formulation of direct compression method and compiles a cause and effect (C&E), which was directly and indirectly impact on critical quality attributes of tablet, that maps out all potential parameters in a manufacturing process. The number of parameters could be very extensive.

2.3.1.3 Risk Assessment by failure mode effects analysis (FMEA)

FMEA provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes were established, risk reduction can be used to eliminate, reduce, or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps.

Table 5 Establish a risk ranking system

Score	Severity	Occurrence	Detection
1	No effect on out put	Failure unlikely	Flawless detection system
2	Minor	Remote failure	Will detect failure
3	Moderate	Occasional failure	Might detect failure
4	Serious	High failure	Almost certain not to detect failure
5	Hazardous	Certain failure	Lack of detection control

2.3.1.4 Identification of critical process parameters

The critical process parameters were identified by using prior knowledge, risk assessment and experience of the formulation and the manufacturing techniques, conclusions will be drawn from the risk-based classification process to list the parameters to be investigated using a first-screening experimental design . The parameters were investigated using a 2-level screening design of experiments.

2.4 Design of experiment

Development of the manufacturing process focused on the unit operations posing greatest potential risk to drug product quality. Using prior knowledge, models, extrapolation and risk assessment processes, the material attributes and process parameters, which could have an impact upon final product quality, were identified.
The number of parameters, in addition to the desired resolution of the design, impacts on the number of experiments required in determining the critical parameters.

Tablet Manufacturing Process

❖ **Weighing and shifting**

Model drug and microcrystalline cellulose, zinc stearate, lactose, colloidal anhydrous silica, Croscarmellose sodium and talc were accurately weighed. API was sifted through 44# mesh and excipients were sifted through 40# mesh.

❖ **Blending**

All the ingredients were loaded in descending order form top to bottom loading type. The samples were taken at a different time, speed and loading level at different locations of the V- Blender after mixing of the blend. All the variables (loading level, speed and time) were optimized with the help of quality attributes of mixing parameter.

❖ **Compression**

After optimization of blending parameters, all the variables of compression (compression speed, compression force, PPD, tooling, punch size) were optimized with the help of quality attributes of compression parameter.

Table 6 CPPs and CQAs parameter

S.No	Unit operation	Critical Process Parameters	Critical Quality Attributes
1	Sizing	Mesh Size, Type Of Screen, Feed Rate, RPM	Sieve analysis, Particle size distribution, Bulk/tapped density,
2	Blending	Type and geometry of mixer, Order of addition, Mixer load level, Number of rotations (time and speed), Agitating bar (on/off pattern)	Sieve analysis, Blend uniformity, Particle size distribution, Bulk/tapped density, Moisture content, Flow properties
3	Compression	Compression speed and force, Feed frame type and speed, Hopper design, height, and vibration , Tablet weight and thickness, Depth of fill, Punch penetration depth,	Target weight, Weight uniformity, Content uniformity, Hardness, Thickness, Tablet porosity, Friability,

2.4.1 Evaluation of Quality Attributes of Mixing and Compression

Table 7 Acceptance Criteria of Hausner ratio and Carr's index

S.No.	Hausner ratio	Compressibility Index (%)	Flow Property
1	1.00-1.11	<10	Excellent
2	1.12-1.18	11-15	Good
3	1.19-1.25	16-20	Fair
4	1.26-1.34	21-25	Passable
5	1.35-1.45	26-31	Poor
6	1.46-1.59	32-37	Very Poor
7	>1.60	>38	Very Very Poor

Table 8 Acceptance Criteria of Angle of repose

S.No.	Angle of repose (degree)	Flow Property
1	25-30	Excellent
2	31-35	Good
3	36-40	Fair
4	41-45	Passable
5	46-55	Poor
6	56-65	Very Poor
7	>66	Very Very Poor

2.5 Weight variations

20 tablets from each composition were weighed individually and average weight was calculated. Then the individual tablet weight was compared with the average tablet weight. The weight variation limits as per IP 1996 are as follows:-

Table 9 Standards for weight variation

S. No.	Average weight of tablet (mg)	Maximum % variation allowed (%)
1	80mg or less	10
2	80 to 250 mg	7.5
3	250 mg or more	5

