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FORMULATION DEVELOPMENT AND EVALUATION OF HERBAL TABLET OF *OUGEINIA OOJEINENSIS, FABACEAE* BARK EXTRACT USING QBD APPROACH

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Abstract:

Ougeinia oojeinensis, *Fabaceae* commonly known as Tinsa, its bark is used to treat various ailments in folk medicine. In this study QbD approach was applied to obtain optimized formulations of directly compressible tablets of *Ougeinia oojeinensis*, *Fabaceae* ethanolic bark extract. To do this, risk assessment as part of QbD was conducted to identify the critical quality attributes (CQAs) from the quality target product profile (QTPPs). The 3^2 factorial design model was used to optimize the tablet formulation using Design Expert software version 12. The nine number of trial batches of tablet was prepared. The tablets were evaluated for various physical properties like hardness, friability, weight variation etc. and various mechanical properties like disintegration time, *in vitro* dissolution study. The optimized formulation was subjected to *in vitro* antidiabetic activity which results were comparable to standard.

***Index Terms* - *Ougeinia oojeinensis*, herbal tablets, direct compression, *in vitro* antidiabetic activity, QbD.**

I. INTRODUCTION

The Quality by Design (QbD) concept in pharmaceutical development has evolved as a systematic method of development strategy offering several benefits, such as high-quality drug products with operational flexibility within optimized ranges of critical factors, regulatory flexibility in drug product application approvals, and post-approval change management. QbD is a systematic step-by-step approach that begins with predefined objectives in the form of a quality target product profile (QTPP), profound drug product formulation and manufacturing process understanding, and process controls based on sound science and quality risk management principles. The identification and optimization of critical material attributes (CMAs) and critical process parameters (CPPs) for the development of design space (DS) through a systematic series of design of experiments (DoE) (Simao et al., 2023). By using QbD approach in the preparation of herbal tablets by direct compression, it is possible to obtain optimum formulation of the herbal tablets which will pass the required tests for quality. Direct compression presents many advantages over other tablet manufacturing methods such as wet granulation and dry granulation methods because it is less costly and less time consuming. It also overcomes the problem encountered in the compression of some drugs into tablets that are prone to degradation when subjected to heating (Ladignon et al., 2020).

Ougeinia oojeinensis (Roxb.) Hochr belongs to the *Fabaceae* family and in Hindi it is known as Tinsa. The reported chemical constituents present in *Ougeinia oojeinensis* plant are lupeol, hydroxlupeol, betulin and isoflavanones such as dalbergioidin, homoferreirin and ougenin. The traditional healers of Chhattisgarh state prescribed *Ougeinia oojeinensis* in the treatment of various diseases such as inflammation, jaundice, diabetes, skin diseases, leprosy etc. Apart from this many researchers worked on different parts of *Ougeinia oojeinensis*, *Fabaceae* and reported their various pharmacological activities. *Ougeinia oojeinensis* bark has been found to have hypoglycemic and hypolipidemic properties which were evaluated on alloxan induced diabetic rats. Bark extract was given orally at a dose of 200 mg/kg for the hypoglycemic activity. Extract also reduces the elevated biochemical parameters like triglyceride, low density lipoprotein, total cholesterol etc. (Tiwari et al. 2020; Samyal et al., 2014; Velmurugan C et al., 2011).

In this research, QbD was applied in the preparation of tablets from the bark extract of *Ougeinia oojeinensis*, *Fabaceae* by direct compression method. As it would be an advantage to make these herbal drugs readily available in tablet form as a potential treatment modality for diabetes mellitus. According to the International Diabetes Federation-2019 estimates, India is home to 77 million diabetic individuals which is projected to grow up to 147.2 million by 2045. Diabetes being a progressive health disorder leads to multiple morbidities and complications (Pradeepa R. and Mohan V., 2021).

Before the extract was subjected for the formulation preparation, preliminary phytoconstituents tests, antioxidant (DPPH) assay were carried out on extract.

II. MATERIALS AND METHODS

2.1. Collection and authentication

Ougeinia oojeinensis bark was procured from the supplier Trustayur and further authenticated.

2.2 Extraction

Coarsely powdered bark of the plant *Ougeinia oojeinensis*, *Fabaceae* was extracted by Hot percolation method with Ethanol at 60-70°C. Extract of bark was concentrated using a rotary vacuum evaporator and then finally kept in a water bath to evaporate the remains of solvents in the extract.

2.3. Preliminary Phytochemical Analysis of Extract

The bark extract are subjected to Preliminary Phytochemical Screening for detection of the alkaloids, steroidal chemicals, phenolic compounds, flavonoids, saponins, and tannins, etc. (Rai D. and Soni V., 2021).

