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RESEARCH ARTICLE

Development and Evaluation of Therapeutically Beneficial Fast Dissolving Tablet Containing Herbal Extracts: A Quality by Design Approach

Akashkumar Shah[1,2]*, Khushbu Patel[3]

1 Research Scholar, Faculty of Pharmacy, Nootan Pharmacy College, Sankalchand Patel University, Visnagar, Gujarat, India
2 Zydus Wellness Institute, Zydus Wellness Research & Development, Ahmedabad, Gujarat, India
3 Associate Professor, Faculty of Pharmacy, Nootan Pharmacy College, Sankalchand Patel University, Visnagar, Gujarat, India

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* **Corresponding author**.

akashn.shah@zyduswellness.com (Orchid ID: 0009-0003-7229-9187)

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Abstract

Objectives: The QbD approach validates the formulation during development, ensuring therapeutic benefits through the careful selection of herbal extracts. **Methods:** Oral dosage forms, especially fast dissolving tablets with different herbal extracts (curcumin, saffron, and gingerol) were developed to get their desired therapeutic actions immediately. Quality by Design (QbD) emphasizes a science-based approach to product development. Design of Experiments (DOE) and ANOVA are used to analyze high-risk Critical Quality Attributes (CQAs). Design Expert software helps determine the optimal quantities of variables in the formulation by analyzing the effects of independent variables to establish design space. **Findings:** The effect of identified independent variables croscarmellose sodium (CCS) and polyvinyl pyrrolidone K30 (PVP K30) were investigated. The impact of independent variables on critical responses Disintegration Time and Friability were analyzed. Both variables were found to have a sizeable impact on both the responses. The optimized formulation with 5mg/tablet of CCS and 0.5mg/tablet of PVP K30 meets the desired QTPP and Pharmacopoeial standards of fast dissolving tablet. ANOVA indicates the p-values of respective variables were 0.0168 and 0.0374 which indicates that the model was significant. The optimized FDT (fast dissolving tablet) formulation with three herbal combinations was found to have a DT of 22.02$\pm$0.83 seconds and hardness of 3.34$\pm$0.18 kg/cm^2 which was highly desired as per formulation perspectives. **Novelty:** The successful development of a fast-dissolving tablet with curcumin, saffron, and gingerol using a QbD approach highlights the unique challenges of formulation compared to other potent APIs. Moreover, achieving both the desired DT and hardness in a formulation with herbal extracts at 23.5% potency is a novel accomplishment. There is no existing QbD approach for a product that combines three different herbal extracts into a fast-dissolving tablet dosage form. Therefore, applying QbD to develop and

optimize the formulation and achieve the desired results is an accomplishment.

Keywords: Herbal Extracts; QbD - Quality By Design; Fast Dissolving Tablets; QTPP-Quality Target Product Profile; DOE-Design Of Experiments; CQA-Critical Quality Attributes

1 Introduction

The pharmaceutical industries continually strive to establish product safety, quality, and efficacy. Regulatory bodies emphasize the need for a science-based approach to enhance process understanding and reduce process variation[(1)]. QbD (Quality by Design) approach encounters in the pharmaceutical industries to avail risk assessment and statistic-based manufacturing proposition to gain process and product understanding and consequently guaranteed quality of the product. It involves developing formulations with design and manufacturing processes to ensure preestablished product quality. Its key components include understanding critical quality attributes, risk management, and creating a design space. Pharmaceutical industries are transforming their R&D processes to align with QbD principles. However, there remains limited understanding and apprehensions regarding its practical application[(2)]. QbD represents a paradigm shift in pharmaceutical development, emphasizing science-based approaches and process control. compliance. With the objective of developing a robust formulation with innovation and originality, the QbD approach is widely recommended by ICH (International Conference on Harmonization) and FDA (Food and Drug Administration). Quality by Design offers a practical guide for integrating QbD into pharmaceutical product development and manufacturing processes[(3)].

QbD approach is being widely adopted by pharmaceutical companies internationally, emphasizing the integration of quality considerations throughout the product lifecycle. It enables pharmaceutical companies to assure that quality is built into product[(4)]. By applying QbD principles, companies can enhance product quality, efficacy and safety. QbD is a structured approach to product development that emphasizes understanding and control of both product and process[(5)].It begins with predefined objectives and integrates sound science, quality risk management, and process control. The goal is to ensure high-quality pharmaceutical products that meet customer satisfaction in terms of service, products, and processes[(6)].

Ayurveda, the ancient Indian system of medicine, has a rich heritage spanning 5,000 years. It extensively utilizes plant-based remedies for treating various human ailments. Ayurveda views human existence as a product interaction between Health, Environment and Awareness. These three elements are often considered deeply interwoven in Ayurvedic concepts. Their association describes "The Meaning of Life". It aimed to build a bridge between Ayurveda and pharmaceutical science and technology. Eminent experts from both fields came together to expand our understanding of health, care and quality of life. These connections link living life with their environment which sculpts nature[(7)].