❖ **Drug content**

Five randomly tablets from each batch were taken and triturated. Powder equivalent to 10 mg of drug was weighed and transferred to10ml volumetric flask and methanol was added and then it was shaken for 5 minutes and finally methanol was added to make up the volume upto 10ml and the solution was sonicated for 5 minutes and filtered through a 0.45µm membrane filter paper. Finally, 50 µg/ml solution was prepared from the stock solution and samples were analyzed by UV spectroscopy. Corresponding concentration were calculated from the calibration curve. As per IP and FDA draft the acceptance criteria of drug content and %RSD are as follows:-

Acceptance criteria

- ❖ **Drug content =** Not less than 98.5 per cent and not more than 102.0 per cent
- ❖ **%RSD**   = Not more than 6%

❖ **Disintrigation test**

Six tablets of each formulation were used to determine disintegration time. Distilled water was used as disintegration medium and temperature was maintained at 37±2°C.

03 Result and Discussion

The Ivermectin was obtained as a gift sample from IPCA Laboratory , Indore (India).The physical appearance and melting point and IR spectra of drug were similar with that reported in mater formula record, which showed the purity of sample.

Solubility of Ivermectin was determined in various solvents. The drug was found to be soluble in Methanol, Ethanol, Methyl ethyl ketone, Acetone, Acetonitrile, and Ethyl Acetate and insoluble in distilled water.

The partition coefficient of Ivermectin was determined in n-octanol: water system which is a measure of drug lipophilicity and an indication of its ability to cross biomembrane. The partition coefficient value of model drug was to be found 6.8, hence as per confirmation to mater formula record, which showed the purity of sample.

Absorption maximum of drug was determined by UV at 248 nm (Model- Shimadzu UV-1700, Japan) in 0.1N HCl and phosphate buffer pH 6.8 (Fig 3 and Fig 4) respectively. The Calibration curves of drug were prepared in 0.1 N HCL and phosphate buffer pH 6.8 in the concentration range of 10-50 µg/ml. A straight line with Regression coefficient (r^2) = 0.999 value 0.1 N HCL and phosphate buffer pH 6.8 (r^2) = 0.9983. (Fig 5 and Fig 6) was obtained which indicates that drug follow Beer's law within the specified concentration range.

3.1 Formulation and Manufacturing Process development

A good formulation also must be easy to manufacture and must produce good products consistently. Optimized formula was taken from industry, which was established and optimized by formulation and development department, after the formulation was optimized, more studies must be conducted to optimize the manufacturing process.

Table 10 Optimized formula for tablet formulation

S.No.	Ingredient	Quantity	
		Prescribed (%)	Quantity /mg of tablet
1.	Ivermectin	37	150
2.	Microcrystalline cellulose	32	129.7
3.	Lactose	27	109.5
4.	Zinc stearte	1	4.05
5.	Colloidal silica	0.5	2.03
6.	Cross-carmalose sodium	2	8.1
7.	Talc	0.5	2.03
	Total	100	405.4

3.2 DOE model for optimization of tablet manufacturing process

3.2.1 Quality target profile

A quality target profile was prepared on the basis of prior knowledge and F&D limit . From this target profile, the initial Critical Quality Attributes were identified to define satisfactory quality of product.

Table 11 Quality Target Profile

S.No	Quality Attribute	Quality Target Profile
1	Dosage form	Tablet, max weight 400mg
2	Potency	150 mg
3	Identity	Ivermectin
4	Appearance	Oval, white, smooth
5	Assay	95-115 %
6	Content uniformity (%RSD)	NLT 98.5 % and NMT 102.0% (NMT6%)
7	Blend uniformity(% RSD)	NMT 5%
8	Hardness	8-17 KP
9	Friability	NMT 1%
10	Weight uniformity	405±5 %
11	Thickness	4.0 ± 0.4 mm
12	Disintrigation	NMT 15 min
13	Dissolution	Not less than 85% in 30 min

3.2.2 Cause and effect analysis

Cause and effect diagram was prepared, after QTPP preparation. This was used to identify all potential variables, such as raw materials, blending, sifting, compression parameters, and environmental factors, which can have an impact on a particular CQAs.