2.4. In vitro antioxidant activity

To demonstrate the antioxidant characteristics of extract, DPPH assay (2, 2-Diphenyl-1- picrylhydrazyl) was performed. DPPH assay was performed using 2 mg/ml stock concentration of extract and standard ascorbic acid and proceeded with further dilutions. After that, the test tubes were kept in complete darkness for 30 min. The change in color and absorbance with change in concentrations was evaluated with UV visible spectroscopy at 517 nm (Baliyan et al., 2022).

The following formula was used to compute the percentage of antioxidants

Radical Scavenging activity (%) = A0 −A1 / A0 × 100

Whereas, A0 - Absorbance of DPPH radicals with methanol

A1- Absorbance of DPPH radicals with sample extract or standard

2.5. QbD Approach (Rahul Koli et al., 2022)

2.5.1. Quality Target Product Profile (QTPP) for Herbal Tablets

The Quality Target Product Profile (QTPP) as pretended in International Council for Harmonization (ICH) Q8 is a vital element of a QbD approach. All product features required for comparable safety and efficacy are included in the QTPP (Zeng JQ et al., 2019). QTPP for herbal Tablet has been developed by considering the dominant drug product quality attributes specifications.

2.5.2. Critical Quality Attributes (CQA)

"A physical, chemical, biological, or microbiological feature or characteristic that should be within an appropriate limit, range, or distribution to ensure the destined product quality" that's a critical quality attribute (CQA) (Lo HW et al., 2019). To discern sufficient product quality, the initial CQAs were defined utilizing QTPP. The typical CQAs of excipients requisite for the creation of Herbal tablets were identified as having a minimum disintegration time of NMT 15 minutes and a maximum hardness of 3-5 kg/cm^2 with a friability of less than 1%.

2.5.3. Risk assessment

To identify all the probable high-risk factors for further study, risk assessment was conducted. Risk Priority Numbers (RPN) were mapped onto three categories during the risk assessment process (high, medium and low). The initial risk assessment for critical input material and formulation components and their impact on the product quality was determined (Pandey AK et al., 2021).

2.5.4. Design of Experiment

The 3^2 full factorial design was applied to the formulation design of the herbal tablets. The two different factors are evaluated in this design at three different levels (table 5.1.). The two independent variables (CQAs) selected are (SSG) sodium starch glycolate (disintegrant) and (MCC) microcrystalline cellulose (binder). There are three different levels for the selected variables as low, intermediate, and high, and they are coded as − 1, 0, and + 1, respectively. The responses are considered as dependent variables, and they are hardness, friability, and disintegration time of the designed and formulated herbal tablets. The software Design Expert version 12 (Stat-Ease) was used for the design of the formulation. The total of 9 runs (formulations) were designed and the relationship of the dependent and independent variables was studied by gaining the surface responses, and finally, the significant model was achieved (Balekundri A. et al., 2020).

2.5.5. Formulation Development of Tablet

The tablets were prepared by direct compression method. The ingredients included were the Powdered bark extract as the active ingredient, sodium starch glycolate (SSG) as disintegrant, microcrystalline cellulose (MCC) as binder and magnesium stearate as lubricant and talc as filler/glidant as shown in table 5.2. The drug concentration used in the formulation was calculated on the basis of their drug tolerance study and effective dose on animal models (Nair et al., 2016). In tablet formulation the drug content per tablet was 200mg. Prior to compression, all the ingredients were sieved using 60 no. mesh. The powder blends were subjected to pre compression evaluation tests, then compressed using a Rimek mini press tablet machine.

1. Independent levels:

Sodium starch glycolate(X1)

Microcrystalline cellulose (X2)

2. Dependent levels:

Hardness (Y1)

Friability (Y2)

Disintegration time (Y3)

Table 5.1.: Levels of independent variables in the tablet design

	Codes Level		Actual mg	
Codes	**X1**	**X2**	**X1(SSG)**	**X2(MCC)**
F1	-1	-1	46	30
F2	-1	0	46	32.5
F3	-1	+1	46	35
F4	0	-1	53	30
F5	0	0	53	32.5
F6	0	+1	53	35
F7	+1	-1	60	30
F8	+1	0	60	32.5
F9	+1	+1	60	35

Table 5.2.: Formula table

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Extract	200	200	200	200	200	200	200	200	200
SSG	46	46	46	53	53	53	60	60	60
MCC	30	32.5	35	30	32.5	35	30	32.5	35
Magnesium stearate	6	6	6	6	6	6	3	3	3
Talc	18	15.5	13	11	8.5	8.5	7	4.5	2
Total weight (mg)	300	300	300	300	300	300	300	300	300

2.5.6. Pre-Compression Evaluation of Powder Blends

After mixing the ingredients and before compression several tests were done according to the established reference procedure to evaluate the powder blends named loose bulk density, tapped bulk density, Carr's index, Hausner's ratio and Angle of Repose (Lachman L et al.).

