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Quality by design approach for anti-hyperthyroid immediate release tablet of carbimazole

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***Abstract*---**The current study to formulate, evaluate and optimize carbimazole immediate release tablet by using quality by design approach. The look at of optimization formula and experimental design had been done with the aid of using design parameter primarily based totally on Box-Behnken design. Immediate release dosage form for rapid efficacy and inhibit the peroxidase enzymes and act as thyroid inhibitor. Method: Immediate release carbimazole tablets were manufactured by dry granulation using Quality by

Design. The optimization of the formulation of tablets is done by examining the profile of the objective quality product. Microcrystalline cellulose, anhydrous lactose and magnesium stearate were all included in experiments designed using the Box-Behnken design. Their concentrations are influenced by the drug disintegration and release factor f2. Result: Optimized batch formulation shows immediate drug release with short disintegration time. In anova models are significant. Conclusion: The utilization of bound together quality by design approach for successful advancement of an IR carbimazole tablet. The effective tablet created with Box-Behnken designs.

Keywords---anti-hyperthyroid, QBD, immediate release, design expert.

Introduction

Dr. Joseph M. Juran is initial present Quality by Design (QbD) in front of world in 1992. Qbd is Minimize deviations and increase the efficiency of manufacture, diminish costs. Rather than depending on end-product testing alone, QbD gives experiences upstream all through the development preparation. Experimental design is a way of establishing the correlations between variables affecting a process and the output of that process that is structured and methodized. This term is also known the Design of Experiments (DoE). [1,16,17] QbD promotes pharmaceutical organizations want to put into effect quality risk control concepts to benefit a higher understanding in their production strategies and make sure higher product quality. [2] Carbimazole is an anti-hyperthyroid drug commonly used to treat Graves' disease, subacute thyroiditis due to toxic nodular goiter, and radioactive iodine therapy. Carbimazole Derivatives of carbethoxy that unexpectedly hydrolyzed to methimazole. Carbimazole inhibits the process of iodination of thyroglobulin. Carbimazole has quite properly gastrointestinal absorption. Thyroid peroxidase performs a crucial role in thyroid hormone synthesis. This drug inhibits the Thyroid peroxidase enzyme and stops the synthesis of the brand-new hormone. The thyroid gland has stored already synthesized hormones which are secreted for about three weeks. So carbimazole takes about three weeks for its effect to develop. CBZ accumulate inside glands because of which their effects last longer than what you would predict from their plasma half-life. For example, Propylthiouracil has a plasma half-life of 1-2 hours however effects of its single-dose last for about eight hours. So, it is given 2-3 times a day. Carbimazole has a plasma half-life of eight hours but the effects of its single-dose last for an entire day so it is given once daily. [3,4]

Materials and Methods

Carbimazole received from Innova Pharmactive Ltd, Nagpur, India. Lactose anhydrous from DFE PHARMA GmbH & Co.KG, Germany. Red iron oxide received from Sensient Technologies GmbH Europe. Microcrystalline cellulose (mcc) received from JRS Pharma Germany.

Quality Target Product Profile for CARBIMAZOLE IR Tablets

QTPP is in brief explanation about Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA) and Non-Critical Quality Attributes (NCQA) that impacts formula of Carbimazole IR Tablets proven in table 1 and 2. [6,12]

Experimental Design

The tablet method changed into optimized the usage of a Box-Behnken design. Lactose Anhydrous, MCC, and Mg. Stearate concentrations have been all impartial elements on this study. Disintegration time and drug release means F2 Factor have been selected as response. The table shows basic design coded values for Carbimazole IR tablet. [5, 13]

Preparation of Carbimazole IR tablet
Direct compression

Tablet was prepared by direct compression method. Weighed quantity of carbimazole, microcrystalline cellulose 112, citric acid anhydrous, Lactose anhydrous, and all ingredients pass through #30 sieves and transferred into the blender for 15min.

Blending

Magnesium Stearate was passed through #60 sieves and transferred into a blender for eight min.