Table 12 CPP and CQA during Unit Operation

S.No	Unit operation	Critical Process parameter	Critical Quality attributes
1	Sizing	Mesh size, Type of screen, Feed rate, Rpm	Sieve analysis, Particle size distribution, Bulk/tapped density,
2	Blending	Type and geometry of mixer, Order of addition, Mixer load level, Number of rotations (time and speed), Agitating bar (on/off pattern)	Sieve analysis, Blend uniformity, Particle size distribution, Bulk/tapped density, Moisture content, Flow properties,
3	Compression	Compression speed and force , Feed frame type and speed, Hopper design, height, and vibration, Tablet weight and thickness, Depth of fill, Punch penetration depth	Target weight, Weight uniformity, Content uniformity, Hardness, Thickness, Tablet porosity, Friability

3.2.3 Risk Assessment by failure mode effects analysis (FMEA)

Failure mode effects analysis (FMEA) process was used to identify the failures modes and risks within a process or product and then eliminates or reduces them. FMEA was used for risk assessment of tablet manufacturing process and identified the critical process parameters of tablet, which was directly impact on critical quality attributes of tablets. An effective FMEA identifies corrective actions required to prevent the probable failures modes and assure the highest possible yield, quality and reliability.

The risk priority rank (RPR) was calculated by multiplying the severity rating, occurrence probability rating and detection probability rating for all of the failure modes.

3.2.3.1 Assessing risk

Risk identification

Assess severity

Model Drug	Hazardous	Serious	Major	Minor
Ivermectin	Nil	Nil	Nil	Nil

Assess probability of occurrence

Model Drug	Frequent	Probable	Occasional	Remote	Very unlikely
Ivermectin	Nil	Nil	Nil	Nil	Nil

Assess probability of detection

Model Drug	Flawless detection system	Will detect failure	Might detect failure	Lack of detection control
Ivermectin	Nil	Nil	Nil	Nil

Table 13 Establish a risk ranking system

Score	Severity	Occurrence	Detection
1	No effect on out put	Failure unlikely	Flawless detection system
2	Minor	Remote failure	Will detect failure
3	Moderate	Occasional failure	Might detect failure
4	Serious	High failure	Almost certain not to detect failure
5	Hazardous	Certain failure	Lack of detection control

3.2.4 Identification of critical process parameters

The critical process parameters were identified on the basis of recommendation of risk assessment of tablet manufacturing process.

Table 14 Identification of critical process parameters

S.No	Process step	Critical process parameter
1	Shifting	❖ Screen size
2	Blending	❖ Blending time ❖ Blending speed ❖ Loading level
3	Compression	❖ Compression speed ❖ Compression force ❖ Punch penetration depth (PPD) ❖ Tooling ❖ Punch size

3.2.5 Design of experiment

Experiment was design by D-optimal design expert software for tablet manufacturing process, after identification of critical process parameters. Tablet was prepared by direct compression method. In this method shifting, blending, and compression are important process steps and specification of critical process parameters were shown in table

1. All the ingredient API and excipients were accurately weighed and sifted through 44# and 40# mesh.

2. Three CPPs of blending (blending time, speed and loading level) were selected and design the experiment by D-optimal design expert software.

3. Four CPPs of compression (compression speed, compression force, PPD, punch size) were selected and design the experiment by D-optimal design expert software.

3.2.5.1 Tablet Manufacturing Process

Table 15 Specification of critical process parameters

S.No	Critical process parameter	Target
1	**Screening** ❖ Screen size	API – 44# Excipients – 40#
2	**Blending**	
	❖ Blending time	10-20 min
	❖ Blending speed	20-25 RPM
	❖ Loading level	40-70 %
	❖ Loading type	Top to bottom
	❖ Order of addition	Descending order
	❖ Humidity	45%
3	**Compression**	
	❖ Compression speed	200-800
	❖ Compression force	1-3 ton
	❖ Punch penetration depth	0.31-0.61 mm
	❖ Tooling	B tooling
	❖ Punch size	9 -11 mm
	❖ Turret speed	20 RPM
	❖ depth of fill(mm)	20 mm
	❖ Humidity	45%

Table 16 Numerical value of three factors in experiment design of blending by using D-optimal design software 6.9

Std	Run	Factor 1 A:Blending tin RPM	Factor 2 B:Blending sp RPM	Factor 3 C:Blending lev % RPM
10	+1	20.0	25.0	70.0
4	2	12.0	24.0	30.0
9	3	15.0	20.0	40.0
16	4	10.0	20.0	50.0
1	5	10.0	25.0	55.0
12	6	12.0	25.0	40.0
6	7	15.0	20.0	40.0
19	8	20.0	22.6	65.0
8	9	20.0	23.5	65.0
17	10	15.0	23.0	70.0
18	11	10.0	22.0	55.0
3	12	10.0	20.0	60.0