2.5.7. Post Compression Evaluation of Formulated Tablets

Weight variation of the tablets were evaluated using an electronic balance. 20 tablets of each formulation were considered for this test according to the official method. Also, hardness, thickness, disintegration and friability of the formulated tablets (six tablets of each formulation) were performed according to compendial method using Monsanto tablet hardness tester, Vernier caliper, friability test apparatus of M/s Roche Friabilator and Disintegration test apparatus (Lachman L et al.).

2.5.8. Statistical Optimization

The evaluation for tablet formulation of the quality of fit of the model was executed by using analysis of variance (ANOVA) technique. Based on comparison of several statistical parameters the best fit model was selected, DOE program supplied statistical parameters such as the R^2 coefficient of determination, SS-sum of squares, Adjusted R^2 , MS-mean of square, F-value-ratio, Fischer's DF-degrees of freedom, and p-probability. Response surface plots, such as Contour and 3-D surface plots, would be used to demonstrate the relationship between the dependent and independent variables. Finally, a graphical optimization technique was used to find the best Formulation (overlay plot) (Koli r. et al., 2022).

2.6. *In-vitro* α amylase activity on optimized batch of tablet

α-amylase was dissolved in phosphate buffer saline (pH 6.8) at a concentration of 0.1mg/ml. Various concentrations of tablet solutions (0.25 ml) were mixed with α-amylase solution (0.010 ml) and incubated at 37 °C for 5 min. Then the reaction was initiated by adding 0.1 ml 1.0% (w/v) starch substrate solution to the incubation medium. After incubation at 37 °C for 3 min, the reaction was stopped by adding 1 ml DNS reagent (1% Dinitrosalicylic acid, 0.05% Na_2SO_3 and 1% NaOH solution) to the reaction mixture and boiling at 100 °C for 5 min. After cooling to room temperature, the absorbance at 540 nm was recorded by a spectrophotometer (Vijayalakshmi P. 2018).

The inhibition percentage was calculated by the following equation:

Inhibition (%) = [(Abs1 − Abs2)/Abs1] × 100

Where, Abs1 = sample and Abs2 = control.

2.7. *In-vitro* dissolution study

In-vitro dissolution study was performed for an optimized batch obtained using DoE. Study was carried out in the USP dissolution test apparatus, type 2 (paddle) for 2 hrs. 900 ml of the dissolution medium phosphate buffer with 2% of SLS pH 6.9 was taken in the vessel and the temperature was maintained at 37±0.5 °C. Dissolution samples were withdrawn at different time intervals and analyzed for drug content by using UV spectrophotometer at 282 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved (Chowdary et al., 2014).

III. RESULTS AND DISCUSSION

3.1. Preliminary Phytochemical Analysis of Extract

Ethanol proves to be the universal solvent. Ethanol was chosen for the extraction as it will not lead to spoilage. Also, evaporation time will significantly be lesser. Based on the phytochemical screening tests performed (Table 3.1), presence of alkaloids, saponins, carbohydrates, flavonoids, phenolic compounds, steroids, tannins were confirmed for extract, while glycosides and proteins were absent. Steroids, tannins, phenolic compounds and flavonoids are believed to be the compounds responsible for antidiabetic properties (Rai D. and Soni V. 2021).

Table 3.1.: Results for phytochemical testing

Phytoconstituents	Result
Alkaloids	Present
Saponins	Present
Carbohydrates	Present
Flavonoids	Present
Phenolic compounds	Present
Steroids	Present
Glycosides	Absent
Tannins	Present
Protein	Absent

3.2. Antioxidant activity (DPPH method)

DPPH scavenging activity of the extract was carried out with ascorbic acid as the reference standard. Concentration range 20–100 µg/ml was selected, and the solutions of both sample and standard used were prepared freshly. The response of the activity showed there was an increase in response with increase in concentration in the selected range. The results are shown in Fig 3.1.

