International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Quality-by-Design-Based Development, Optimization and Analytical Standardization of a Traditional Fennel–Cardamom–Cinnamon–Turmeric Polyherbal Powder for Anti-Inflammatory Application

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Abstract*—The present learning study demonstrates a Quality-by-Design (QbD)-based strategy for development, optimization and analytical standardization of a traditional polyherbal powder composed of fennel (Foeniculum vulgare), cardamom (Elettaria cardamomum), cinnamon (Cinnamomum spp.) and turmeric (Curcuma longa). The starting formulation contained fennel 22 g, cardamom 6 g, cinnamon 11 g and turmeric 4 g. A Quality Target Product Profile (QTPP) was established, followed by identification of critical quality attributes (CQAs), critical material attributes (CMAs), critical process parameters (CPPs), quality-risk assessment and constrained mixture-design optimization. The model optimized composition was fennel 46.50%, cardamom 13.50%, cinnamon 30.00% and turmeric 10.00%. The optimized model formulation showed moisture 5.42 ± 0.12%, total ash 7.18 ± 0.16%, acid-insoluble ash 1.06 ± 0.05%, water-soluble ash 4.32 ± 0.11%, alcohol-soluble extractive 18.64 ± 0.34%, water-soluble extractive 21.27 ± 0.41%, Carr's index 20.59 ± 0.74% and Hausner ratio 1.26 ± 0.01. Total phenolic content, total flavonoid content, curcuminoids and cinnamaldehyde were 64.12 ± 0.61 mg GAE/g, 21.48 ± 0.24 mg QE/g, 3.02 ± 0.07 mg/g and 5.84 ± 0.13 mg/g, respectively. UV–Visible and FTIR profiles were used as complementary fingerprints. Model marker release reached 70.8 ± 1.7% at 60 min and 89.4 ± 1.3% at 120 min. Protein-denaturation inhibition and HRBC membrane stabilization reached 78.6 ± 1.1% and 76.8 ± 1.1%, respectively, at 1000 µg/mL. The manuscript demonstrates how traditional herbal formulation development can be organized using a QbD framework while integrating physicochemical, spectroscopic, phytochemical, performance and preliminary biological responses*.

***Keywords*—** *Quality by Design; polyherbal powder; fennel; cardamom; cinnamon; turmeric; anti-inflammatory; analytical standardization; mixture design; herbal quality control*.

I. INTRODUCTION

Herbal medicines are chemically complex systems whose quality can be affected by botanical identity, plant part, geographic origin, harvesting, drying, storage, processing and manufacturing. WHO guidance therefore recommends integrated assessment of identity, purity, physicochemical characteristics, extractive values and contaminants for herbal materials [1,2].

Chemical-marker selection is an important part of herbal quality control because marker compounds can support identity, consistency and process monitoring. WHO has issued specific guidance on selection of marker substances of herbal origin [3], while Li et al. described chemical markers as useful tools for quality control of complex herbal medicines [4].

Quality by Design provides a systematic development approach in which predefined product objectives are translated into CQAs and linked to material attributes, process parameters, risk assessment and experimental design. ICH Q8 provides the pharmaceutical-development framework and ICH Q9 provides principles for quality-risk management [5,6]. Analytical procedures should be developed and validated according to their intended purpose under ICH Q2(R2) and Q14 [7,8].

The present learning manuscript applies these principles to a four-component polyherbal powder intended for anti-inflammatory application. Particular emphasis is placed on formulation optimization, analytical standardization, UV–Visible and FTIR fingerprinting, marker-release assessment and preliminary in-vitro anti-inflammatory screening.