Characterization of IR tablet
Bulk Density

Bulk density is important parameter for pharma product, formulation and development of solid dosage form. The finding out how an awful lot powder which can suit in a volume of blender. Weigh 25gm of granules into the 100ml measuring cylinder and measure preliminary volume. Bulk density is measured by–

$$\text{Bulk Density} = \frac{\text{Wg}}{\text{Vb}}$$

Wg = Granules weight, Vb = Bulk volume (Including void volume)
2.4.2. Tapped Density

Another essential function is the tapped density (tapped bulk density), that is, the best packing density of a powder (or combination of powders) achieved suffering from well defined. After mechanical tapping of graduated measuring cylinder then tapped density is obtained. It is measured through tap density tester. After one hundred times tapping is carried out then tapped quantity is measured. Tapped density evaluated by formula –

$$\text{Tapped Density} = \frac{\text{Wg}}{\text{Vt}}$$

Wg = Granules weight, Vt = Tapped bulk volume

Compressibility Index (Carr's index).

Carr's index is evaluated with given formula

$$\text{Carr's index} = \left[\frac{\text{Tapped density} - \text{Bulk or pored Density}}{\text{Tapped density}}\right] \times 100$$

The compressibility index value is much less than 20% has appropriate powder flow property.

Table 1
QTPP of Carbimazole IR Tablet

<table>
<tr><td colspan="2">QTPP Element</td><td>Target</td><td>Justification</td></tr>
<tr><td colspan="2">Dosage form</td><td>Tablet</td><td>Dosage form complying pharmaceutical equivalence Requirement</td></tr>
<tr><td colspan="2">Dosage design</td><td>Immediate release</td><td>Immediate release design needed to meet label claims.</td></tr>
<tr><td colspan="2">Route of administration</td><td>Oral</td><td>Pharmaceutical equivalence requirement: Same administration route</td></tr>
<tr><td colspan="2">Dosage strengths</td><td>Carbimazole IR tablet 5mg</td><td>Pharmaceutical equivalence requirement: Same strength</td></tr>
<tr><td colspan="2">Container closure system</td><td>Blister Pack</td><td>Needed for safety, commercial requirements</td></tr>
<tr><td colspan="2">Pharmacokinetics</td><td>Bioequivalent with reference product</td><td>Bioequivalence requirement.</td></tr>
<tr><td rowspan="11">Drug product quality attributes</td><td>Description</td><td rowspan="10" colspan="2">Pharmaceutical equivalence requirement: Meeting the equal or different applicable (quality) standards (i.e. identity, assay, purity, and quality)</td></tr>
<tr><td>Identification</td></tr>
<tr><td>Weight variation</td></tr>
<tr><td>Tablet Hardness</td></tr>
<tr><td>Friability</td></tr>
<tr><td>Assay</td></tr>
<tr><td>Dissolution</td></tr>
<tr><td>Water content (by KF)</td></tr>
<tr><td>Uniformity of dosage units</td></tr>
<tr><td>Related substances</td></tr>
<tr><td>Microbial limits</td></tr>
<tr><td>Stability</td><td>24 Months</td><td>Needed for commercialization</td></tr>
</table>

Table 2
Critical and Non-Critical Quality Attributes for Carbimazole IR Tablet

Drug Product quality attributes		Target	Is this critical?	Justification of Criticality
Physical attributes	Description & Colour	Round, Un-coated Tablets	No	Commercial Requirement
	Size & shape	Same as RLD	No	Commercial requirement
Identification		To comply	No	Both formulation and process does not impact identification
Water content (by KF)		To be decided	Yes	Formulation, process & storage might also additionally impact water content material of drug product
Weight variation		Complies with Pharmacopeial requirement	Yes	Manufacturing process impact weight variation of drug product.
Tablet Hardness		To Be Decided	Yes	Both formulation and process impact the Tablet Hardness.
Friability		NMT 0.5%w/w	Yes	Both formulation and process impact the Friability.
Uniformity of dosage units (Content uniformity)		Complies with requirement for uniformity of dosage units	Yes	Both formulation and process impact the uniformity.
Assay		95.0-105.0% of label claim	Yes	Process & storage can also additionally have an effect on the assay value of drug product
Related Substances		As per BP/EP/ICH	Yes	To meet BP/EP/ICH Requirement for impurities.
Dissolution		Shall be decided on reference product evaluation	Yes	Formulation, system and storage circumstance have an effect on drug release profile good.
Microbial Limits		Meet relevant pharmacopoeia criteria	Yes	Both formulation and process may impact microbial stability

