DOI: 10.55522/jmpas.V11I6.4520 ISSN NO. 2320–7418

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Research article

Development of directly compressible polyherbal tablets by using QbD approach a novel immunomodulatory material

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ABSTRACT

A Quality by Design (QbD) strategy was used to develop and optimise a polyherbal tablet formulation in this study. Initial risk assessments of critical materials were conducted using the Risk Priority Number, and the effects of critical parameters (amount of microcrystalline cellulose and croscarmellose sodium) were proposed using a randomised complete factorial design. To further the findings, a Design of Experiments (DoE) approach was used to formulate four trial formulations, with independent variables of microcrystalline cellulose (MCC) 5 % -15 % and croscarmellose sodium (CCS) 0.5 % -5 %, and responses measured in friability and disintegration time, which were found to be 0.35–0.91 % and 11.4–15.5 minutes, respectively. Three formulations (F-1, F-2, and F-4) fulfilled the acceptable criteria and one formulation (F-1) had independent variables microcrystalline cellulose and croscarmellose sodium, out of four formulation trials (F-1 to F-4) were chosen for short-term stability study due to their better disintegration and friability profiles. The formulation factors X1: microcrystalline cellulose and X2: croscarmellose sodium were found to have a substantial impact on the responses Y1: Disintegration time (min) and Y2: Friability (%). This study proved that using quality by design to analyse quality characteristics and optimise polyherbal tablet formulation gives better results.

Keywords: Quality by Design, Polyherbs, Tablet, Direct compression, Immuno-modulator.

Received - 02-11-2022, Accepted- 11-12-2022

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INTRODUCTION

Since the ancient times, around 80% of human population in the world relies on ayurveda or herbal for their essential medical requirements. treatment of many diseases and disorders with phytomedicines is considered and observed as very safe with no or minimal side effects. Many medicinal plants and their preparations are practised at home as remedies for treating and preventing various diseases and disorders. For example, medicinal plants and their crude parts such as Ashwagandha, Guduchi, Licorice and Pippali are used to cure or treat several common ailments [1]. Herbs have been an integral part of society since the beginning of human civilization. They have been used both because of their culinary as well as features of medicinal value Herbal medicine has provided numerous benefits to the pharmaceutical industry [2].

Around 500 therapeutic plants have been referenced in ancient literature, and around 800 plants have been utilised in indigenous medical systems [3]. Herbal medications, often referred as plant materials or herbals, are used to alleviate injuries or illnesses by using whole plants or segments of plants [4].Herbal medications are defined by the World Health Organization (WHO) as "complete, labelled medical products incorporating significant chemicals, aerial or secretive components of the plant, or other plant material or mixtures" [5].The World Health Organization implements precise rules for evaluating herbal medication adherence, efficacy, and quality. On April 21, 2022, the new WHO worldwide centre for traditional medicine was launched in Jamnagar, Gujarat, India [6].

In 2020, the global market for herbal ayurvedic was estimated to be around US$ 185 billion. The industry is anticipated to expand at a CAGR (Compound annual growth rate) of around 11% to around US$ 430 billion by 2028 mentioned in (Figure 1) [7].