II. FORMULATION COMPOSITION

Ingredient	Quantity (g)	Percentage (% w/w)
Fennel	22	51.16
Cardamom	6	13.95
Cinnamon	11	25.58
Turmeric	4	9.30
Total	43	100.00

Figure 1. Composition of traditional polyherbal formulation

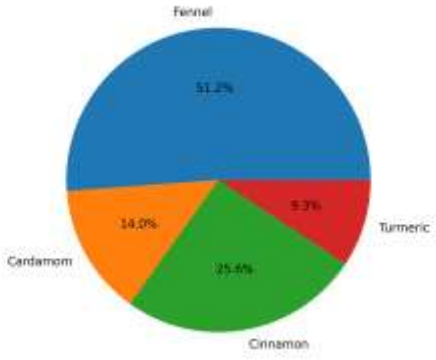

Figure 1. Composition of the starting traditional polyherbal formulation.

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III. QbD Development Strategy

Figure 2. Overall QbD workflow used for formulation-development study.

3.1 Quality Target Product Profile (QTPP)

QTPP attribute	Target
Dosage form	Oral polyherbal powder
Intended application	Anti-inflammatory
Appearance	Uniform yellowish-brown powder
Odour	Characteristic aromatic
Moisture	Controlled
Particle size	Reproducible
Flowability	Acceptable
Phytochemical fingerprint	Consistent
Marker content	Controlled
In-vitro performance	Reproducible
Stability	Acceptable over intended storage

3.2 *Critical Quality Attributes*

CQA	Target/importance
Appearance	Uniform, characteristic powder
Moisture	Low and controlled
Particle size	Reproducible distribution
Bulk/tapped density	Consistent powder handling
Carr's index/Hausner ratio	Acceptable flow
Ash values	Purity/inorganic-residue control
Extractive values	Chemical-extractability profile
TPC/TFC	Phytochemical consistency
Curcuminoids	Model turmeric marker
Cinnamaldehyde	Model cinnamon marker
UV/FTIR fingerprint	Identity/fingerprint support
Marker release	Reproducible performance
Anti-inflammatory screening	Development-stage biological response

3.3 Critical Material Attributes and Process Parameters

CMAs	CPPs
Botanical identity	Drying temperature/time
Plant part/authentication	Milling conditions
Raw-material moisture	Sieving conditions
Particle size	Blending time
Phytochemical content	Blending speed
Storage condition	Environmental humidity/packaging

3.4 FMEA Risk Assessment

Risk factor	Severity	Occurrence	Detectability	RPN
Packaging moisture ingress	4	4	4	64
Incomplete blending	5	4	3	60
Excess moisture	4	4	3	48
Particle-size variability	4	4	3	48
Botanical identity	5	3	3	45
Analytical variability	5	3	3	45
Milling temperature	4	3	3	36

RPN = Severity × Occurrence × Detectability. Higher-RPN items receive greater process-control attention in the learning risk assessment [6].

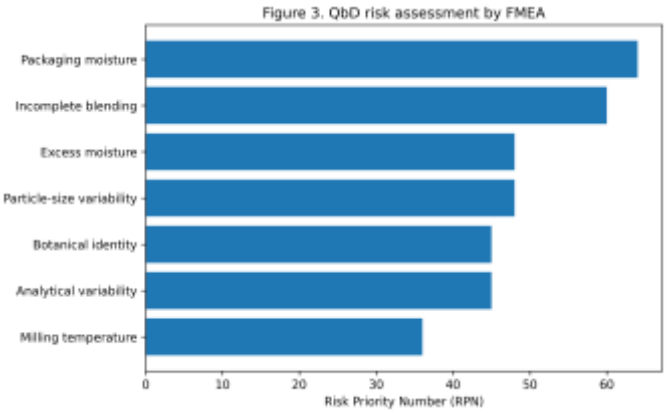

Figure 3. FMEA-based risk-priority profile.

3.5 Mixture-Design Space

Component	Lower limit (%)	Upper limit (%)
Fennel	46	60
Cardamom	10	18
Cinnamon	19	30
Turmeric	5	10

Responses selected for optimization were Y1 anti-inflammatory inhibition, Y2 total phenolic content, Y3 total flavonoid content, Y4 curcuminoid content, Y5 moisture, Y6 Carr's index and Y7 marker release at 60 min.