Ayurveda, often referred to as the "Science of Life," extends beyond physical symptoms. It encompasses spiritual, mental, and social health. The theory of Tri-Dosha (Kapha, Pitta, and Vata) forms the cornerstone of Ayurveda. Balancing these three doshas is crucial for well-being. Ayurveda's rich database includes knowledge about patients, diseases, diagnosis, pharmacology, and therapeutics[(8)]. Integrating this ancient wisdom with modern scientific methods can lead to the emergence of "Designer" Medicines—tailored treatments that consider holistic health. Ayurveda, with its logical and philosophical foundation, offers a treasure trove of insights for creating innovative pharmaceuticals. The future of medicine will likely blend ancient and modern therapeutic approaches. A holistic, personalized approach will maximize benefits for patients and communities. Ayurveda, with its profound understanding of health

and balance, holds promise as a source of future medicines. By bridging ancient wisdom and modern science, we can unlock new frontiers in healthcare[9].

Saffron is one of the oldest spices, with a history dating back to ancient times. Its origin is believed to be the Middle East, although some authors suggest Central Asia or the islands of southwest Greece. From this primary zone, saffron spread to China, India, and Middle Eastern countries. The Arabs further disseminated saffron throughout the Mediterranean valley and Morocco, where it was likely brought into being by the 9th century. Saffron contains several bioactive compounds, including crocin, crocetin, and safranal. These components contribute to its pharmacological activities, making it a promising therapeutic agent. Saffron has been used for centuries in culinary applications, as a dye, and for its medicinal properties rooted in folk medicine. Research highlights Saffron's antioxidant and antibacterial properties and potential therapeutic benefits[10].

Turmeric (*Curcuma longa* L.) is a traditional Indian herb with a potent marker called curcumin. Curcumin is the yellow polyphenolic pigment found in turmeric and has been used for centuries in ancient medicine, cooking, and food coloring. Curcumin exhibits antioxidant activity, which helps protect cells from oxidative damage. Curcumin has anti-inflammatory properties and may be effective in managing inflammatory conditions. Curcumin exhibits anti-fungal and anti-microbial effects as well. Turmeric has protective effects on the kidneys and liver. It can be beneficial in managing ulcers and diabetes. Some studies suggest that curcumin may play a role in cancer prevention[11].

Ginger (*Zingiber officinale*), a versatile spice has been used for centuries across various cultures for both culinary and medicinal purposes. As per Ayurveda in India, ginger is a staple in Ayurvedic medicine. Ginger is now cultivated worldwide, from Africa to Asia. Ginger is used to block excessive clotting (which can contribute to heart disease), reduce cholesterol, and combat arthritis. Ginger is used globally as a nausea remedy, anti-spasmodic, antibacterial, antifungal, antioxidant, and anti-inflammatory agent[12]. Gingerol is the principal bioactive marker in ginger. Along with gingerol, paradols, and shogaol are phenolic compounds also found in ginger. These compounds are contributing to antioxidant and anti-inflammatory properties. Terpenes are aromatic compounds also found in ginger and are responsible for ginger's spicy flavor[13].

Fast dissolving tablets need to disintegrate quickly in the mouth, which often compromises their mechanical strength. Ensuring that the tablets are strong enough to withstand handling, packaging, and transportation while still dissolving rapidly is a significant challenge. Many herbal extracts have bitter or unpleasant tastes. Effective taste masking is crucial to ensure patient compliance. This often involves using flavoring agents, sweeteners, or taste masking techniques to mask the taste without affecting the tablet's disintegration properties. Herbal extracts can be highly hygroscopic, meaning they absorb moisture from the air. This can affect the stability and shelf life of the tablets. Ensuring uniform distribution of the active ingredients in each tablet is critical, especially given the natural variability of herbal materials. Achieving rapid disintegration while maintaining tablet integrity is a delicate balance. The choice of superdisintegrant and its concentration is crucial to ensure that the tablets dissolve quickly in the mouth without compromising their mechanical strength (hardness). Herbal active ingredients can be sensitive to environmental conditions such as light, heat, and humidity. Ensuring the stability of these ingredients throughout the shelf life of the product is essential. At last, ensuring that the final product is acceptable to patients in terms of taste, mouthfeel, and ease of use is crucial. This involves extensive testing and optimization to ensure that the tablets are pleasant to use and effective[14].

The main research gap in herbal formulation development lies in integrating advanced development and process control technologies, along with a comprehensive understanding and control of these processes. Recent literature indicates a need for research to develop effective awareness strategies and implement new approaches. To advance herbal product development, it is crucial to conduct further research aimed at harmonizing regulatory requirements globally. There is a research gap in developing formulations containing more than two herbal extracts using a QbD approach. Therefore, this area is of interest for further exploration[15] .

Adopting QbD aligns with regulatory guidelines and ensures that herbal formulations consistently meet quality criteria, leading to safer and more effective products. By identifying and controlling critical quality attributes and process parameters, QbD minimizes the risk of product failures and recalls, reduces development and manufacturing costs, and enhances process understanding. This systematic approach fosters innovation and ensures reliable, effective treatments, building consumer trust and satisfaction[15].

2 Methodology

Turmeric extract and ginger extract were procured from Konark Herbals & Healthcare Pvt Ltd (Gujarat, India). Saffron was procured from Orion Resources (J&K, India). Other ingredients including Croscarmellose Sodium, Polyvinylpyrrolidone K30, Mannitol, Magnesium Stearate, Stevia, Menthol, and Flavours were procured from local vendors as per required pharmacopoeial grades.

2.1 QTPP (Quality Target Product Profile) of Therapeutically Beneficial Fast Dissolving Tablets

As per the ICH (International Council for Harmonization) Q8 guidelines, QTPP is an essential component of QbD methodology. The QTPP is a subsequent synopsis of the quality characteristics of a drug product. It defines the quality attributes necessary to ensure safety, efficacy, and desired product quality. QTPP considers labeled use, safety, and efficacy [14] . The QTPP for fast dissolving tablet containing herbal extracts was created after consideration of the essential quality parameters of the products [16].