3.2.5.2 Evaluation of Quality Attributes of mixing and compression

Table 17 Response of critical quality attributes of mixing and compression

Run	Response					
	Bulk density (gm/cm^3)	Tapped density (gm/ cm^3)	Hausner ratio	Carr's index	Angle of repose (deg)	BUA (%RSD)
1	0.62	0.66	1.10	15.0	23	14.2
2	0.65	0.70	1.20	18.8	27	8.66
3	0.56	0.72	1.18	18.7	23	4.80
4	0.65	0.70	1.32	21.2	22	9.24
5	0.55	0.70	1.14	18.2	22	7.44
6	0.62	0.72	1.27	15.1	20	4.22
7	0.60	0.70	1.28	19.7	22	5.65
8	0.50	0.70	1.20	16.1	26	9.51
9	0.62	0.79	1.25	17.4	24	5.41
10	0.68	0.72	1.21	20.8	28	4.73
11	0.64	0.77	1.28	19.1	28	8.35
12	0.50	0.72	1.22	17.6	23	8.00

3.3 Selection of optimized blend batch

The blends were selected on the basis of DOE result and graphs. As per IP and FDA draft, the quality attribute of mixing parameters were very close limit in the case of run 3, 6, 10 and 14.

After selection of the blend (run 3, 6, 10 and 14), all the ingredient API and excipients were reweighed and sifted through 44# and 40# mesh and blended in V- blender at a selected blending time, speed and loading level. All other parameters like that's type and geometry, loading type and order of addition were constant, according to previous experiments.

Table 18 Selected blends from DOE result

S.No	Selected run	Critical process parameters		
		Blending time (min)	Blending speed (RPM)	Loading level (%)
1	3	15	20	55
2	6	10	22.5	40
3	10	15	20	40
4	14	10	25	55

3.4 Design space of compression

The blend was selected after evaluating the quality attributes of mixing. Tablets were prepared of selected blend by direct compression method by using tablet compression machine (Cadmach Remek) and evaluate the quality attributes of tablet. The quality attributes of tablet parameters included thickness, breaking force, friability, weight variation, content uniformity, disintrigation test, dissolution and assay.

Table 19 Specifications of compression machine

S. No.	Compression machine parameter	Specification
1	Machine model no.	CMD4 D-20/MT
2	Type of tooling	B
3	Output tablet\min(Min/Max)	350/670
4	Max. dia. of tablet(mm)	25
5	Max. depth of fill(mm)	20
6	Upper punch penetration(mm)	1/4", 7/32", 3/16", 5/32",1/8"
7	Max. thickness of tablet(mm)	8
8	Turret speed(rpm)Min/Max	20 RPM
9	Production capacity(pcs\hr)	15,600/hr
10	Motor(HP)	2
11	Humidity	45%
12	Temperature	23-24ºC

Following parameters were used for design space:-

Factor 1- Compression force = 1-3 ton

Factor 2- Compression speed = 200-800

Factor 3- Punch penetration depth= 0.31-0.61 inch

Factor 3- Punch size=9mm, 10mm, 11mm

Response 1- Thickness = mm

Response 2 – Hardness = KP

Response 3- Friability = %

Response 4- Assay = %

Response 5- Average weight = mg

Response 6- Content uniformity = %RSD

Response 7- Disintegration time = min

Response 8- Dissolution = Q

Table 20 Numerical value of four factors in experiment design of compression by using D-optimal design software

Std	Run	Factor 1 A:ompression ton	Factor 2 B:Compressi rpm	Factor 3 C:PPD inch	Factor 4 D:punch size mm
9	1	1.00	200.	0.310	10.0
19	2	2.00	200.	0.460	10.0
15	3	1.00	800.	0.460	9.00
18	4	3.00	500.	0.460	10.0
12	5	3.00	800.	0.460	11.0
7	6	1.00	200.	0.610	9.00
17	7	1.00	500.	0.460	10.0
4	8	3.00	200.	0.310	11.0
5	9	1.00	800.	0.610	11.0
10	10	2.00	200.	0.310	9.00
3	11	1.00	500.	0.310	9.00
20	12	2.00	800.	0.460	10.0
13	13	3.00	200.	0.460	9.00
22	14	3.00	800.	0.610	9.00