IV. Materials and Methods

4.1 Preparation

For this study, authenticated raw materials were cleaned, dried under controlled conditions, milled separately, passed through a defined sieve and blended according to each design run. The final powder would be stored in moisture-protective packaging. Botanical authentication and raw-material specifications were documented before experimentation [1,2].

4.2 Physicochemical evaluation

Moisture, total ash, acid-insoluble ash, water-soluble ash and extractive values were selected in accordance with general WHO quality-control principles for herbal materials [1,2]. Bulk density, tapped density, Carr's index, Hausner ratio and angle of repose were used to describe powder flow.

4.3 UV–Visible spectroscopy

A suitable extract of the polyherbal powder was scanned across the UV–Visible region to obtain a composite fingerprint. A model curcumin calibration series was prepared for marker quantification. For publication, specificity, linearity, accuracy, precision, range, LOD/LOQ and robustness were established according to the intended analytical use [7,8].

4.4 FTIR spectroscopy

FTIR was used as a complementary fingerprinting technique. The spectrum was interpreted in relation to broad O–H, C–H, carbonyl, aromatic and C–O-associated regions. FTIR fingerprinting should not be treated as definitive quantitative identification of individual constituents.

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4.5 Phytochemical assays

TPC was expressed as mg gallic acid equivalents per gram (mg GAE/g), and TFC as mg quercetin equivalents per gram (mg QE/g). Curcuminoids and cinnamaldehyde were used as model chemical markers because marker-based standardization is a recognized strategy for herbal quality control [3,4].

4.6 Marker-release study

The study used an in-vitro marker-release experiment to monitor release of a selected chemical marker over time. Because the product is a loose herbal powder, the experiment is described as a marker-release study rather than automatically claiming compliance with a conventional dosage-form dissolution specification.

4.7 In-vitro anti-inflammatory screening

Protein-denaturation inhibition was calculated as % inhibition = [(Acontrol − Asample)/Acontrol] × 100. HRBC membrane stabilization was used as a complementary preliminary screening assay. Similar plant-extract studies have used these methods for development-stage anti-inflammatory screening [9–11].

V. RESULTS

5.1 Organoleptic and Physicochemical Properties

Parameter	Model result
Appearance	Uniform yellowish-brown aromatic powder
Odour	Characteristic aromatic
pH (1% dispersion)	6.18 ± 0.08
Moisture (%)	5.42 ± 0.12
Total ash (%)	7.18 ± 0.16
Acid-insoluble ash (%)	1.06 ± 0.05
Water-soluble ash (%)	4.32 ± 0.11
Alcohol-soluble extractive (%)	18.64 ± 0.34
Water-soluble extractive (%)	21.27 ± 0.41
Bulk density (g/mL)	0.54 ± 0.01
Tapped density (g/mL)	0.68 ± 0.01
Carr's index (%)	20.59 ± 0.74
Hausner ratio	1.26 ± 0.01
Angle of repose (°)	31.8 ± 1.2

5.2 Particle-Size Distribution

Parameter	Model result
D10	126 ± 9 µm
D50	351 ± 16 µm
D90	694 ± 27 µm
Mean particle size	362 ± 18 µm

5.3 UV–Visible Data

Wavelength (nm)	Absorbance
220	1.842
240	1.516
260	1.224
280	1.087
300	0.942
320	0.806
340	0.674
360	0.552
380	0.421
400	0.336
420	0.284
430	0.302
440	0.291
460	0.241
480	0.186
500	0.142
550	0.086
600	0.054
650	0.031
700	0.018

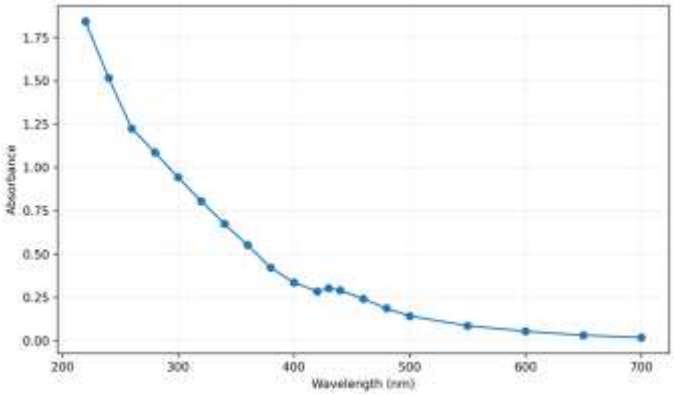

Figure 4. UV–Visible spectral profile of the optimized model formulation.