2.2 CQA (Critical Quality Attributes) of Therapeutically Beneficial Fast Dissolving Tablets

CQA refers to physical, chemical, biological, and microbiological parameters or characteristics of the product that must fall within appropriate limits, ranges, or distributions to ensure the desired product quality. Controlling or monitoring CQA is crucial to achieving consistent quality of the product. Identification of CQAs for the excipients required to make fast dissolving oral solid tablet formulations containing herbal extracts were established as having the fastest disintegration time with the lowest friability [16].

2.3 Risk Assessment

A risk assessment of any product was carried out, to identify high-risk attributes and how they can be controlled during the development phase. The Risk Priority Number (RPN) is a scoring methodology used for the risk assessment process to rank the severity, possibility of occurrence, and noticeability of potential problems. It helps prioritize which risks are addressed first based on their overall influence (Low, Medium, and High) [17].

For the development and evaluation of therapeutically beneficial fast dissolving solid oral tablet dosage form, a CCD (Central composite design) was applied. In this representation, two formulation variables were analyzed with three levels. Physicochemical responses of all formulations were analyzed. Croscarmellose Sodium (Disintegrating Agent X1), Polyvinylpyrrolidone K-30 (Binder X2) were selected as formulation variables which are independent and altered at three different levels, which were classified as lowest (- 1), medium (0) and highest (+1) levels. The response variables in this study were disintegration time (Y1) and friability (Y2) in second and percentage respectively.

Table 1. Independent variables with three levels for DoE batches

Sr. No.	Independent Variables	Levels		
		-1	0	1
1	Croscarmellose Sodium	4	5	6
2	Polyvinylpyrrolidone K-30	0.4	0.5	0.6

2.4 DOE-Design of Experiments

The primary goal of DOE (Design of Experiments) is to explore and understand the variation in a system or process. DOE is a systematic and efficient method to study the relationship between multiple feed in variables (also known as factors) and key outturn variables (referred to as responses). By carefully designing experiments, we can identify cause-and-effect relationships and optimize the output [16]. Design Expert (DE) version -23.1 (USA, Minneapolis, Stat-Ease Inc.) was used to perform such experiments. Nine experimental formulations were developed and examined with the help of software, as per Table 2. DOE-Design of Experiment program was applied to determine the appropriate response of the independent variables [18].

Table 2. Combinations of factors according to (3^2) factorial experiment of design

Run	Coded Values		Experimentation Values	
	X1	X2	X1	X2
1	-1	-1	4	0.4
2	-1	0	4	0.5
3	-1	1	4	0.6
4	0	-1	5	0.4
5	0	0	5	0.5
6	0	1	5	0.6

Continued on next page

Table 2 continued

7	1	-1	6	0.4
8	1	0	6	0.5
9	1	1	6	0.6

X1 Croscarmellose Sodium is the concentration & X2 is the concentration Polyvinylpyrrolidone K-30

2.5 Preparation of Therapeutically Beneficial Fast Dissolving Tablets with herbal extracts

Fast dissolving solid oral tablet containing herbal extracts was developed using wet granulation process. Based on the literature, ingredient selection for fast dissolving formulation was carried out. Table 3 shows the formulation trial batches of fast dissolving tablets containing herbal extracts that have been developed. All the herbal extracts, including Saffron, Turmeric extract and ginger extract were precisely weighed and individually passed through sieve size 80. The dose determining criteria of all the extracts were based on Ayurvedic pharmacopoeia, a drug to extract ratio of herbal extract and literature search. Drug-excipients compatibility criteria were kept in mind while screening the excipients for the formulation.

Pass the rest of all ingredients individually through sieve size 40. Because of the hygroscopic nature of all the above herbal extracts, they were geometrically mixed with an equal weighed quantity of mannitol. Polyvinylpyrrolidone K-30 (PVP K30) was weighed and mixed with warm water to make a translucent granulating solution. The other ingredients like Mannitol (remaining), Croscarmellose sodium, Stevia, and Menthol were mixed with the above herbal ingredient mixture in RMG (Rapid Mixture Granulator). The granulating solution of PVP K30 was sprayed in RMG at a slow speed (40 RPM) and keeping chopper on for 5 minutes. Then the speed of RMG was increased to fast (80 RPM) for the next 5 minutes (keeping the chopper off during this process). Passed the wet granulated mass through sieve size 10. Dried the wet granules at 45-55°C in the oven until the granules will dry and moisture content reaches between 1.5 to 2.0%. After drying, the granules were passed through sieve size 20. The dried granules were further blended with magnesium stearate and flavour for five minutes. After mixing, these free-flowing granules were taken to the compression machine for the tableting process.

Compression machine (CADPRESS, 16 station pilot scale hybrid, Cadmach Machinery, Ahmedabad, Gujarat, India) was kept ready with B-tooling, 5.5 mm diameter, round shaped punch sets. Tablet with the description of yellow to dark yellow coloured, plain, round, and biconvex shape was produced. Tablets had an average weight of 100mg with complying other physical parameters.