Evaluation of Carbimazole IR Tablet

Weight Variation

This action is the obstruction of tablets or granules to a scraped area or crack. Some kinds of forces are caused by collisions. If any tablets lamination, capping, or breaking in direction of the test. Friability loss is generally expressed in lack of weight in percentage. The limit of weight reduction isn't always extra than 1%. Calculated by Following equation –

$$\text{Friability loss (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}}$$

Thickness and Diameter

The thickness of the tablet is the simply layered variable connected with the tablet compression process and it's measured by micrometre (calibrated vernier calliper). The limit of thickness variation is ± 5%. 10 or 20 Tablets are picked from each batch measured by micrometer.

Hardness

Erweka Hardness is a tester to use for degree hardness. Erweka Hardness is a tester to use for measure hardness. 4-10 kg hardness for oral tablets. Newton (N), Pound (lb), Kilogram (kg), and Kilopond (kp) are units of measurement of tablet hardness.

Disintegration Test

Disintegration test is time required for tablet convert into disintegrants. It's measured by disintegrants apparatus. Randomly select 6 tablets and put into each 3 inches glass tubes placed into 900ml media with 37^{o}C ± 0.2^{o}C temp is maintained. The disintegration tablets pass the test after all tablets are breaks into the fine particles properly. [10]

Table 3
Coded value for Design of Experiment

Sr. No.	Name	Low (-1)	High (+1)
1	Lactose Anhydrous	-1	1
2	Cross-carmellose	3	3.75
3	MCC 112	-1	1

Table 4

Composition of design of Experiment Batches

Composition	Quantity in mg/tablet														
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Carbimazole	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Lactose anhydrous	-1	0	0	0	-1	1	-1	0	-1	0	1	1	1	0	0
Red iron oxide	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Microcrystalline cellulose	1	0	1	-1	0	1	0	0	-1	-1	0	-1	0	1	0
Citric Acid Anhydrous	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Cross-Carmellose	3	3	3.75	3.75	3.75	3	2.25	3	3	2.25	3.75	3	2.25	2.25	3
Pregelatinized Starch 1500	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.7
Silica colloidal anhydrous	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6

In-Vitro study
Dissolution study

Dissolution equipment used for dissolution take a look at the USP Dissolution Apparatus 2 (paddle) is at 50 rpm. 0.1 N HCl is dissolution media (500ml) for 60min and temperature are maintained at with 37^{o}C ± 0.5^{o}C. The time interval for product profile is 0,5,10,15, 20,30,45, and 60 mins and Recovery at 2 hundred RPM for profile. 10ml withdrawn and replace by clean media it occurs after every time interval. Sample is diluted with 0.1 N HCl after withdrawn, filtered and analysed on UV at 289nm using 0.1N HCl for blank. Then calculate the percent drug release.

Assay of Tablet
Preparation of carbimazole standard solution

25mg weight of carbimazole standard right into a 50 ml volumetric flask. Add 35 ml diluent and 15 min sonicate for dissolve. Then placed at room temperature for stable. Volume make-up and blend well. Pipette out the 5 ml of this Carbimazole Standard stock Solution to twenty-five ml volumetric flask and quantity make up.

Preparation of carbimazole sample solution

Weigh 20 tablets and take the average weight. Before crush the tablet smooth, clear and dry mortar and pestle and crush till the fine particle of powder. Weigh the sample powder equal to 50 mg of Carbimazole and switch it to 50 mL volumetric flask. Add 25 ml diluent via way of means of the usage of pipette and sonicate for 15 mins with intermittent shaking in cold water. Finally make up the extent with diluent. Maintained the temperature of sonicator at 15 ^{0}C-20 ^{0}C. Pipette out 3ml of this solution and transferred into 200ml volumetric flask with diluent. Sonicate for 15-20 min. Both preferred and sample solution are analyzed via way of means of UV spectrophotometer.