Figure 1: Graphical Abstract

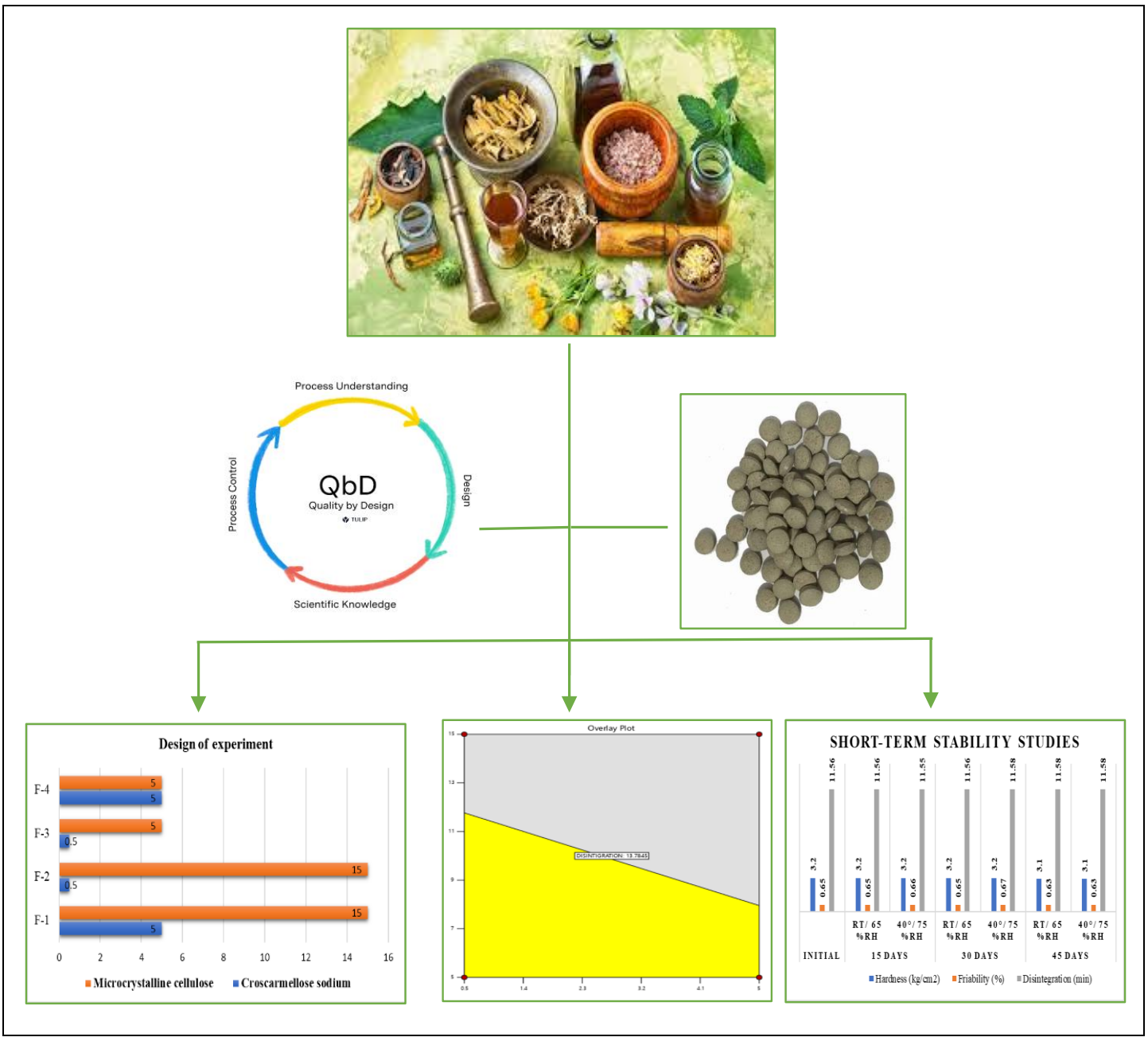
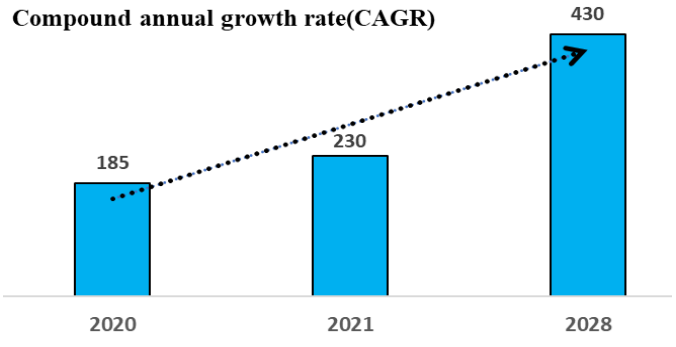


Figure 2: Compound annual growth rate



Corona virus 2019 (Covid-19) is a contagious disease that causes severe acute respiratory syndrome. Corona virus 2 (SARS-COV-2) previously known as 2019 novel corona virus. The first cases were seen in Wuhan China [8]. The current outbreak was officially declared as pandemic on 11 March 2020. Tiredness, fever, and a dry cough are the most numerous examples. Some people have aches and pains, and even some nasal congestion, discomfort, a runny nose, sore throat, and diarrhoea. It was disclosed that traditional remedies may alleviate the symptoms of cov-19[9].While there is no cure for covid-19, it is prudent to take cautious action to increase our immunity during several trying times [10].Many plant-based medicines have flavonoids, alkaloids, phenols and tannins that exhibit antiviral and antimicrobial properties [11].In the current context of pandemic, a lot is spoken on hygiene, social distancing and food to prevent impact on health. This proposal is an effort to identify few ayurvedic botanicals used in Jwara, Kasa, Shwasaroga, Krimi and Pratishyaya Chikista with corroborated anti-viral and immune-modulatory

activities as main or adjuvant therapy for community self-reliance in the wake of COVID-19 pandemic [12].