Table 3. Formulation trial batches of Fast Dissolving Tablet containing herbal extract

Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9
Herbal Extracts^ (Curcumin, Saffron, Gingerol)	23.5	23.5	23.5	23.5	23.5	23.5	23.5	23.5	23.5
Croscarmellose Sodium	4	4	4	5	5	5	6	6	6
Polyvinylpyrrolidone K-30	0.4	0.5	0.6	0.4	0.5	0.6	0.4	0.5	0.6
Mannitol	61.1	61	60.9	60.1	60	59.9	59.1	59	58.9
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Stevia	10	10	10	10	10	10	10	10	10
Menthol	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Flavour (Peppermint)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Total (mg)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

^Herbal extracts are the mixture of Curcumin (12mg), Saffron (1.5mg) and Gingerol (10mg). Total 23.5 mg.

2.6 Physical Properties of the Fast-Dissolving Tablets

The compressed fast dissolving solid oral tablets were tested for their physical properties such as mean weight, disintegration time, friability, hardness and thickness by pharmacopoeial methodology. The moisture value of the oral solid tablet was determined using a halogen moisture analyzer[19].

2.7 Statistical Analysis

Analysis of variance (ANOVA) is a statistical method used to compare two or more means. It was developed by the statistician Ronald Fisher. ANOVA allows us to test whether there are significant differences between the means of different groups. The

most effective model was chosen based on statistical evaluation such as Mean of square (MS), Sum of squares (SS), adjusted R2, R2-coefficient of determination, Fischer's ratio (F value), Degrees of freedom (DF), and Probability (P) generated from Design expert software v23.1 [20].

To demonstrate the relationship between dependent and independent variables, response surface plots such as 3-D response surface plots and contour plots were employed. The plots previously mentioned were used to investigate the effects of different variables on a particular response at a specific time. At the end, for the identification of the optimized formulation overlay plots were used [20].

2.8 Validation Study of Optimized Formulation Batch

Validation study of an optimized formulation batch of solid oral tablets from herbal extracts with the predicted levels was done. The outcome of responses from experimental values versus expected values was quantitatively compared for the purpose of justifying the selected experimental strategy.

2.8.1 Control – Strategy

A control strategy is an assurance that the developed formulation will be manufactured with the desired quality and consistency. In view of product knowledge and existing processes, a control-strategy considers a comprehensive picture of how quality can be maintained. The metrics and qualities connected to active herbal ingredients and excipients, as well as the corresponding methods, control and constant monitoring frequency, are all part of the control-strategy [21].

2.8.2 Stability study

Stability studies for statistically enhanced final product was conducted as per regulations provided in the guidelines of ICH (International council for harmonization) Q1A (R2). The stability samples were kept in a proper Alu-Alu strip pack for at least 180 days (6 Months) at 30° ± 2°C / RH 75 ± 5 % (Long term condition) and at 40°±2°C/ RH 75±5% (Accelerated conditions). The formulation was examined for parameters like average weight, thickness, disintegration time, friability, moisture content and hardness after 1 month, 3 months and 6 months of stability study [22].

3 Results and Discussion

The QTPP summarizes the required quality of a drug product to ensure safety and efficacy. The QTPP (Quality Target Product Profile) of fast dissolving solid oral tablet presented in (Table 4) includes data on dosage form and its design, dosage strength, route of administration, drug product quality attributes, packaging material information and its storage conditions. CQAs were defined from QTPP as per the criticality of the product type and formulation. Table 3 summarizes the CQAs of fast dissolving oral solid tablets, as well as the explanation for their criticality. CQAs of oral solid tablet formulation were disintegration time (sec) (Y1) and friability (%) (Y2).

Table 4. CQA'S and QTPP for therapeutically useful oral solid tablet formulation

QTPP Components	Target	Rationale of requirements
Dosage Form	FDT (Fast Dissolving Tablet)	Patient Compliance
Dosage Design	Immediate Release Fast Dissolving Tablet	Patient Acceptability & Compliance
Route of Administration	Oral route	For Buccal & esophageal adsorption
Dosage Strength	23.5 mg	Required for Therapeutic action
Pharmacokinetics	Maximum Bioavailability	Pharmaceutical Equivalence
Stability	Stable for 3 Month in accelerated study	As per ICH Guidelines
Storage condition	Store in cool and dry place	To keep product stable throughout the shelf life.
Alternativeadministration method	None	None
Packaging material information	Suitable for the finished product quality criteria	Required to get the targeted expiry date with required product qu
Quality Attributes of Drug Product		
Appearance	Tablet confirming to shape, size and description	Patient Acceptability & Compliance
Hardness	2 - 5 kg/cm^2	Resistance of breaking and drug release

Continued on next page

Table 4 continued

Disintegration Time	NMT 3 Min	Required to meet Pharmacopoeial requirement
Friability	NMT 1.0%	Required to meet Pharmacopoeial requirement
Critical Quality Attributes		
Disintegration Time	NMT 3 Min	Required for immediate drug release from the product
Friability	NMT 1.0%	Required for Product intactness

Table 5. Initial risk assessment of critical material attributes (CMA) impacts on Critical Quality Attributes (CQAs)

Product CQA	Active Ingredients	Disintegrating Agent	Binder	Filler	Glidant	Sweetener
Assay	ML	LL	LL	LL	LL	LL
Hardness	LL	LL	ML	LL	LL	LL
Disintegration Time	LL	**HL**	**HL**	LL	LL	LL
Friability	LL	**ML**	**HL**	LL	LL	LL
Moisture Content	LL	ML	ML	LL	LL	LL

LL- Low level, ML- Medium level, HL-High level

Considering previous scientific data and knowledge, an Initial Risk Assessment of herbal active ingredients and excipients was taken into consideration to reach the QTPP. Herbal extracts were discovered to be a crucial input ingredient among them. Table 5 summarizes the preliminary assessment of risk for this critical material and Table 6 summarizes the preliminary assessment of risk for product variables with logic.