Similarity Factor

The f2 values had been decided for the examinations of each activity with the reference profile. The f2 is applied for in vitro disintegration profile examination. The states of the disintegration profiles ought not to be essentially unique. It is an estimation of the similarity in percentage (%) dissolution between two curves. The

limits of similarity factor are ≥50 and F2 factor are determined by following equation.

$$f2 = 50 \times \log \{\left[1 + \left(\frac{1}{N}\right)\sum_{i=1}^{N}(R_t - T_t)^2\right]^{-0.5} \times 100\}$$

When, N is the range of null points, Rt is reference product profile with time period t, Tt is the check product profile on the identical time point. For a disintegration profile to be thought of as comparative, the value of f2 ought to be somewhere in the range of 50 and 100. [9,18,19]

Results

Box-Behnken designs are used for carbimazole IR tablet. Some important response from summary of data is shown in Table 6.

Discussion

Impact of factors on Drug release
ANOVA Summary

The Model F-value of 5.44 that show the model is significant. There's solely a 3.84% probability that an F-value this large may occur because of noise. P-values under 0.0500 indicate that the model is significant. During this case, B2 could be a significant model term. Values larger than 0.1000 indicate the model terms aren't significant. If there are several in significant model terms (not tally those needed to support hierarchy), model reduction might improve your model. The lack of fit F-value of 22.50 implies the lack of fit is significant. There's only a 4.29% chance that an absence of fit F-value this massive may occur because of noise. Significant lack of fit is dangerous; we would like the model to fit.

Graphical Model

From Interaction Graph it was clear that AB interaction was significant. Spread of the points on the right side of the graph (where Lactose anhydrous Concentration is high) was smaller than the spread between the points at the left side of the graph (where MCC was low). In other words, the effect of MCC concentration was less significant at high level of Lactose anhydrous. Therefore, Experiment could run at higher Lactose anhydrous concentration and reduce MCC concentration.

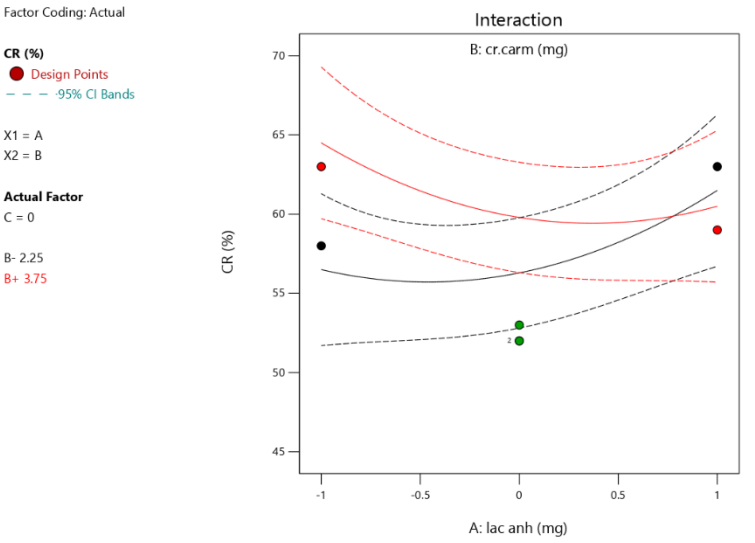

Figure 1. Interaction plot showing the impact of concentration A: Lactose anhydrous and B: cross-carmellose on drug release at 1 h from Carbimazole IR tablet