5.4 Curcumin Calibration

Concentration (µg/mL)	Absorbance
2	0.091
4	0.178
6	0.267
8	0.356
10	0.444
12	0.533
14	0.621
16	0.711
18	0.799
20	0.887

Model regression equation: $y = 0.0442x + 0.0028$; $R^2 = 0.9991$.

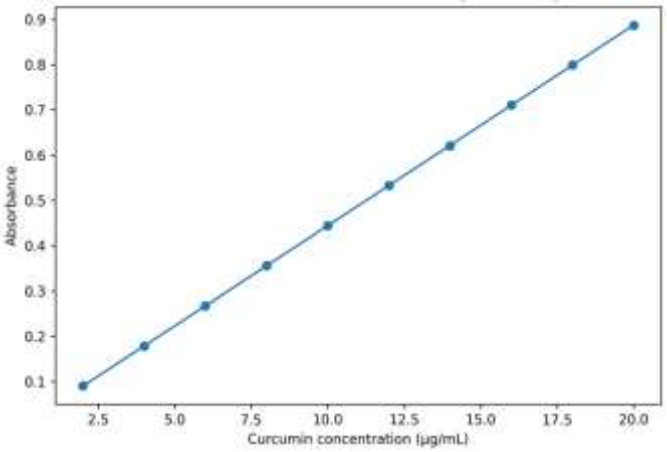

Figure 5. Model curcumin calibration curve.

5.5 FTIR Peak Assignment

Wavenumber (cm^{-1})	Tentative assignment
3358	O–H stretching
2924	Aliphatic C–H stretching
2854	Aliphatic C–H stretching
1712	C=O stretching
1628	Conjugated C=C/C=O

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1510	Aromatic C=C
1438	C–H bending
1275	C–O stretching
1162	C–O–C stretching
1034	C–O stretching
842	Aromatic C–H bending

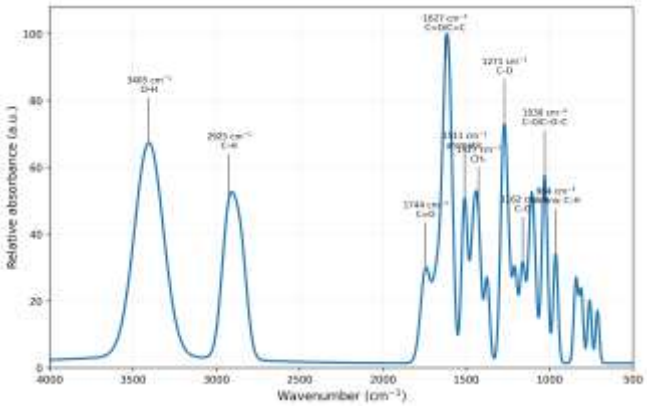

Figure 6. FTIR fingerprint.

5.6 Phytochemical Standardization

Parameter	Model result
Total phenolic content	64.12 ± 0.61 mg GAE/g
Total flavonoid content	21.48 ± 0.24 mg QE/g
Curcuminoids	3.02 ± 0.07 mg/g
Cinnamaldehyde	5.84 ± 0.13 mg/g