Table 6. Preliminary risk assessment of formulation variables on product CQAs

Formulation Variables	Product CQAs	Justification
Disintegrating Agent	Assay	Disintegrating Agent will not affect the Assay of FDT. Hence, risk is ranked low.
	Hardness	Hardness of FDT may affect disintegration time and hence the risk is medium.
	Disintegration Time	Disintegrating Agent will be influencing DT Hence it is critical in formulation. Proper selection of Disintegrating Agent with optimum concentration is most important factor for FDT formulation development. Hence, risk is ranked high.
	Friability	Disintegrating agents affects friability due to moisture uptake in the formulation. It may lead to lose some part or break some part of tablet. Hence, their impact on tablet flexibility is important. Proper selection of Disintegrating Agent is most important factor for FDT formulation development. Hence, risk is ranked high.
	Moisture Content	Disintegrating agent's impacts on moisture content due to moisture uptake in the formulation. Hence, their impact on tablet is important. Proper selection of Disintegrating Agent is most important factor for FDT formulation development. Hence, risk is ranked medium.
Binder	Assay	Binder will not affect the Assay in the FDT formulation directly. Hence, risk is ranked low.
	Hardness	Binder quantity in FDT formulation may influence disintegration time and hence the risk is medium.
	Disintegration Time	Binder will be affecting DT Hence it is critical in formulation. Proper selection of Binder with optimum concentration is most important factor for FDT formulation development. Hence, risk is ranked high.

Continued on next page

Table 6 continued

	Friability Moisture Content	Binder affects friability due to physical strength of tablet in the formulation. It may lead to losing some part or breaking some part of tablet. Hence, their impact on tablet flexibility is important. Proper selection of Binder is most important factor for FDT formulation development. Hence, risk is ranked high. Binder may impact on moisture content due to moisture uptake in the formulation. Proper selection of Binder is most important factor for FDT formulation development. Hence, risk is ranked medium.
Filler	Assay Hardness Disintegration Time Friability Moisture Content	Filler will only provide bulk to the tablet. It will not affect any other CQAs of the FDT. Hence, the risk is ranked low.
Glidant	Assay Hardness Disintegration Time Friability Moisture Content	Glidant will not affect any other CQAs of the FDT. Hence, the risk is ranked low.
Sweetener	Assay Hardness Disintegration Time Friability Moisture Content	Sweetener will not affect any other CQAs of the FDT. Hence, the risk is ranked low.

Formulation elements that had a major impact on CQAs were thoroughly explored and exposed to the design of experiments on the basis of the preliminary risk assessment study. Crucial materials of the therapeutic ingredient (natural extracts) were also exposed to the control method.

DoE comprised two primary formulation variables whose deviations were deemed to be the most dangerous to the final product's quality profile. These variables were rated as high-level risk depending on their RPN -Risk Priority Number. The key formulation factors for the design of experimentation were croscarmellose sodium concentration (mg) (X1) and PVP K30 (mg) (X2). Oral solid tablets were developed and optimized using a randomized 3^2 central composite design.

Table 7 shows the experimental trials with variables that are independent and analyzed responses for the proposed oral fast dissolving solid tablet formulation containing herbal extract. Table 8 shows data on the physical responses of the factorial batches. Physical responses were taken on the formulation batches number B1 to B9 and confirmed the suitability of all physical parameters.

Table 7. Formulation details of fast dissolving tablet –Variables and Responses based on design expert (v23.1)

Standard	Run	Variable 1	Variable 2	Response 1	Response 2
		A: Croscarmellose Sodium	B: Polyvinylpyrrolidone K-30	Disintegration time (Sec)	Friability (%)
2	1	4	0.4	26.24±0.12	0.78±0.10
4	2	4	0.5	34.68±0.28	0.38±0.24
6	3	4	0.6	41.74±0.44	0.41±0.23
9	4	5	0.4	26.24±0.32	0.82±0.12
8	5	5	0.5	22.12±0.43	0.28±0.08
7	6	5	0.6	40.14±0.15	0.34±0.37
1	7	6	0.4	24.46±0.32	0.79±0.30
3	8	6	0.5	24.98±0.32	0.35±0.12
5	9	6	0.6	38.18±0.15	0.38±0.14

Statistical optimization of fast dissolving oral tablet was carried out by comparing all statistical parameters provided by Design Expert v23.1 software. Table 9 represents outcome of statistical data summary by applying ANOVA (analysis of variance).