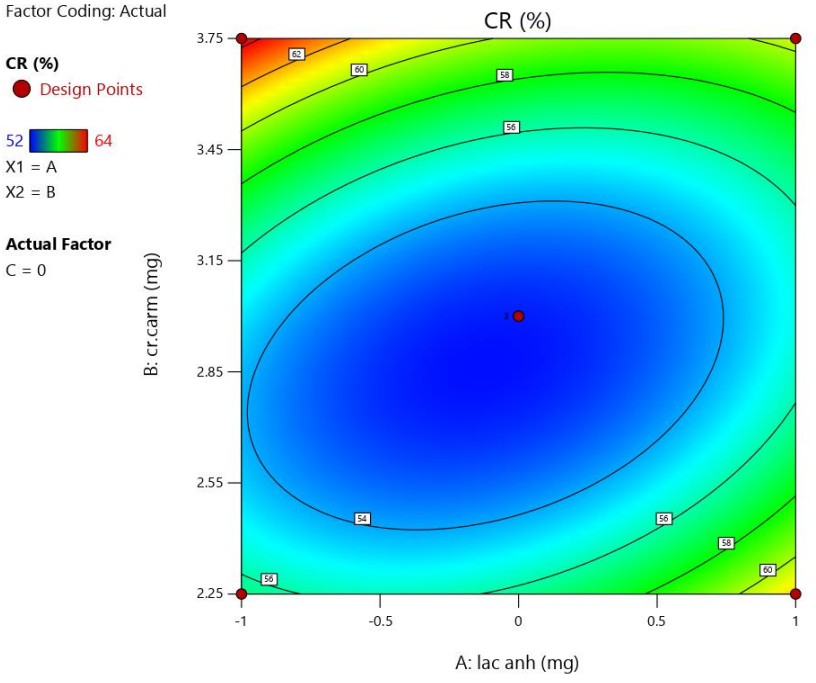

Figure 2. Contour plot showing the impact of concentration A: Lactose anhydrous and B: cross-carmellose on drug release at 1 h from Carbimazole IR tablet

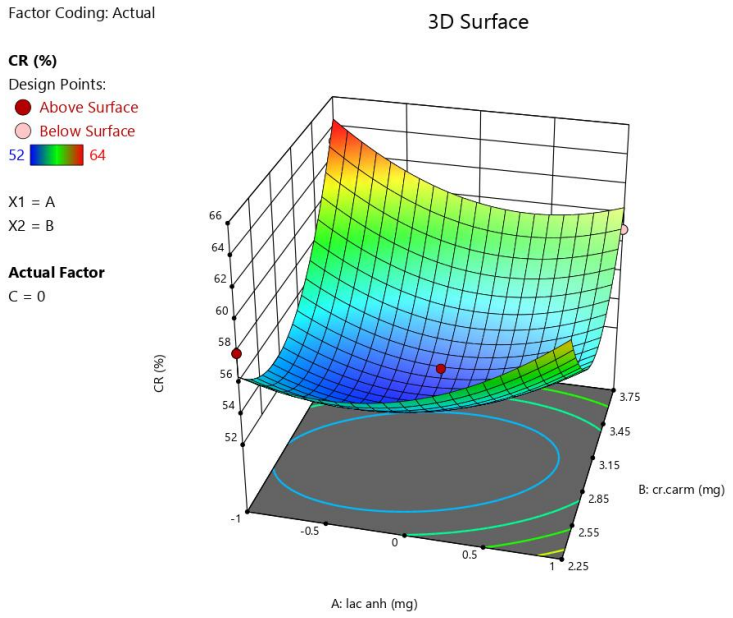

Figure 3. Response 3-D surface plot displaying the effect of concentration A: Lactose anhydrous and B: cross-carmellose on drug release at 1 h from Carbimazole IR tablet

Impact factor on Disintegration Time
ANOVA Summary

The Model F-value of 8.95 implies the version is significant. There is handiest a 1.33% chance that an F-value this huge may want to arise because of noise. P-values much less than 0.0500 suggest model phrases are significant. In this situation A^2, B^2, C^2 are big version phrases. Values more than 0.1000 suggest the version phrases aren't significant. If there are numerous in significant version phrases (now no longer counting the ones required to help hierarchy), version discount can also additionally enhance your model. The Lack of Fit F-value of 19.46 implies the Lack of Fit is significant. There is handiest a 4.93% danger that a Lack of Fit F-value this huge may want to arise because of noise. Significant lack of fit is bad we need the version to fit.

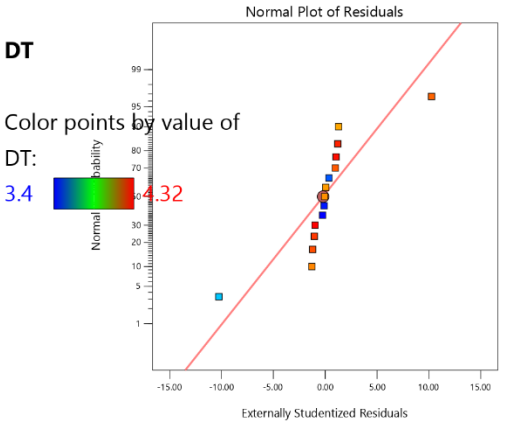

Figure 4. Interaction plot showing the impact of concentration A: Lactose anhydrous and B: cross-carmellose on Disintegration time of Carbimazole IR tablet