Table 21 Response of critical quality attributes of tablet

Run	Response							
	Hardness (KP)	Friability (%)	Average weight (mg)	Thickness (mm)	Assay (%)	CU (%RSD)	DT (sec)	Disso (Q)
1	10.0	0.19	408.1	4.05	97.5	3.40	22.0	98.7
2	14.0	0.52	403.6	3.80	98.3	4.50	47.0	87.5
3	4.50	0.60	398.2	3.97	93.5	4.90	13.0	96.7
4	4.90	0.49	415.5	3.44	96.4	2.90	15.0	98.5
5	9.09	0.51	409.4	4.50	91.3	5.70	25.0	98.6
6	10.1	0.23	406.3	4.55	99.4	6.40	23.0	98.2
7	13.1	0.28	400.7	4.51	98.4	4.30	43.0	96.5
8	11.4	0.45	389.3	4.59	95.4	7.80	30.0	99.6
9	10.0	0.18	406.5	4.55	94.9	5.60	22.0	98.0
10	15.6	0.52	402.5	4.65	97.8	3.50	46.0	93.4
11	17.3	1.53	404.3	3.70	99.3	5.80	119	84.2
12	13.1	0.54	407.7	3.90	96.5	4.60	43.0	96.4

3.6 Selection of optimized batch at a compression step

The critical process parameters of tablet were selected on the basis of DOE result and graphs. As per IP and FDA draft, the quality attribute of tablet parameters were very close limit in the case of run 1, 2, 12, 17, 19 and 20.

The blend was compressed, after selection of the critical process parameters of tablet (run 1, 2, 12, 17, 19 and 20)

Table 22 Selected compression parameter from DOE result

S.No	Selected run no.	Critical process parameters			
		Compression force (ton)	Compression speed (speed)	PPD (inch)	Punch size (mm)
1	1	1	200	0.31	10
2	2	2	200	0.46	10
3	12	2	800	0.46	10
4	17	1	800	0.61	11
5	19	2	500	0.53	10
6	20	2	500	0.31	10

3.7 Evaluation of critical quality attributes of tablet parameters

The quality attribute of tablet parameters were evaluated after compression of blend at an each selected compression run. The quality attributes of tablet parameters included thickness, hardness, friability, weight variation, content uniformity, disintrigation test, dissolution and assay. As per IP and FDA draft, the quality attribute of tablet parameters were very close limit in the case run 20.

Table 23 Response of critical quality attributes of tablet

Run	Response							
	Hardness (KP)	Friability (%)	Average weight (mg)	Thickness (mm)	Assay (%)	CU (%RSD)	DT (sec)	Disso (Q)
1	11.2	0.25	410.3	3.96	92.3	4.2	19	98.3
2	13.8	0.67	403.2	3.83	89.6	4.6	42	85.6
12	12.3	0.48	398.4	3.90	93.5	4.3	49	98.8
17	8.9	0.23	401.2	4.02	98.4	3.5	25	97.5
19	14.9	0.54	408.5	4.10	96.4	1.67	89	90.2
20	11.9	0.34	401.3	4.04	97.5	3.1	45	97.7

3.8 Trial Batch Run

Trial batch was run, after optimization of blending and compression parameters.

All the ingredient API and excipients were accurately weighed and sifted through 44# and 40# mesh. The ingredients were blended at a optimized speed (20 RPM), time (15 min), 55% loading level and other blending parameters like that's type and geometry, loading type and order of addition were constant according to pervious experiment. After blending of the materials evaluated the critical quality attributes of mixing and results were shown in table.

After blending of the ingredients, compressed the tablets at an optimized compression force (2 ton), compression speed (500), PPD (0.31 inch), punch size (10 mm) and other compression parameters like that's Turret speed, depth of fill, humidity, temperature, tolling were constant. After compression of blend, the quality attribute of tablet parameters were evaluated and results were shown in table.