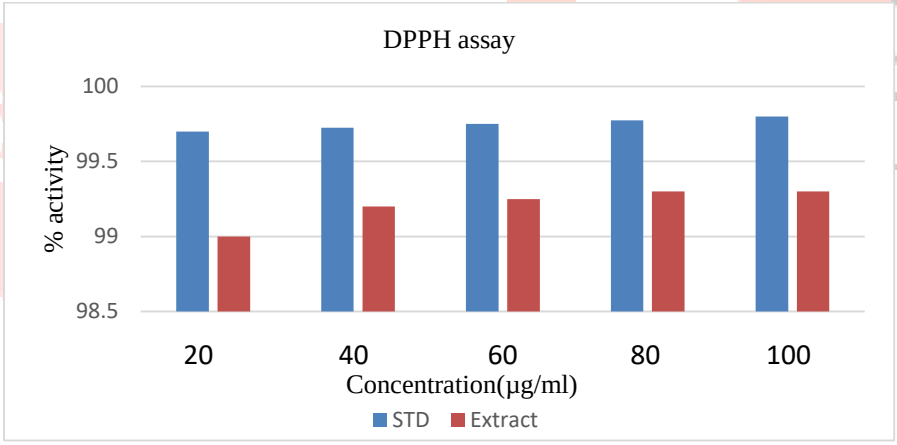

Fig. 3.1.: Results for antioxidant activity

3.3.1. QTPP, CQAs, and CPP`s

The QTPP is a list of quality attributes for a drug product that must be met in order for it to be safe and reliable. The QTPP for Herbal tablet includes the dosage form, dosage design, method of administration, dosage strength, drug product quality features, container closing mechanism, and storage conditions. (Table 3.2).

Table 3.2: QTPP for Herbal tablet.

QTTP elements		Target	Justification
Dosage form		Tablet	For patient acceptability
Dosage design		Conventional release tablet	For patient compliance
Route of administration		Oral	The dosage form is designed to be administered orally
Dosage tolerance		200 mg	Therapeutic dose
Drug product quality attributes	Appearance	The form and size of the tablets fits the description	Patient appropriateness & tractability
	Hardness	3-5kg/cm^2	As per Pharmacopoeial specifications
	Disintegration time	NMT 15mins	
	Friability	NMT 1%	
Container closure system		The container closure system qualified as a suitable product	To meet the target shelf-life and maintain tablet integrity throughout storage
Storage condition		Store in air-tight container in a cool place	Preserving the quality and integrity of the product throughout storage

Table 3.3: CQA's for Herbal tablet

Quality attributes of drug product		Target	Is this a CQA?	Justification
Physical attributes	Appearance	Tablet confirming to description shape and size	No	Colour, shape and appearance are not directly linked to safety, quality and efficacy
	Taste	Bitter	No	The taste is not directly linked to safety and efficacy, but the taste can affect patient acceptability.
Hardness		3-5 kg/cm^2	Yes	To resist damage during handling, packaging, shipping and also soft enough to disintegrate properly
Disintegration time		NMT 15 mins	Yes	Failure to disintegration time directly impact dissolution and lead to affect efficacy
Friability		NMT 1%	Yes	In order to meet Pharmacopoeial specification.

The initial CQA's were defined from QTPP to identify adequate quality profile of the product. Table 6 condenses the critical quality attributes (CQAs) of Herbal tablet formulation along with justification for criticality of these selected quality attributes. Hardness (Y1), Friability (Y2) and Disintegration time (Y3) were regarded as CQAs of the formulation of Herbal tablets. (Table 3.3).

In order to satisfy the quality target product profile (QTPP), an initial risk assessment of drug substance (herbal extract) and formulation variables (excipients) was conducted. The initial risk assessment and rational argument for formulation factors are summarized in (Table 3.4).

Table 3.4: Justification for the formulation variables preliminary risk assessment.

Formulation variables	Drug product CQA	Justification
SSG level	Disintegration time	The SSG is used as disintegrant; increase or decrease in SSG level can have a high impact on disintegration time. Risk is high.
	Hardness	A higher level of SSG can decrease the Hardness of the tablet. Risk is medium.
	Friability	More SSG can increase the friability of tablets. Risk is medium.
MCC level	Disintegration time	Increase or decrease in MCC level can have an impact on disintegration time via tablet hardness. Risk is high
	Hardness	MCC is used as a binder, an increase or decrease in MCC level can have an impact on hardness and friability. Risk is high.
	Friability	
Magnesium stearate	Disintegration time	Since magnesium stearate is used in very low amount, it has no impact on hardness, disintegration time as well as friability.
	Hardness	
	Friability	
Talc	Disintegration time	Talc has less impact on disintegration. It is not anticipated that the small amount of talc in the formulation would affect disintegration. Low risk exists.
	Hardness	Talc is used as filler; it has no impact on tablet hardness as well as friability. Risk is low
	Friability	

3.3.2. Pre-compression evaluation of powder blends of DoE batches

In the formulation of the herbal tablets, the pre-compression parameters performed were angle of repose (θ), loose bulk density (g/ml), tapped bulk density (g/ml), Carr's Compressibility Index, and Hausner's ratio. For the better compression of the tablet, it is important that the pre-compression parameters show a better response. The response reveals the flow properties, and compressing properties. Data of the pre-compression parameter is presented in Table 3.5.