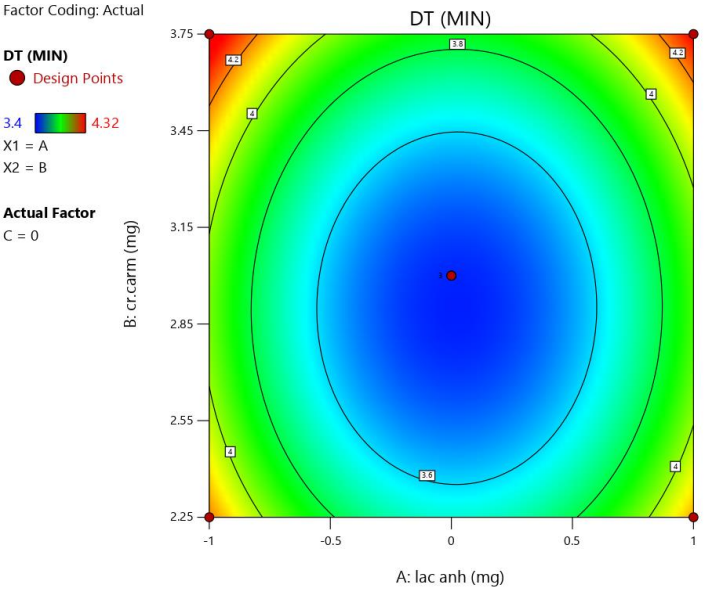

Figure 5. Contour plot showing the impact of concentration A: Lactose anhydrous and B: crosscarmellose on Disintegration time of Carbimazole IR tablet

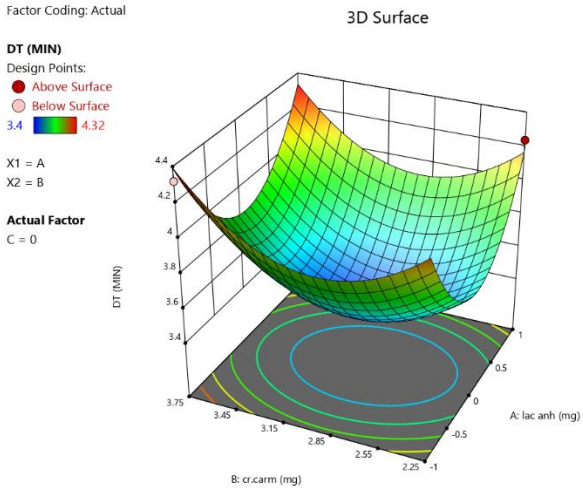

Figure 6. Response 3-D surface plot displaying the effect of concentration A: Lactose anhydrous and B: crosscarmellose on Disintegration time of Carbimazole IR tablet

Impact Factor on Friability
ANOVA Summary

The Model F-value of 6.30 implies the version is significant. There is most effective a 2.83% chance that an F-value this big ought to arise because of noise. P-values much less than 0.0500 suggest model phrases are significant. In this example B, A^2, B^2, C^2 are significant model phrases. Values more than 0.1000 suggest the model phrases aren't significant. If there are numerous insignificant model phrases (now no longer counting the ones required to help hierarchy), version discount might also additionally enhance your version. The Lack of Fit F-value of 25.61 implies the Lack of Fit is significant. There is best a 3.78% chance that a Lack of Fit F-value this big ought to arise because of noise. Significant lack of fit is bad we need the version to fit.