Table 24 Optimized critical process parameters

S.No	Unit operation	Critical process parameter	Optimized result
1	Blending	Blending speed	20 RPM
		Blending time	15 min
		Loading level	55 %
2	Compression	Compression force	2 ton
		Compression speed	500
		PPD	0.31 inch
		Punch size	10 mm

3.9 Evaluation of critical quality attributes of blending and compression

Table 25 Evaluation of critical quality attributes of blending and compression

S.No	Critical quality attributes	Response
1	**BLENDING**	
1.1	Bulk density (gm/ cm^3)	0.63
1.2	Tapped density (gm/ cm^3)	0.72
1.3	Carr's index	12.5
1.4	Hausner ratio	1.14
1.5	Angle of repose (deg.)	25
1.6	BUA (%RSD)	3.54
2	**COMPRESSION**	
2.1	Hardness (KP)	11.4
2.2	Friability (%)	0.24
2.3	Thickness (mm)	3.98
2.4	Average weight (mg)	402.1
2.5	Content uniformity (%RSD)	2.40
2.6	Assay (%)	96.8
2.7	Disintrigation (sec)	39
2.8	Dissolution (Q)	97.6

4.0 Summary and Conclusion

Design of experiments (DOE) and statistical analysis have been widely applied to formulation development and useful in process optimization. The effect of each process parameters on each response were identified and evaluated by using risk assessment and DOE model. A formula was taken from industry, which was optimized by formulation and development department and applied risk assessment and DOE model for optimization of the manufacturing process parameters. Failure mode effects analysis (FMEA) process is a way to identify the failures modes and risks within a process and then eliminates or reduces them.

Experiments were designed by D-optimal design expert software for tablet manufacturing process, after identification of CPPs. Tablet was prepared by direct compression method.

All the ingredients were accurately weighed and sifted. Nineteen experiments were design for blending optimization, by D-optimal design expert software. All ingredients were loaded in descending order from top to bottom loading type in 50 L V- blender and they were mixed at different time interval, speed and loading level, according to nineteen experiments. Sampling was done by sampling thieves from 10 point sampling location in V blender and evaluated CQAs of mixing. The quality attribute of mixing parameters were very close limit in the case of run 3, 6, 10 and 14 as per IP and FDA draft. All the ingredients were reweighed, sifted and blended in V- blender at a selected blending time, speed, loading level and evaluated CQAs of mixing. The quality attribute of mixing parameters were very close limit in the case run 3. This blend was used for tablet preparation. The results were found under the limit and these optimized parameters were used for further manufacturing of commercial tablet batches.

From the above observations, it can be concluded that the risk assessment and DOE model can be applied for the optimization of critical process parameters with the help of critical quality attributes.Statistical optimization experimentation and analysis provides strong assurances to comply regulatory agencies regarding superior product quality.

Conflict of Interest

Author declairs that there is no conflict of interest.

REFERENCES

1. Rekhib GS, Ranjani V. Nellorec and Hussaind AS ; Identification of critical formulation and processing variables for metoprolol tartrate extended-release (ER) matrix tablets; Journal of Controlled Release 59; 1999; 327–342

2. Glodele M and Liebowitz S ; Process robustness of tablet formulation; Pharmaceutical Engineering; 2006; 1-11

3. Stuart C. Porter, Richard P. Verseput and Charles R. Cunningham; Process optimization using design of experiments; Pharmaceutical Technology; 1997;1-7

4. Sabir A, Evans B and Jain S ; Formulation and process optimization to eliminate picking from market image tablets; International Journal of Pharmaceutics; 2001; 123–135

5. Brian A.,C. Carlin; The Future of Compaction Pharmaceutical Tableting in the Twenty-First Century; Pharmaceutical Technology; 2004; 42-46

6. Patel R and Baria A; Formulation development and process optimization of theophylline sustained release matrix tablet; International journal of pharmacy and pharmaceutical sciences; 2009; 1- 13

7. Ahsan M, Hasin A, Yasmin T, and Proma FA; Assessment of the Risks for workers using FMEA: A Case Study in a Pharmaceutical Industry; International Conference on Industrial Engineering and Operations Management Dhaka; 2010; 1-12

8. Condran G; Utilization of the quality overall summary-health canada perspective health products and food branch direction aliments; 2005; 5-7

9. Patil SB, Shahi1 SR, Udavant YK, Atram SC, Salunke RJ and Gajendra B; Formulation and evaluation of quick dispersible tablet of olanzapine; IJPRD; 2009; 1-14