Table 3.5: Results for pre compression parameters of blend

PARAMET-ERS	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%w/w)	Hausner's Ratio	Angle of repose (degrees)
F1	0.701±0.001	0.794±0.005	11.7±0.2	1.13±0.122	33.69±0.101
F2	0.739±0.004	0.782±0.005	5.49±0.52	1.05±0.011	29.24±0.06
F3	0.683±0.004	0.729±0.008	6.31±0.04	1.06±0.011	29.74±0.404
F4	0.675±0.005	0.760±0.034	11.1±0.26	1.12±0.055	30.37±0.125
F5	0.675±0.013	0.739±0.044	8.66±0.51	1.09±0.051	28.61±0.137
F6	0.739±0.038	0.771±0.037	4.15±0.26	1.04±0.026	29.74±0.404
F7	0.658±0.067	0.739±0.004	10.96±0.89	1.12±0.119	33.17±0.015
F8	0.666±0.02	0.771±0.041	13.61±0.33	1.15±0.06	35.13±0.334
F9	0.675±0.004	0.771±0.042	12.45±0.63	1.14±0.051	34.60±0.258

Fig. 3.2.: Formulated Tablets

The formulated tablets were brown in colour and had a round shape with characteristic odour (fig 3.2). It is bitter in taste.

3.3.3. Post-compression evaluation of tablet of DoE batches

Post compression parameters are the quality control aspect of the compressed tablet. Variation in the ratio of binder and disintegrant is responsible for the variation in response of hardness, friability, and disintegrations. The other quality control parameters reported are thickness and weight variation. Collective results of post-compression are shown in Table 3.6.

Table 3.6: Results for post compression parameters of tablets

Parameters	Weight variation (%)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (mins)
F1	4.99	4.01	3	0.99	15.05
F2	4.97	4.02	3.2	0.92	13.54
F3	5	4.02	3.5	0.96	11.11
F4	5.02	4.04	2.9	1.00	12.57
F5	4.97	4.01	3	0.918	9.35
F6	5.04	4.04	3.3	0.98	9.57
F7	5.02	4.01	2.5	1.07	6.07
F8	5	4.02	2.8	0.97	5.23
F9	4.97	4.02	3	1.02	2.15

3.3.4. Design of experiment

The Design Expert 12 software is used in the present study for the formulation design. The 3^2 factorial design is applied where two independent variables are selected, binder (microcrystalline cellulose) and disintegrant (sodium starch glycolate), which have three different levels, low (−1), intermediate, (0) and high (+1), which are considered. Based on these variables, nine different formulations are designed with varying ratios of the binder and disintegrant. The results obtained by conducting evaluation parameters of tablets are added to the software DoE for obtaining the results for model significance. The responses are recorded in the form of hardness, friability, and disintegrant for all the nine formulations .The response data is shown in the Table. 9 and response surfaces are shown for hardness (Fig. 3.3), friability (Fig. 3.4), and disintegration time (Fig. 3.5). Increase in binder will increase the hardness and decrease in the friability; and disintegration time will increase. Increase in the concentration of disintegrant will reduce the disintegration time and decrease the hardness level. Hence, the optimum ratio of the binder and disintegrant is required. The formulation F5 shows the optimum ratio. The DoE surface response of all Y1, Y2, and Y3 showed that the model was significant as the p value was less than 0.05% (table. 3.7) and the overlay plot (Fig. 3.6) of the trials shows that formulation F5 satisfies all the criteria better among all the nine formulations and is further considered for investigation.

Table 3.7: Statistical optimization of tablets

Response	Sum of squares	DF	Mean square	p value	R^2	Model
Y1(Hardness)	0.6533	2	0.3267	0.0001	0.9671	Significant
Y2(Friability)	0.0178	5	0.0036	0.0067	0.9841	Significant
Y3(Disintegration time)	134.50	2	67.25	0.0002	0.9399	Significant