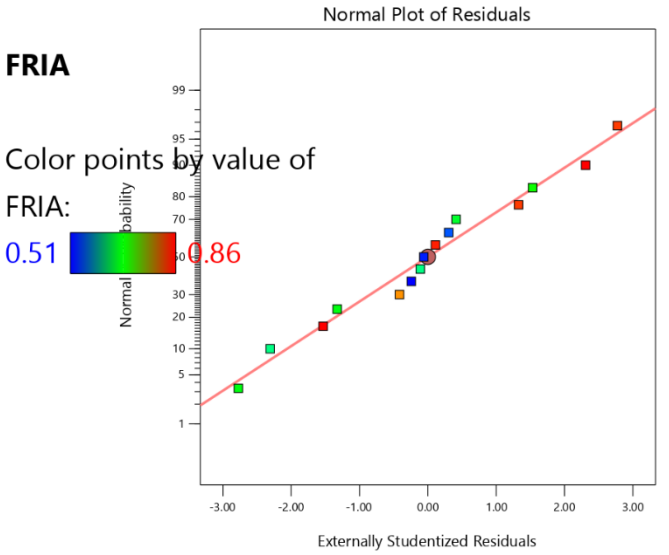

Figure 7. Interaction plot showing the impact of concentration A: Lactose anhydrous and B: crosscarmellose on Friability of Carbimazole IR tablet

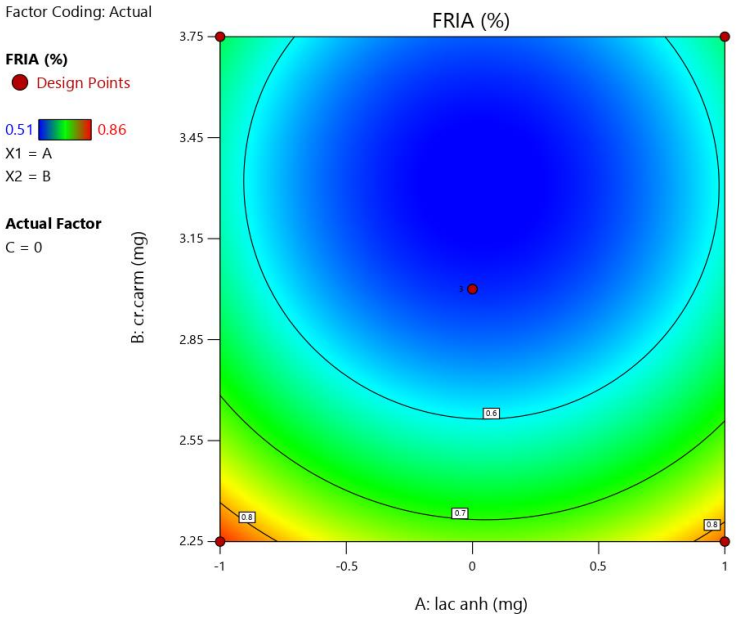

Figure 8. Contour plot showing the impact of concentration A: Lactose anhydrous and B: crosscarmellose on Friability of Carbimazole IR tablet

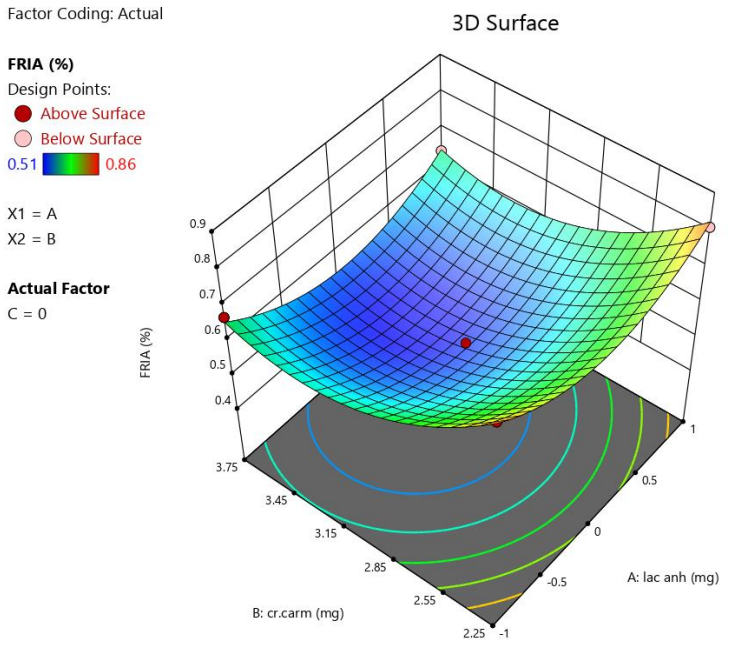

Figure 9. Response 3-D surface plot displaying the effect of concentration A: Lactose anhydrous and B: crosscarmellose on Friability of Carbimazole IR tablet

Evaluation of Optimized batches

F6 batch was found to be optimized batch from the DOE study with F2 factor of Drug was 64%.