Table 8. Physical responses of factorial batches

Batches	Average Weight (in mg)	Thickness (in mm)	Hardness (in kg/cm^2)	Disintegration time (in sec)	Friability (in %w/w)	Moisture Content (in %w/w)
B1	100.14±0.32	3.50±0.28	2.12±0.12	26.24±0.12	0.78±0.10	1.78±0.10
B2	100.28±0.12	3.52±0.32	3.51±0.15	34.68±0.28	0.38±0.24	1.82±0.15
B3	99.78±0.88	3.51±0.22	3.21±0.24	41.74±0.44	0.41±0.23	1.64±0.12
B4	100.12±0.39	3.49±0.26	2.31±0.36	26.24±0.32	0.82±0.12	1.73±0.84
B5	100.02±0.34	3.50±0.48	3.34±0.18	22.12±0.43	0.28±0.08	1.62±0.93
B6	99.72±0.22	3.52±0.12	3.63±0.12	40.14±0.15	0.34±0.37	1.82±0.37
B7	100.45±0.29	3.50±0.44	1.81±0.72	24.46±0.32	0.79±0.30	1.62±0.73
B8	100.27±0.45	3.51±0.12	3.01±0.72	24.98±0.32	0.35±0.12	1.73±0.92
B9	99.91±0.73	3.50±0.22	3.31±0.18	38.18±0.15	0.38±0.14	1.56±0.38

Independent variables & their respective response were analyzed together using polynomial-equations and statistical rendering using software Design Expert v23.1.

Table 9. ANOVA (Analysis of Variance) - Statistical summary

Response	MS	DF	SS	F Value	P Value	R^2 Value	Predicted R^2 Value	Adjusted R^2 value	Model Significance
Y1	173.79	2	347.59	8.72	0.0168	0.7441	0.5688	0.6587	Significant
Y2	0.1325	2	0.2650	5.97	0.0374	0.6655	0.3361	0.5540	Significant

MS is mean of squares, DF is degree of freedom, SS is sum of squares, F value is ratio of Fischer's, P value is probability, R2 value is regression coefficient.

As per the ANOVA, Both the responses implicate P-Value less than 0.05 stipulating model terms are significant. The predicted R^2 is in rational agreement with the adjustment R^2. So that the variation is less than 0.2 indicating more significance of the model.

Table 10. Coefficient in terms of coded factors

Factor	DF	Estimated Coefficient	Standard error
Intercept	1	30.98	1.49
A-CCS	1	-2.51	1.82
B-PVP K30	1	7.19	1.82

The Coefficient estimates in Table 10, represent the anticipated change in response as per unit change in factor value. When rest factors had kept constant. The intercept in an orthogonal design is the comprehensive mean reciprocation of all the runs.

Contour plots and Response surface plots were created to graphically portray the influence of each component on responses (Figures 1, 2, 3 and 4). Graphical demonstration of both the plots shows that increasing the amount of X1 variable has less effect on the Y1 response while increasing the amount of X2 variable increases the value of Y1 response. It indicates that as the concentration of PVP K-30 increases, DT (sec) soars. On other side as the quantity of CCS increases, DT (sec) remains unaltered. Figures 1 and 2 show that X2 variable has a more substantial effect on Y1 response than X1 variable.

On the basis of coefficient derived from the study ANOVA, as mentioned in Table 10, it had been revealed that X1 variable, which is independent having a negative sign, represents a significant influence on the Y1 response, whereas the variable has a positive sign, indicating that it has negligible on the said response. The Response Surface and Contour Plot shows that when the concentration of variable X2 is high, the response value of Y2 falls means when the amount of PVP K-30 is high, the percentage of Friability reduces (Figures 3 and 4). The concentration of Croscarmellose sodium has a negligible effect on friability. As a result, it may be argued that X2 variable has a large influence on response Y2.

It was decided to create a design space for fast dissolving oral solid tablet formulation containing herbal extracts. Based on product quality requirements, the parameters examined for establishing design-space include disintegration time (in seconds) of a maximum of 60 seconds and Friability percentage of a maximum 1.0%. Based on the above criteria, it brings out the design-space based on a multi-dimensional combination of ingredients, which leads to the determination of the right operating ranges for producing therapeutically effective fast dissolving solid tablet dosage form with respect to the target product profile. The specific region with yellow colour in the design space (Overlay plot) denoted in Figure 5 demonstrates the space or area of optimum ranges of operation.

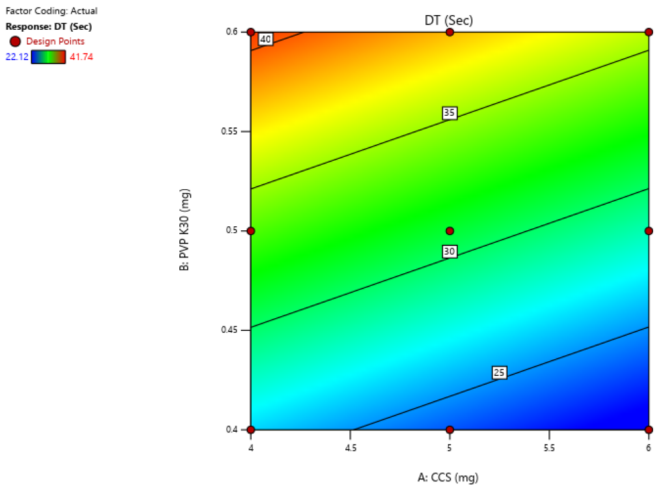

Fig 1. Contour - Plot - Response for Y1 [DT - Disintegration Time (in sec)]