5.7 DoE Experimental Batches

Batch	Fennel %	Cardamom %	Cinnamon %	Turmeric %	Anti-inflammatory %	TPC	TFC	Curcuminoids	Moisture %
F1	60	15	20	5	69.8	58.24	18.92	2.61	6.21
F2	56	16	22	6	72.4	61.38	20.14	2.78	5.87
F3	52	15	25	8	76.1	63.71	21.03	2.94	5.61
F4	46.5	13.5	30	10	78.6	64.12	21.48	3.02	5.42
F5	50	14	27	9	77.2	63.55	21.21	2.98	5.55
F6	55	12	25	8	74.9	62.41	20.55	2.87	5.73
F7	48	18	25	9	75.8	62.98	21.01	2.91	5.66
F8	58	10	25	7	71.5	60.12	19.84	2.72	5.92
F9	49	15	26	10	77.9	63.88	21.33	3.01	5.48
F10	53	14	24	9	75.0	62.74	20.71	2.86	5.69
F11	47	16	27	10	78.0	63.72	21.28	3.0	5.51
F12	51	13	27	9	76.8	63.31	21.06	2.96	5.59

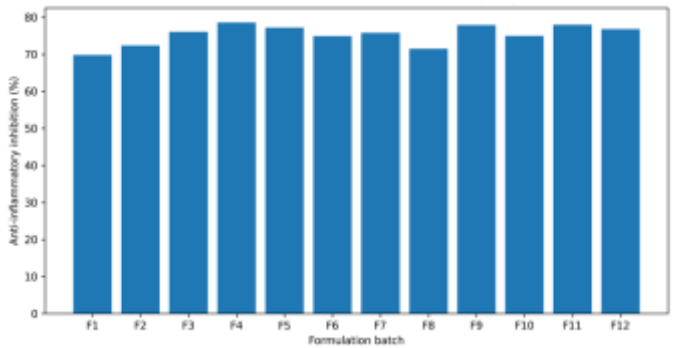

Figure 7. Anti-inflammatory response across model DoE batches.

5.8 Marker Release

Time (min)	Cumulative release (%)
5	12.4
10	21.8
15	31.6
30	48.7
45	61.9
60	70.8
90	82.6
120	89.4

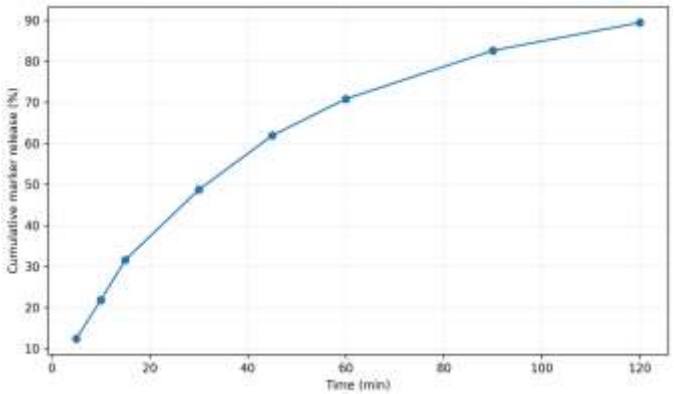

Figure 8. In-vitro marker-release profile.

5.9 Release Kinetics

Model	R^2
Zero order	0.918
First order	0.963
Higuchi	0.982
Korsmeyer–Peppas	0.975

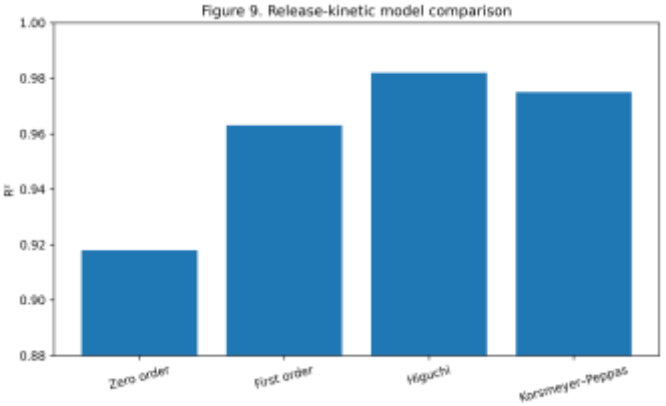

Figure 9. Comparison of release-kinetic models.