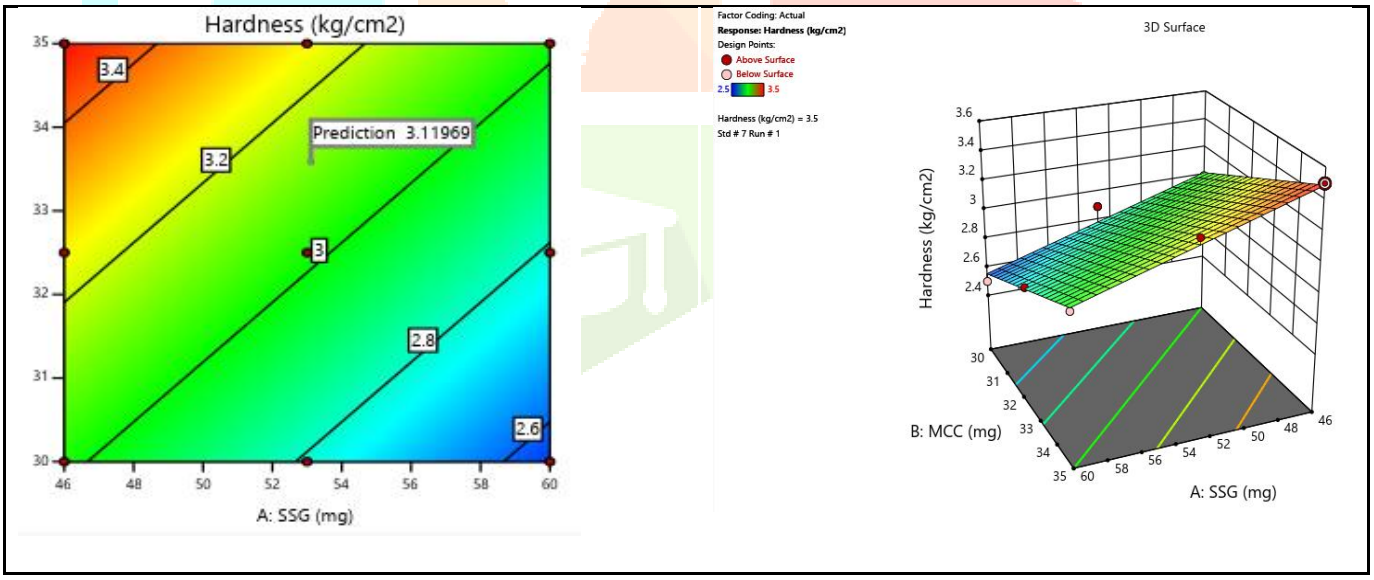

Fig. 3.3: Hardness response

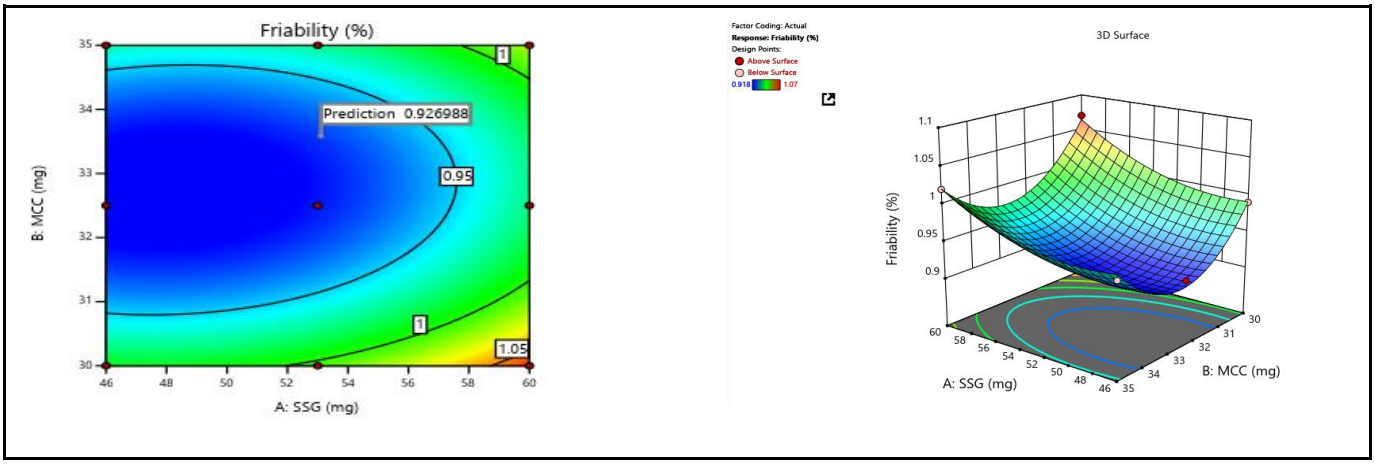

Fig. 3.4: Friability response

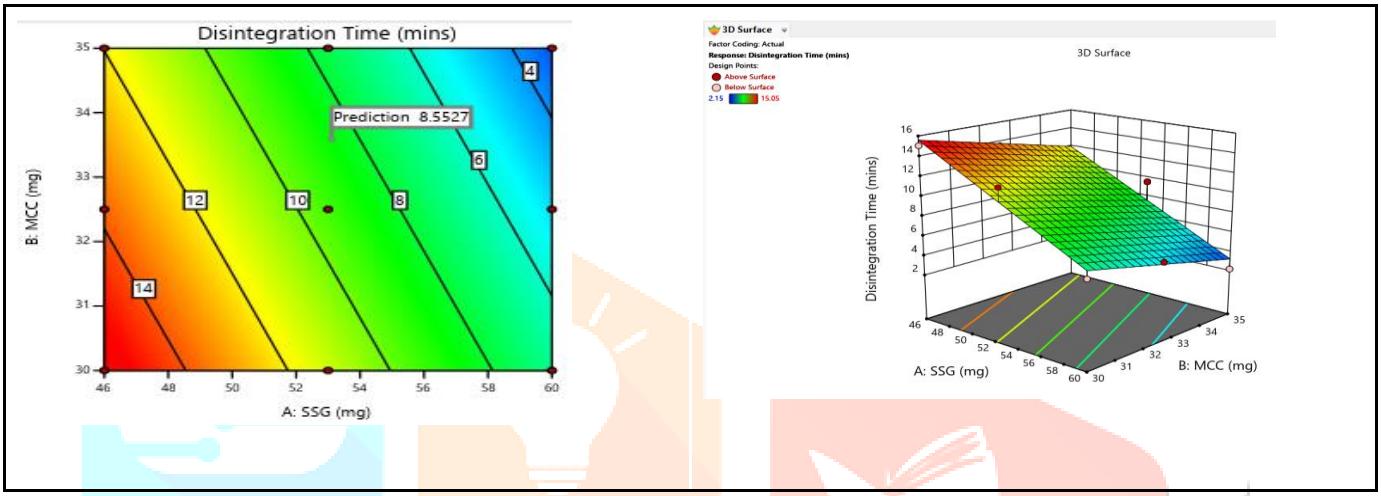

Fig. 3.5: Disintegration time response

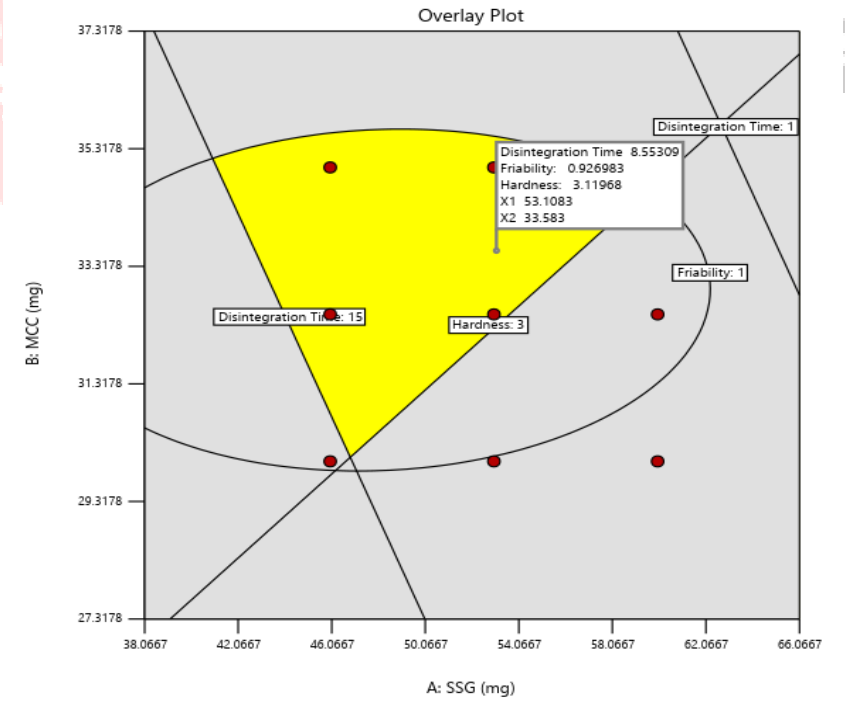

Fig. 3.6 Overlay plot for Tablet Formulation

3.4. *In vitro* α amylase activity on optimized tablet batch

In vitro anti-diabetic activity was done by using the α-amylase inhibition assay method. Tablets possess significant anti diabetic activity as compared to standard Acarbose.