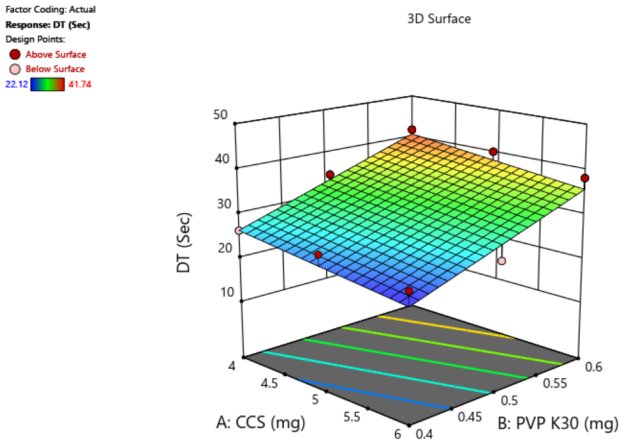

Fig 2. RSP - Response Surface Plot for Response Y1 [DT - Disintegration Time (in sec)]

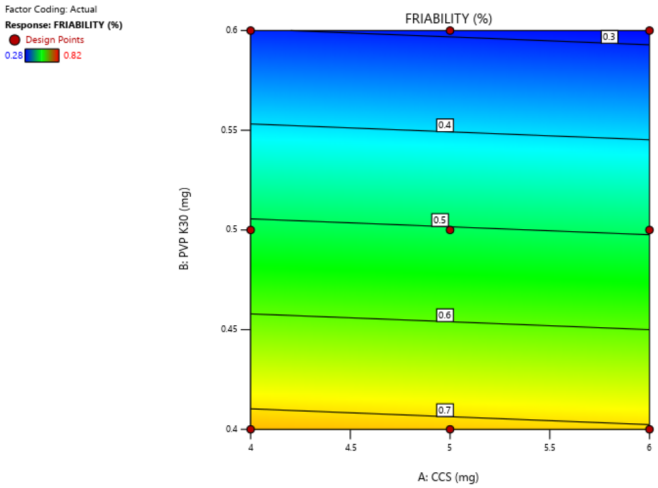

Fig 3. Contour - Plot - Response for Y2 [Friability (in %)]

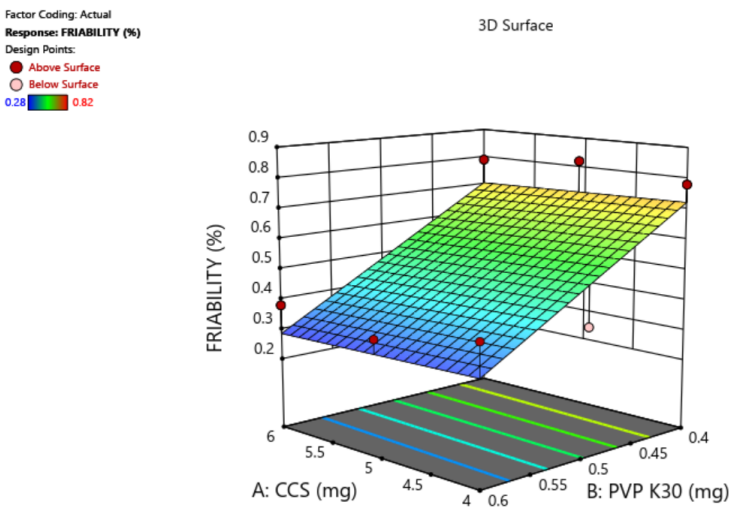

Fig 4. RSP - Response Surface Plot for Response Y2 [Friability (in %)]

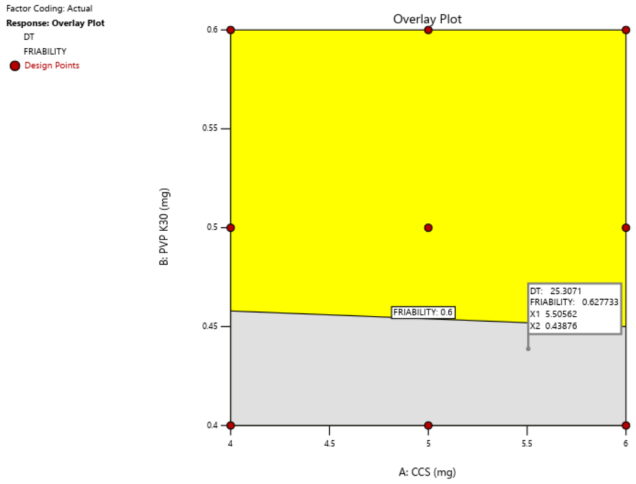

Fig 5. Overlay-plot with design-space shows that B-5 formulation trial (CCS - 5mg and PVP K-30 0.5mg) falls in design-space region

As per the outcome of design-space, B-5 batch drops within the optimum operating range with respect to variables and responses. As a result, formulation B-5 (PVP K-30 with 0.5 mg quantity and CCS with 5 mg quantity) met the QTPP and CQA criteria for fast dissolving oral solid tablet containing herbal extract. As a result, B-5 was chosen as the final optimized formulation.

Tables 11 and 12 revealed the results. Predicted mean and actual mean values of the optimized formulation's (B-5), CQAs are practically identical. There is excellent concurrence between experimental outcomes and model predictions. This implies that there is statistical equality between theinvestigational and forecasted values. It exemplifies the creditability of selected formulation variables, their levels and applied model. 3^2 CCD (Central composite design) was carried out for DoE-design of experiments. Formulation B-5 was further taken for accelerated stability study and evaluation.