"A systematic approach to development that begins with established objectives and stresses product and process understanding and process control, based on strong science and quality risk management," is how Quality by Design (QbD) is defined [13]. Despite the widespread use of herbal pharmaceuticals, Zhang et al. (2013) declare that there have only been a small number of examples of QbD adoption in the production of herbal drugs [14]. Considering that Because of the complicated chemical properties and many process factors, knowledge-based techniques are commonly actualized during the manufacture of ethnomedicinal products, but often fail to enhance process understanding [15]. As a result, developing Fabrication processes under the QbD framework is critical, which aims to move the formulation process away from verifiable trial-and-error approaches and toward regulated and carefully controlled settings to ensure high product quality throughout the life cycle [16]. It is therefore important that a QbD model should be implemented for the development of herbal medicines in order to achieve a significant level of safety, efficacy, and quality for commercial herbal products [17].

Based on the Ayurvedic and scientific literature, the Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy), India issued an advisory where it recommended the use of number of immune-boosting herbal medicinal drugs among that we have chosen most immune-boosting medicinal plants for our study to prepare polyherbal tablet formulation by applying QbD approach, those are *Tinospora cardifolia* (Guduchi), *Piper longum* (Pippali), *Glycyrrhiza glabra* (Licorice) and *Withania somnifera*(Ashwagandha) for self-care which will develop immunity against severe infection caused by COVID-19 [18-21].

MATERIALS AND METHODS

Chemicals

All Herbal extracts were procured as a gift sample from Sami-Sabsina Group Limited Bengaluru respectively. Moreover, croscarmellose sodium, microcrystalline cellulose and magnesium stearate were purchased from HiMedia laboratories Pvt. Ltd, Mumbai. Furthermore, lactose monohydrate from Loba Chemie Pvt. Ltd and Talcum powder from S D fine-chem limited Mumbai respectively.

QBD approach

Quality Target Product Profile (QTPP) for Polyherbal Tablets

The Quality Target Product Profile (QTPP) as pretended in International Council for Harmonisation (ICH) Q8 is a vital element of a QbD approach. All product features required for comparable safety and efficacy are included in the QTPP [22]. QTPP for herbal Tablet has been developed by considering the dominant drug product quality attributes specifications.

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 what a critical quality attribute (CQA) is [23]. To discern sufficient product quality, the initial CQAs were defined utilizing QTPP. The typical CQAs of excipients requisite for the creation of Polyherbal remedies were identified as having a minimum disintegration time of NMT15 minutes and a maximum hardness of 3-5 kg/cm2 with a friability of less than 1%.

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 [24].

Formulation design

In this study DoE approach was implemented, which involves controlled variable and as the outcome of the controlled variable response is obtained. Croscarmellose sodium and Micro crystalline cellulose were considered as independent variables in this study while the responses were friability in percentage and disintegration time in minutes. Considering these variables, 4 formulations were developed by the Design Expert® software (version 13) where the percentage of highest and lowest limits of the controlled variables were 0.5%-5% and 5%-15% for croscarmellose sodium and microcrystalline cellulose respectively. Software generated amounts of two variables are given in (Graph1) and the overall formulation composition of 4 different batches are shown in (Table1).

Formulation of polyherbal tablets

Direct compression method was applied in this study to prepare polyherbal tablets [25]. Initially, herbal extracts and excipients were carefully weighed for 20 tablets per formulation and passed through mesh filter number 60. With the exception of the lubricant, all excipients were properly triturated for 30 minutes in a mortar and pestle with the extracts. Previously sieved and accurately weighed amount of magnesium stearate (lubricant) and talcum powder was then added and mixed further for another 10 minutes. After mixing, physical property characterization tests were done to evaluate the powder mixture followed by compression in M/s Rimek Mini press single rotary tablet press machine.

Figure 3: (Graph 1) Software generated amount (in percentage) of two variables in different formulations.