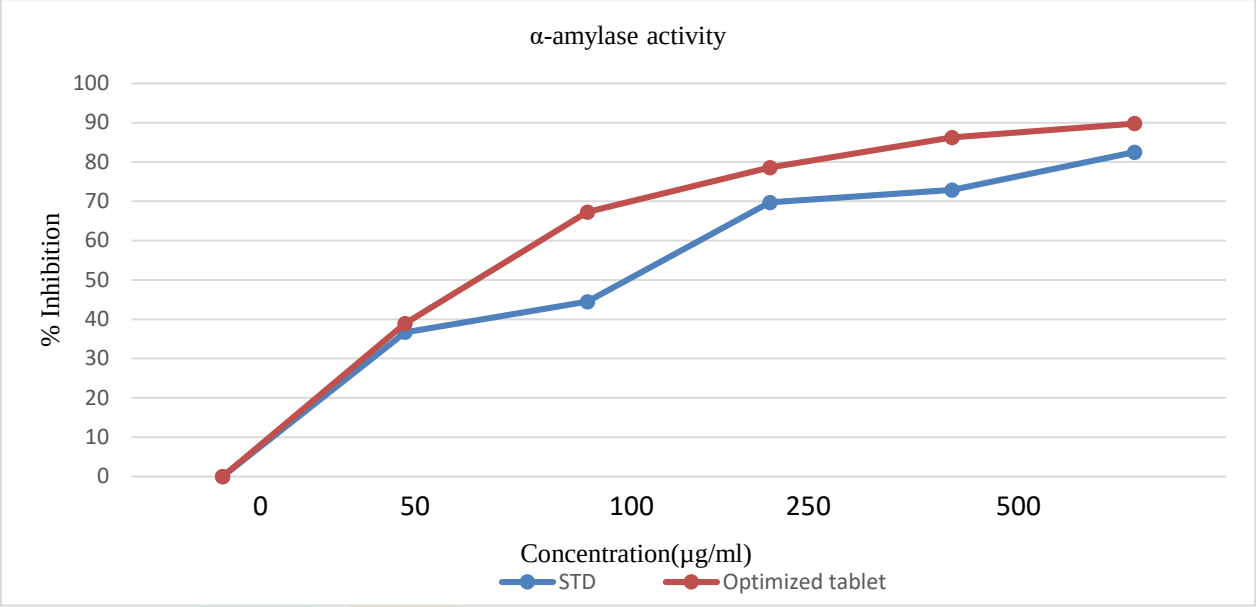

Fig. 7: In vitro Anti-diabetic activity of optimized tablet compared to standard

3.5. *In-vitro* dissolution study

The dissolution study was done for an optimized batch of Ougeinia oojeinensis extract tablets. The % cumulative release at 120 minute time interval of extract tablets was found to be 93.64%. This revealed that the F5 tablet batch showed a linear drug release profile.

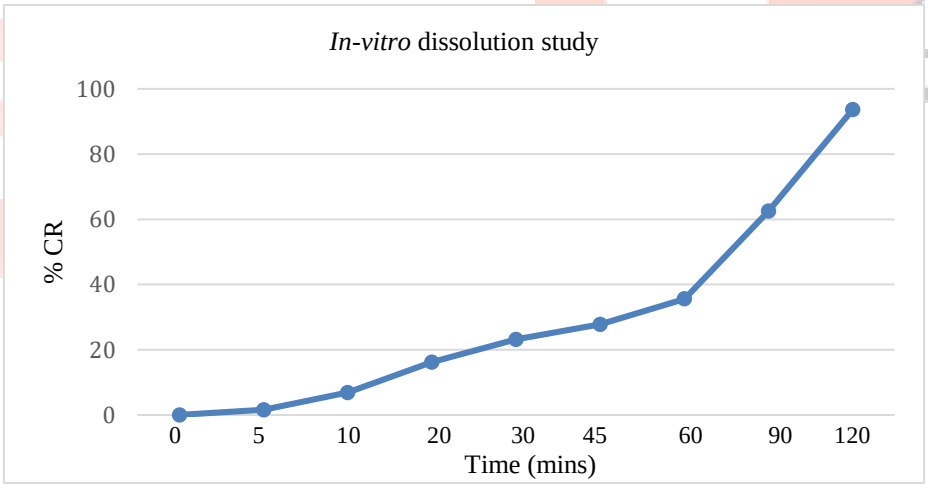

Fig. 8: % Cumulative Release of optimized tablet

IV. CONCLUSION:

The current study describes the successful implementation of a QbD approach in order to certify a good compassion of the manufacturing process, as well as to optimize the formulation of Herbal tablets. As a means of obtaining the end product with the appropriate quality, the desired QTPP and CQA's were predetermined. The main objective of the study was to formulate herbal tablets from ethanolic extract of *Ougeinia oojeinensis*, *Fabaceae* bark. It shows the presence of various phytoconstituents which imparts the medicinal value. The DPPH assay results showed the presence of antioxidant property comparable to the ascorbic acid. The 3^2 factorial design was applied by using the design of experiment software, and the 9 different formulations for tablets were prepared with variation in disintegrating agent and binding agent ratios. The powder blend of F5 formulation passed flow properties and showed an excellent compressibility index, angle of repose; and showed promising results for hardness, friability and Disintegration time. From the experiments, it can be concluded that if formulation parameters were operated within the suggested design space, high risk can be converted to low level of risk. Further, optimized batch of tablets have shown great antidiabetic activity when compared to standard acarbose. Based on the study results it can be concluded that *Ougeinia oojeinensis* bark extract can be effectively formulated in the form of tablets with expected patient compliance.

V. ACKNOWLEDGEMENT

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VI. CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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