Evaluation of IR Granules

Table 5
Evaluation of Carbimazole IR Granules

Sr. No.	Parameter	Results of optimized F6 Batch
1	Bulk density	0.58
2	Tapped density	0.69
3	Compressibility index (%)	15.94%
4	Hausner's ratio	1.18
5	LOD	2.02%
6	Angle of repose	32°57' (Good)

Compressibility index of IR granules was found to be 15.94%. Hauser's ratios are fond to be 1.18 and these values are within the range. Therefor these values are indicating that IR granules are good flow ability properties.

Table 6
Design of experiment and responses for Carbimazole IR Tablet

Std	Run	Factor1 A: Lactose Anhydrous Mg	Factor2 B: Cross-carmellose Mg	Factor3 C: MCC Mg	Response1 Cumulative Release %	Response2 DT Min	Response3 Friability %
7	1	-1	3	1	53	4.2	0.68
14	2	0	3	0	52	3.42	0.52
12	3	1	3	1	59	4.27	0.68
10	4	0	3.75	-1	63	4.19	0.64
3	5	-1	3.75	0	63	4.32	0.67
8	6	0	3.75	1	64	4.23	0.69
1	7	-1	2.25	0	58	4.29	0.85
13	8	0	3	0	52	3.48	0.54
5	9	-1	3	-1	61	4.31	0.84
9	10	0	2.25	-1	57	3.58	0.86
4	11	1	3.75	0	59	4.25	0.64
6	12	1	3	-1	56	4.17	0.84
2	13	1	2.25	0	63	4.24	0.81
11	14	0	2.25	1	57	4.18	0.86
15	15	0	3	0	53	3.4	0.51

In vitro studies
Dissolution

Dissolution studies of immediate release Carbimazole tablet were carried out in 500ml of 0.1 N HCl in paddle apparatus (USP Type-2) at 50 rpm and 370C ± 0.50C. Cumulative Drug release product profile of F6 batch shown in figure 10

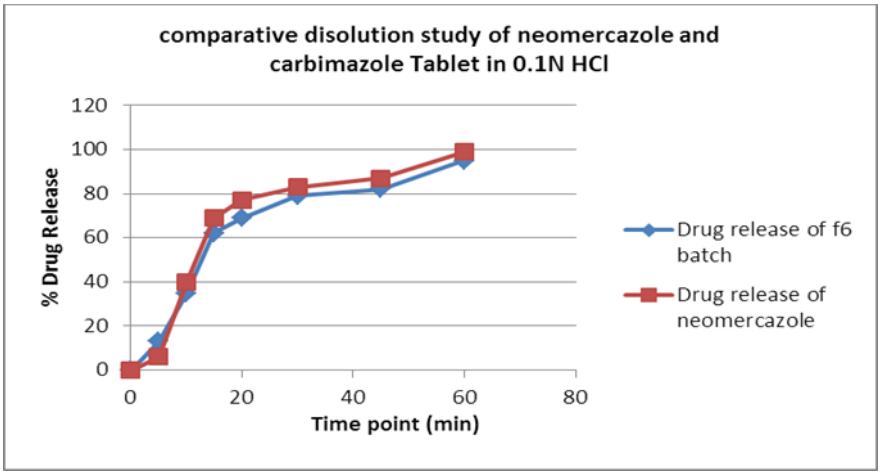

Figure 10. Comparative dissolution study of marketed product and carbimazole tablet

Comparative % drug release of optimized batch (F6) with Innovator product

Comparative Dissolution investigation of improved batch (f6) and marketed item were done. It was found that carbimazole drug release product profile IR released tablet show comparative with marketed product.

Conclusions

The current study epitomizes the use of unified QbD approach for effective development of an IR carbimazole tablet. The successful tablet developed by using Box-Behnken designs with lactose anhydrous, mcc, magnesium stearate these are the factor used in Design of experiments. These ingredients are not reacting with other ingredients. Cumulative release, disintegration time, friability are responses and in anova study models are significant. From the outcome it was obviously clear that factor Concentration builds the disintegration time. The development of optimized batch from Box-Behnken design can be used as 5-15 mg per day it's all depend on their response towards hyperthyroidism.

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