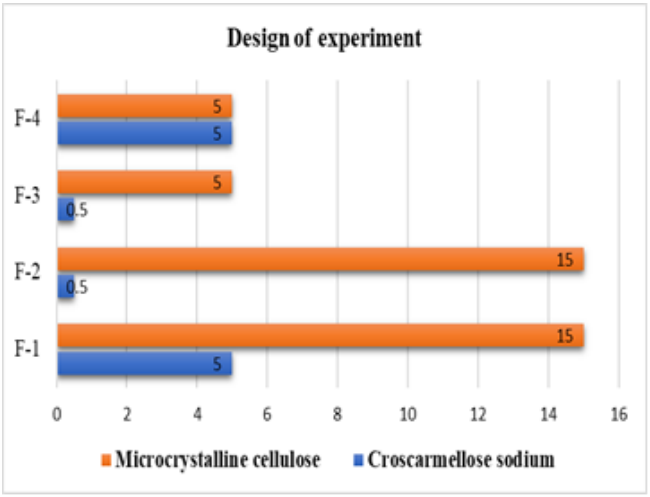


Table 1: Composition of Ashwagandha, Guduchi, Licorice and Pippali extracts (all measurements are in mg).

Formulation number	F-1	F-2	F-3	F-4
Ashwagandha	150	150	150	150
Guduchi	150	150	150	150
Licorice	150	150	150	150
Pippali	100	100	100	100
Croscarmellose sodium	27.5	2.75	2.75	27.5
Microcrystalline sodium	82.5	82.5	27.5	27.5
Lactose monohydrate	30	54.75	109.75	85
Talcum powder	06	06	06	06
Magnesium stearate	04	04	04	04

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 (World Health Organization, 2012), Carr's index, Hausner's ratio and Angle of Repose (Pharmacopoeia, U.S., 2004) [26].

Characterization of physical properties of formulated tablets

Weight variation of the tablets were evaluated using an electronic balance of Electro lab India Pvt. Ltd. 20 tablets of each formulation were considered for this test according to 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 of Campbell Electronics Mumbai, Vernier calipers of Mitutoyo Japan, friability test apparatus of M/s Roche Friabilator and Disintegration test apparatus of M/s Electrolab, India Respectively [27].

Statistical optimization

The evaluation 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 programme supplied statistical parameters such as the R2 coefficient of determination, SS-sum of squares, Adjusted R2, 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. The effect of host of factors on the reaction at a given time was investigated using these charts. Finally, a numerical optimization technique (desirability approach) and a graphical optimization technique were used to find the best Formulation (overlay plots) [28].

Stability studies

In terms of the Q1A (R2) standards of the International Council for Harmonization (ICH), stability tests were conducted for statistically optimised formulations. The samples were kept for 45 days in a capped high-density polyethylene (HDPE) bottle that was kept at normal temperature (27°2°F/ RH 65%) and under accelerated circumstances (40°2°F/ RH 755%). After 15 days, 30 days, and 45 days, the tablets were taken and analysed for hardness, disintegration, and friability [30-31].

RESULTS AND DISCUSSION

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 polyherbal tablet includes the dosage form, dosage design, method of administration, dosage strength, drug product quality features, container closing mechanism, and storage conditions. (Table 2).

Table2 (a): QTPP for polyherbal tablet.

QTPP Elements		Target	Justification
Dosage form		Tablet	For patient appropriateness
Dosage design		Conventional release tablet	Patient appropriateness & tractability
Route of administration		Oral	Dosage form deliberate to be administered orally
Dosage tolerance		550mg	Therapeutic dose
Drug product Quality Attributes	Appearance	The form and size of the tablet fits the description.	Patient appropriateness & tractability
	Hardness	3-5 kg	As per Pharmacopoeial specifications
	Friability	NMT 1.0%	
	Disintegration	NMT 15 min	
Container closer system		This medication product's container closure system was found to be appropriate.	To meet the target shelf-life and maintain tablet integrity throughout storage, this is recommended.
Storage condition		Store in air-tight container in a cool place.	preserving the quality and integrity of the product throughout storage

Table 2(b): CQA's for polyherbal tablet

Quality Attributes of Drug product	Target	Is this a CQA?	Justification
Disintegration time	NMT 15 min	Yes	In order to meet Pharmacopoeial specification.
Friability	NMT 1.0%	Yes	In order to meet Pharmacopoeial specification.