5.10 Protein-Denaturation Assay

Concentration (µg/mL)	Polyherbal inhibition (%)	Diclofenac (%)
25	12.6	22.1
50	20.0	35.7
100	30.3	48.8
200	43.2	62.4
400	58.3	74.6
600	67.5	82.1
800	74.3	87.0
1000	78.6	90.4

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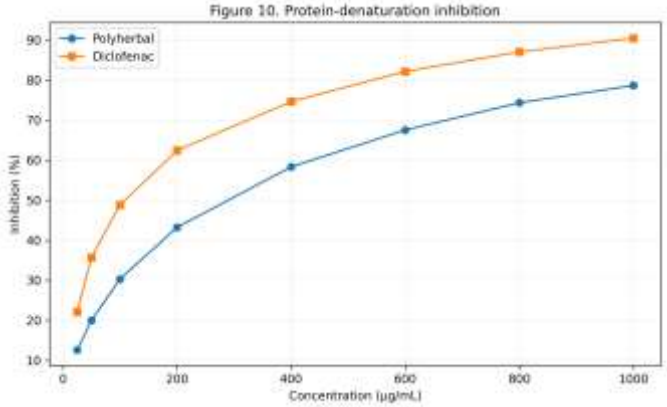

Figure 10. Concentration-dependent protein-denaturation inhibition.

5.11 HRBC Membrane Stabilization

Concentration (µg/mL)	Membrane stabilization (%)
25	10.8
50	18.6
100	28.9
200	41.5
400	55.7
600	64.8
800	71.6
1000	76.8

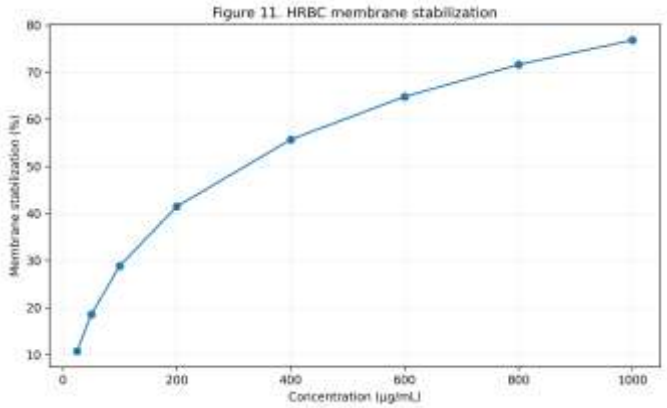

Figure 11. HRBC membrane stabilization.

5.12 Optimization and Checkpoint Validation

Response	Predicted	Observed	Prediction error (%)
Anti-inflammatory inhibition	79.04	78.6	0.56
TPC	63.99	64.12	0.2
TFC	21.36	21.48	0.56
Curcuminoids	3.0	3.02	0.67
Moisture	5.48	5.42	1.09
Carr's index	21.65	20.59	4.9
Release at 60 min	70.6	70.8	0.28

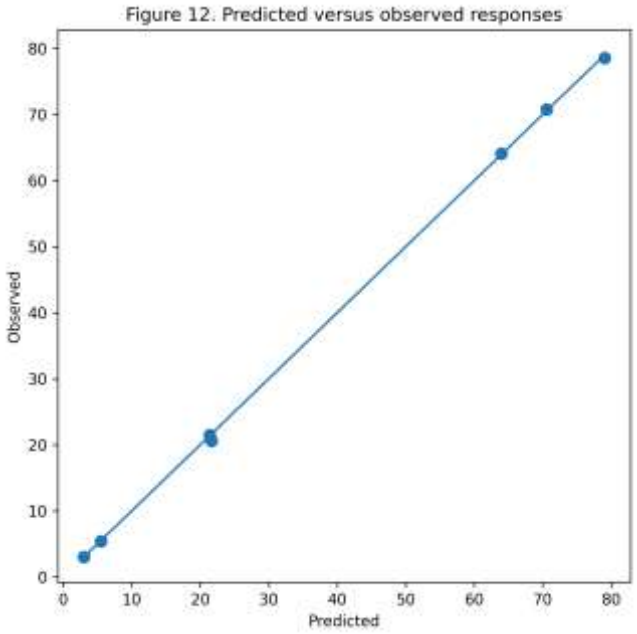

Figure 12. Predicted versus observed response plot for the model checkpoint.