10. Novack V; GSK Control Strategy Case Studies Workshop on implementation of ICH Q8/Q9/Q10 and Other Quality Guidelines Beijing, China; Dec 2008

11. Nutek ; DOE-I Basic Design of Experiments, Inc. Quality Engineering Seminar and Software Bloomfield Hills, MI, USA

12. Nagar M, Panwar KS, V. S. Chopra, Indu Bala and Trivedi P; Quality by design: A systematic approach to pharmaceutical development Scholars Research Library Der Pharmacia Lettre; 2010; 111-130

13. Gohel MC; A review of co-processed directly compressible excipients; J Pharm Pharmaceut Sci; 2005; 76-93

14. Narayanagounder S and Gurusami K; A New Approach for Prioritization of Failure Modes in Design FMEA using ANOVA; World Academy of Science, Engineering and Technology 49; 2009; 524-532

15. Gohel MC, Parikh RK, Brahmbhatt BK and Aarohi R. Shah Improving the Tablet Characteristics and Dissolution Profile of Ibuprofen by Using a Novel Coprocessed Superdisintegrant; AAPS PharmSciTech; 2007; 8

16. Bolourtchian N, Hadidi N, Foroutan SM and Shafaghi B; Formulation and Optimization of Captopril Sublingual Tablet Using D-Optimal Design; Iranian Journal of Pharmaceutical Research; 2008; 259-267

17. Lionberger RA, Lee SL, Lee LM, Andre Raw and Lawrence X. Quality by Design: Concepts for ANDAs ; AAPS Journal; 2008; 268-276

18. Leesawat P, Laopongpaisan A and Sirithunyalug J; Optimization of Direct Compression Aspirin Tablet Using Statistical Mixture Design; Journal of CMU; 2004; 97-115

19. Moreton CR; Optimization of Direct Compression Aspirin Tablet Using Statistical Mixture Design; Pharma science fair; 2009; 1-24

20. Wigmore D; Pharmaceuticals Manufacturing of tablet dosage form; Women and Health Protection; 2009; 1-61

21. Lawrence X.; Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control; CDER and FDA presentation; 2004; 1-24

22. Chiozza ML, Ponzetti C; FMEA: A model for reducing medical errors; Clinical Chimical Acta ; 2009; 75–78

23. Singh S, Jagota N, Venkateshwaran TG, and Saunders R; Criticality Assessment- Identification of critical quality attributes (CQAs) and critical process parameters (CPPs) for a MR Dosage form (DP); pfizer presentation; worldwide pharmaceutical science; AAPS Annual Meeting; 2009; 1-24

24. Coulson L; Continuous quality verification – An approach to process validation; EMEA / Efpia QbD application workshop; 2009; 1-24

25. Hwang R, Noack RM; Application of design of experiments to pharmaceutical formulation development; International Journal of Experimental Design and Process Optimization; 2011; 58 - 65

26. Garcia T, Cook G, Nosal R; PQLI key topics- Criticality, design space and control strategy; Journal of Pharmaceutical Innovation; 2008; 60-68

27. Zomer S, Gupta M; Application of Multivariate tools in pharmaceutical product development to bridge risk assessment to continuous verification in quality by design environment; Journal of Pharmaceutical Innovation; 2010; 109-118

28. Huang J, Kaul G. Cai C; Quality by design, case study: An integrated multivariate approach to drug product and process development; International Journal of Pharmaceutics; 2009; 23-32

29. Long CP, Quaid MCJ; Strategic Approaches to Process Optimization and Scale-up; Pharmaceutical Technology; 2005; 1-7

30. Shivhare M and Creath GM; Practical Considerations for DOE Implementation in Quality By Design ; Bio Process International; 2010; 22-30

31. Vogel M; Design-Expert Software Enables Z Corp Printer Design; Pharmaceutical Technology; 2010; 1-7

32. Hiyama Y; Quality overall summary and common technical document; 2009; 1-59

33. Patel A, Chudasama AR; Preformulation and quality overall summary - regulatory Insights ; Journal of Pharmaceutical Information; 2009; 917-923

34. Dahiya S, Khar RK., Aruna C; Opportunities, challenges and benefits of using HACCP as a quality risk management tool in the pharmaceutical industry, John Wiley & Sons, Ltd; 2009; 95-96.

35. EU Guidelines; Quality Management System Volume 4, Brussel Belgium; 2009; 2-8