The initial CQA's were defined from QTPP to identify

adequate quality profile of the product. T-3 condenses the critical quality attributes (CQAs) of polyherbal tablet formulation along with justification for criticality of these selected quality attributes. Disintegration time (min) (Y_1) and friability (%) (Y_2) were regarded as CQAs of the formulation of polyherbal tablets. (Table 2).

In order to satisfy the quality target product profile (QTPP), an initial risk assessment of drug substance (herbal extracts) and formulation variables (excipients) was conducted. An initial risk evaluation was performed on each of the four plant extracts. The initial risk assessment and rational argument for formulation factors are summarised in (Table 3).

Table 3: Justification for the formulation variables' preliminary risk assessment.

Formulation variables	Drug product CQA	Justification
MCC Level	Disintegration	MCC is used as diluent, increase or decrease MCC level can have high impact on disintegration time via tablet hardness. Risk is high.
	Friability	MCC is used as diluent increase or decrease in MCC level can have high impact on friability. Risk is high.
CCS Level	Disintegration	The CCS is used as disintegrant increase or decrease in CCS level can have high impact on disintegration time. Risk is high.
	Friability	More number of CCS can increase friability of tablet, but this can be overcome by increasing tablet hardness during compression. Risk is medium.
Lactose Level	Disintegration	The lactose is used as filler, it generally has no impact on disintegration time as well as friability. The risk is low.
	friability	
Talc Level	Disintegration	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.
	Friability	Talc has no impact on tablet friability. Risk is low
Magnesium stearate Level	Disintegration	since magnesium stearate is used in very low amount, it has no impact on disintegration time as well as friability.
	Friability	

Design space and formulation optimization

This study was meant to evaluate the effects of several formulation aids on the preparation of directly compressed polyherbal tablets. To evaluate this, DoE was implemented, where different concentrations of two formulation excipients were considered and their effects were reflected on friability and disintegration time. Before focusing on the statistical approach, initial screening was done through evaluating friability and disintegration time of each of the formulations to infer whether they comply with the compendial specifications of these two physical properties of tablet dosages forms (Table4).

Table 4: Composition of Polyherbal Tablets- Variables and Responses as per Design Expert.

Std	Run	Factor 1	Factor 2	Response 1	Response 2
		A: conc. of CCS (mg)	B: conc. of MCC (mg)	Disintegration time (Min.sec)	Friability (%)
4	1	27.5	82.5	11.46	0.65
3	2	2.75	82.5	12.37	0.91
1	3	2.75	27.5	15.58	0.59
2	4	27.5	27.5	14.46	0.35

To meet the disintegration time limit so, the rest of the 3 formulations were selected to implement the DoE approach by taking into consideration the predicted (generated by the software) and the experimented values of the dependent variables. The contour diagram and the 3D surface response diagram provided in (figure 2) indicate the best formulations showing friability and disintegration time data close to experimental results. The ANOVA results presented in (Table 5) could be used to predict the significant responses of each actual component for given levels.

In this context, the combined effects of MCC and CCS were studied to provide a design space with dependent variables within the acceptable range i.e., friability <1% and disintegration time between 3 to15 min. The Figure 3(yellow region) indicates the acceptable design space which was taken for D-optimal design conducted through design expert version 13 software to generate predicted values for friability and disintegration time as shown in (Table 4). Decreasing the concentration of MCC and CCS, it was assumed that the friability would be lower and the disintegration time would be higher. Here we found three formulations (F-1, F-2 and F-4) having friability and disintegration time of predicted value very close to the experimental value but (F-1) is selected as optimized batch due to their better disintegration and friability values (Table 6). For the other 1 formulation (F-3) their differences were so high that, there was less chance to get a successful formulation from that.