Table 11. Point Predictions vs Actuals for variables

Variables	Predicted Mean	Actual Mean
Croscarmellose sodium (mg)	5.51	5.0
Polyvinylpyrrolidone K-30 (mg)	0.4388	0.50

Table 12. Point Predictions vs Actuals for responses

Response Value	Predicted Mean	Standard Deviation	Actual Mean	Standard Deviation
Disintegration Time (Sec.)	25.307	4.9231	22.12	0.43
Friability (%)	0.6278	0.1643	0.28	0.08

To ensure consistent product quality during manufacturing, a control strategy has been evolved. The control proposal contained variables that were assessed for high levels of risk in the original risk assessment & required to be managed within their sanctioned value range. CMAs of active materials (herbal extracts), are comprised of a control strategy of fast dissolving oral solid tablet formulation incorporating herbal extracts, as are the estimates used to limit the risk connected with these CMAs.

Table 13. Stability Study of optimized formulation B5

Evaluation Parameters	Initial	1 Month		2 Month		3 Month	
		Long Term	Accelerated	Long Term	Accelerated	Long Term	Accelerated
		30°C/75%RH	40°C/75%RH	30°C/75%RH	40°C/75%RH	30°C/75%RH	40°C/75%RH
Appearance	Yellow coloured Round, Biconvex Tablets	Yellow coloured Round, Biconvex Tablets	Yellow coloured Round, Biconvex Tablets	Yellow coloured Round, Biconvex Tablets	Yellow coloured Round, Biconvex Tablets	Yellow coloured Round, Biconvex Tablets	Yellow coloured Round, Biconvex Tablets
Weight Variation (mg)	100.02±0.34	100.12±0.54	100.32±0.24	100.18±0.56	100.43±0.44	100.22±0.24	100.63±0.54
Thickness (mm)	3.50±0.48	3.50±1.08	3.52±1.68	3.50±0.98	3.54±1.48	3.50±0.78	3.55±1.48
Hardness (kg/cm^2)	3.34±0.18	3.24±0.58	3.14±0.08	3.04±0.38	2.94±1.18	3.01±0.48	2.84±0.88
Disintegration Time (sec.)	22.12±0.43	21.28±0.53	20.12±0.73	22.02±0.83	18.15±0.63	20.62±0.73	16.52±0.63
Friability (%)	0.28±0.08	0.29±0.28	0.32±0.78	0.28±0.78	0.38±0.38	0.31±0.08	0.28±0.88
Moisture Content (%)	1.62±0.93	1.74±0.63	1.82±0.96	1.72±0.76	1.92±0.83	1.82±0.90	1.98±0.63

Table 13 indicates the outcome of the stability study performed on the optimized batch (B-5) in accordance with ICH stability study directions. The physical parameters of formulation batch B-5 did not deviate notably. Hardness, friability, disintegration time and moisture content values changed a bit as per the expected within limits. According to this research, the optimized final batch formulation is stable for 3 months as per ICH guideline criteria.

Development of fast dissolving tablet with three different therapeutically active herbal extracts (Curcumin, Saffron and Gingerol) was successfully done with QbD approach. Development of fast dissolving formulations with Herbal extracts itself is a challenge in comparison with other potent pharmaceutical drugs. While handling herbal extracts, it is always a challenge to achieve disintegration time and hardness in the formulation. Things are a bit complicated when combination of herbal extracts is used with potency of 23.5%. Applying QbD in such a product, optimizing the formulation and getting desired results is the accomplishment.

The Quality by Design (QbD) approach guarantees that the final product consistently adheres to established quality standards, resulting in safer and more effective herbal formulations. Implementing QbD facilitates more efficient compliance with regulatory requirements by aligning with guidelines that prioritize a science-based approach to product development. By pinpointing and managing critical quality attributes and process parameters, QbD significantly reduces the likelihood of product failures and recalls. By optimizing processes and reducing variability, QbD can lower costs related to product development and manufacturing, resulting in fewer batch failures and less waste. The systematic methodology of QbD deepens the understanding of the manufacturing process, fostering innovations and continuous improvements over time. The aim of QbD is to guarantee that herbal formulations are both safe and effective for consumers. By rigorously controlling product quality, patients receive treatments that are both reliable and effective. This fosters trust and satisfaction among consumers, which is crucial for the success of any therapeutically active product.

4 Conclusion

This study concludes that QbD approach can be successfully used to formulate fast dissolving solid oral tablet with three different herbal extracts including curcumin, gingerol and saffron. The trials with the suitable experimental model were aided by Design-Expert®(v23.1). The risk assessment study directed to control the risk from high level to low level. Formulation developed within the design space can be able to obtain final product CQAs with essential QTPP. The results were statistically analyzed and observed that croscarmellose sodium (CCS) and polyvinyl pyrrolidone (PVP K30) had a significant effect on the responses. Even though herbal extracts are 23.5% [The mixture of Curcumin (12%), Saffron (1.5%) and Gingerol (10%)] in the formulation, which impacts critical parameters like DT & Hardness jointly unlike pharmaceutical drugs or API. ANOVA study revealed that the model is fit, and states work well; in addition, the suitable selection of QTPP and CQAs was the key to finding desired quality in the final product. The optimized FDT with these herbal combinations was found to have a DT of 22.02$\pm$0.83 sec and hardness 3.34$\pm$0.18 kg/cm^2; Additionally, stability study data supported the robustness of the optimized formulation. With higher patient compliance, FDTs containing multiple extracts are seen as a promising alternative for administration and inspiring further similar research.

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