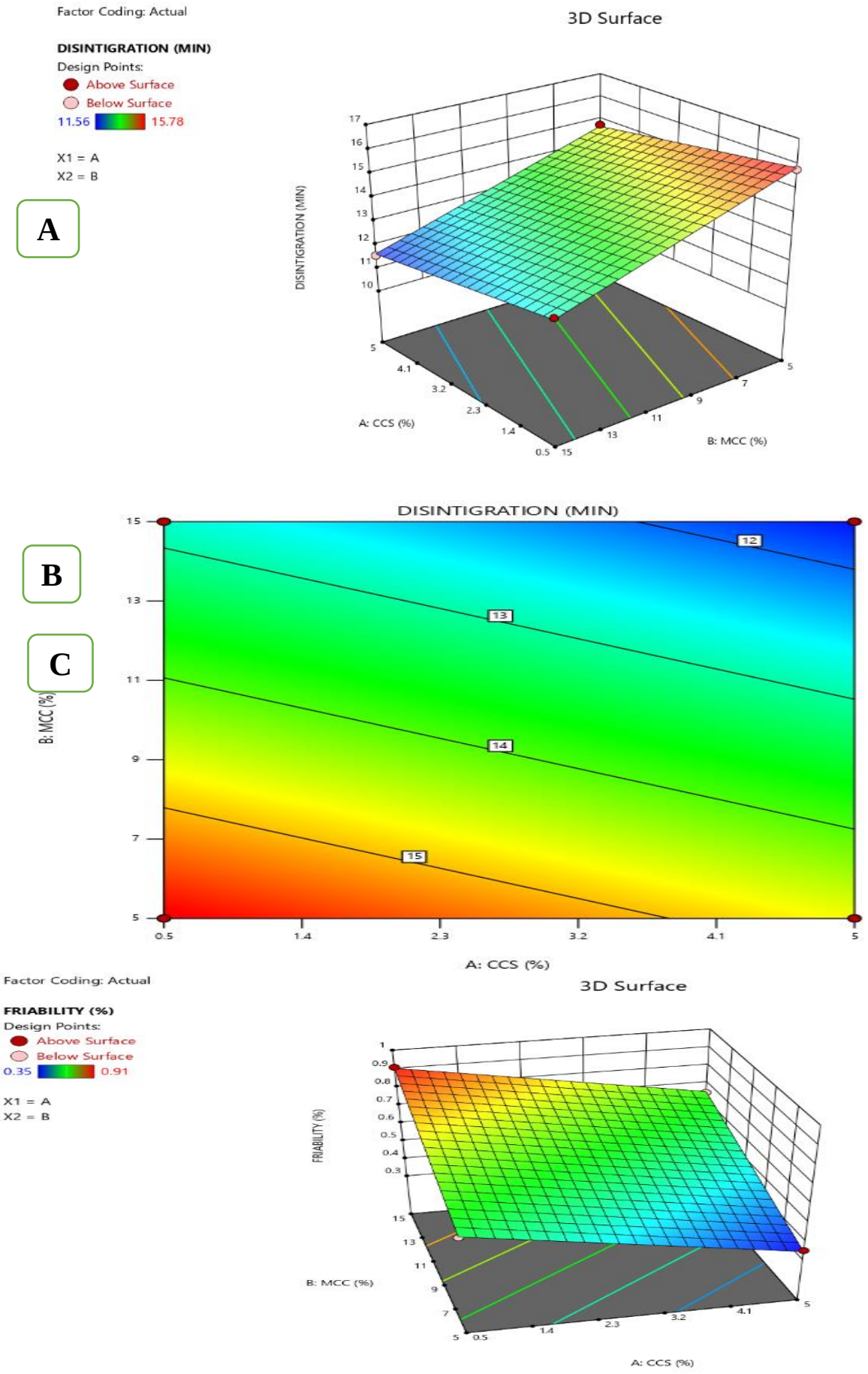
Table 5: Summary of statistical parameters – analysis of variance test (ANOVA)

Response	SS	DF	MS	F-value	P-value	R^2	Adjusted R^2	Model significance
Y_1	10.69	2	5.35	254.23	0.0443	0.9980	0.9941	Significant
Y_2	0.1586	2	0.0793	793.00	0.0251	0.9994	0.9981	Significant

Table 6: Optimized batch criteria

Responses	OF1 Experimental
Disintegration time (min)	11.46
Friability (%)	0.65

Figure 3: (A & C) Response surface plot for response Y_1 disintegration and Y_2 friability and (B & D) contour plot for response Y_1 disintegration and Y_2 friability.



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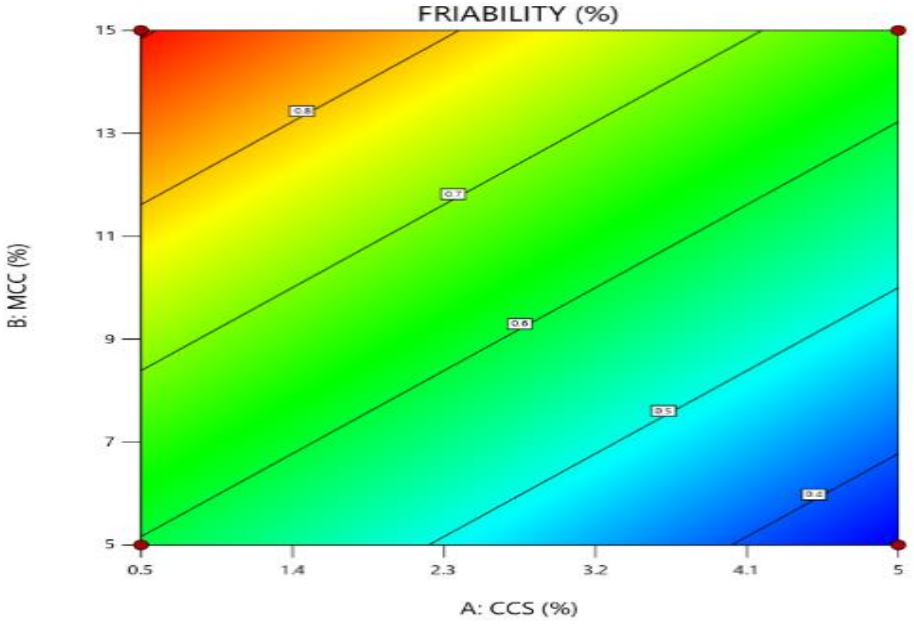
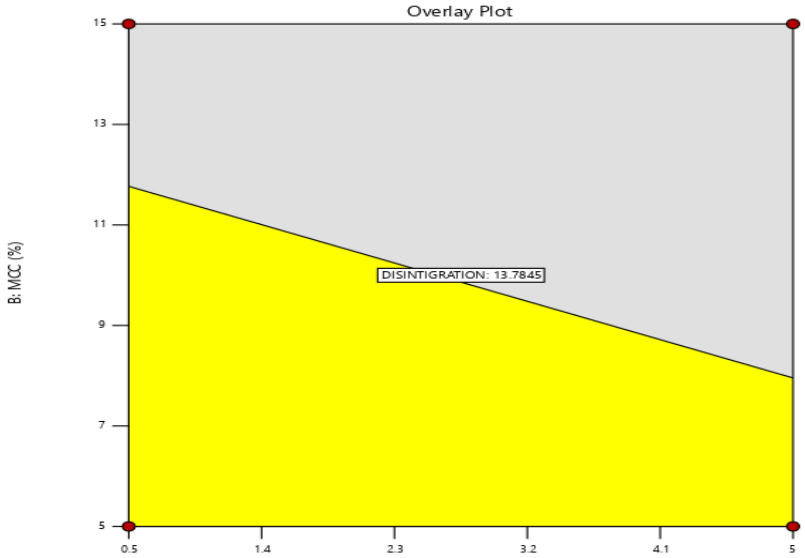


Figure 4: Plot overlay displaying the design space Indicating formulation F1, F2 and F4 falling in design space.



Flow properties of the granules

Generally, Angle of Repose less than 40, Compressibility index or Carr's index up to 20 and Hausner's ratio value less than 1.25 are indicative parameters of fair to excellent flow properties of granule or powder blend (Pharmacopoeia, U.S., 2004).

Table 7: The powder mixture's flow characteristics.

Formulation number	Bulk density(gm/ml)	Tapped density (gm/ml)	Carr`s index (%)	Hausner's ratio	Angle of repose
F-1	0.433±0.025	0.534±0.024	13.59±0.361	1.144±0.020	36.2±0.416
F-2	0.458±0.028	0.533±0.020	18.9±0.5567	1.24±0.0450	36.5±0.231
F-3	0.468±0.020	0.517±0.003	9.76±0.416	1.156±0.041	37.3±0.536
F-4	0.449±0.019	0.523±0.007	16.23±0.416	1.153±0.047	36.2±0.556

In this experiment, all 4 formulations indicated good flow property as the Carr's index was within the range of 9.76 ±0.416-18.9 ± 0.556, Hausner's ratio 1.144 ± 0.020-1.24 ± 0.045and Angle of Repose 36.2± 0.416-37.35 ± 0.5366 (Table 7).

Physical properties of formulated tablets

The physical properties of the formulated tablets were established according to the procedures mentioned in the materials and methods section. The diameters of the tablets were 12 ± 0.002 mm, thickness 6.7 ± 0.08 to 6.9±0.07 mm, hardness or crushing strength 3.1 ± 0.09 to 3.7 ± 0.05 kg/cm2, average weight 698 ±2.3 to 704 ± 2.6 gm and friability were 0.35 - 0.91%. For all 4 formulations. All physical characteristics of the formulated tablets of 4 different formulations exhibited acceptable compliance with the compendial specification. (Table 8).

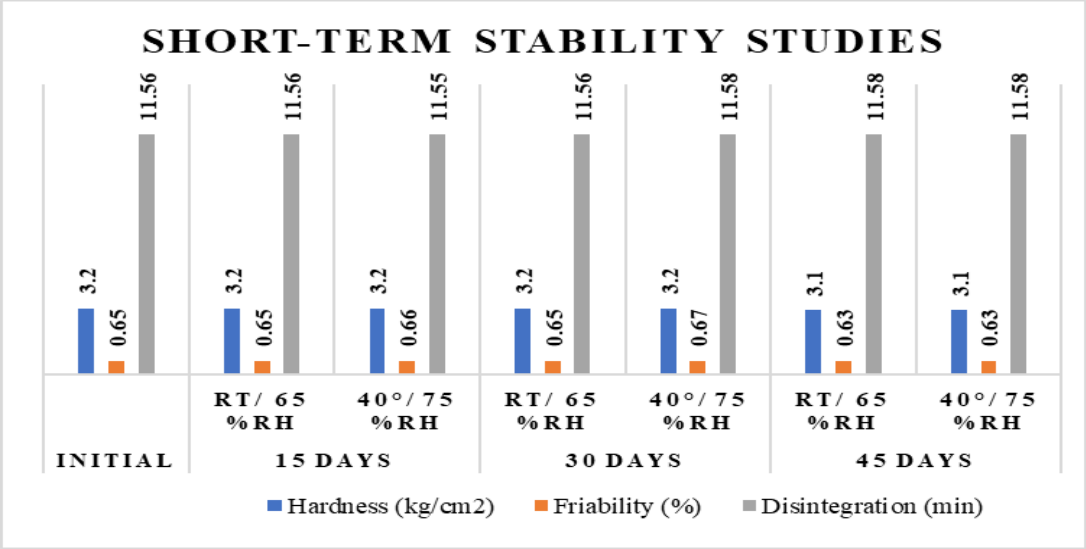
Table 8: Physical properties of formulated tablets.

Formulation Batch	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Weight variation (%)	Disintegration time (min.sec)
F-1	6.7±0.08	3.2±0.052	0.65±0.02	702±1.4	11.46±0.05
F-2	6.8±0.05	3.5±0.076	0.91±0.04	698±2.3	12.37±0.02
F-3	6.9±0.07	3.7±0.054	0.59±0.01	703±1.5	15.58±0.07
F-4	6.8±0.08	3.1±0.097	0.35±0.03	704±2.6	14.46±0.03

Stability studies

The results of a stability analysis conducted on the optimised batch (OF1) in line with ICH stability criteria are showed in (Graph 2). The physical properties of the formulation batch OF1 did not vary significantly. Hardness, friability, and disintegration time all changed slightly. However, these modifications stayed within the established parameters. According to the experiments, the enhanced formulation is stable for 45 days.

Figure 5: (Graph 2) Short term stability studies.



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 polyherbal tablets. As a means of obtaining the end product with the appropriate quality, the desired QTPP and CQA's were predetermined. 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. Based on the findings of this investigation, it is clear that using the specified excipients at somewhat greater levels than their mid-range values in this experiment resulted in superior and acceptable tablet qualities.

ACKNOWLEDGEMENT

The authors are very thankful to Principal Dr. S. S. Jalalpure and Vice Principal Dr. M. B. Patil for their support and guidance.

Declaration of interest: Authors declare no conflict of interest.

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How to cite this article

Rahul Koli, V S Mannur, Sachin Gudasi, Rohan Singadi, Adiveppa Nashipudi, 2022. Development of directly compressible polyherbal tablets by using qbd approach a novel immunomodulatory material. Journal of medical pharmaceutical and allied science V 11 - I 6, Pages - 5476 – 5484. Doi: 10. 55522/jmpas.V11I6.4520.