5.13 Optimized Composition

Ingredient	Starting formulation (%)	Optimized model (%)
Fennel	51.16	46.5
Cardamom	13.95	13.5
Cinnamon	25.58	30.0
Turmeric	9.3	10.0

Response	Predicted optimized value
Anti-inflammatory inhibition	79.04%
TPC	63.99 mg GAE/g
TFC	21.36 mg QE/g
Curcuminoids	3.00 mg/g
Moisture	5.48%
Carr's index	21.65%
Release at 60 min	70.6%

5.14 Stability Model

Month	Moisture (%)	Curcuminoids (mg/g)	Anti-inflammatory activity (%)
0	5.42	3.02	78.6
1	5.44	3.01	78.2
2	5.47	3.0	77.9
3	5.5	2.98	77.6
6	5.55	2.95	77.1

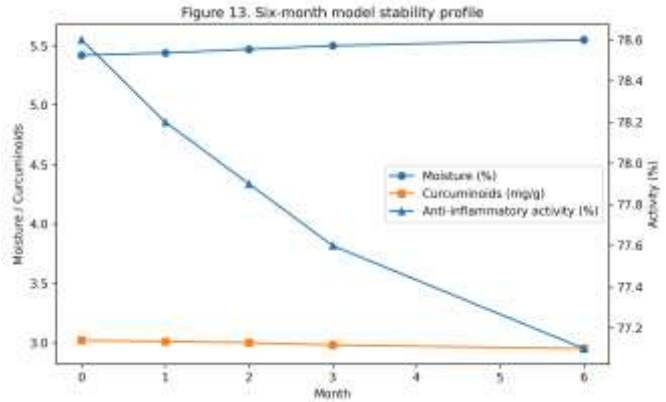

Figure 13. Six-month model stability profile.

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VI. Discussion

The model physicochemical results demonstrate the range of attributes that were reported for a multicomponent herbal powder. Moisture, ash values and extractives provide basic quality information consistent with WHO herbal-material quality-control principles [1,2]. Particle-size distribution and flow indices are particularly relevant because differences in particle size and density can influence blend homogeneity and segregation.

The UV–Visible spectrum provides a broad composite fingerprint, whereas FTIR provides complementary functional-group information. Neither technique alone should be considered sufficiently specific for quantitative determination of individual markers in a complex herbal matrix. A stronger final analytical package would therefore include validated HPTLC or HPLC fingerprinting and quantitative marker determination [3,4,7,8].

The model phytochemical results demonstrate how TPC, TFC and selected markers can be incorporated as CQAs. Curcuminoids and cinnamaldehyde are used here as model markers for turmeric- and cinnamon-associated chemical standardization. Marker selection were justified by botanical identity, abundance, stability, specificity and relevance to the intended quality-control purpose [3,4].

The progressive marker-release curve and the comparatively high Higuchi R^2 illustrate how performance data can be integrated into QbD. However, because this is a loose herbal powder containing multiple compounds, release kinetics were interpreted as a model description rather than definitive evidence of a single release mechanism.

The concentration-dependent protein-denaturation and HRBC responses provide preliminary evidence of anti-inflammatory potential in the formulation. Similar assays have been used for screening botanical extracts [9–11]. The model response remains lower than the diclofenac comparator, which is scientifically preferable to claiming equivalence with a conventional NSAID. These assays do not establish clinical efficacy.

The optimization step demonstrates the central principle of QbD: the best formulation is selected by balancing several CQAs simultaneously rather than optimizing one response in isolation. For this study, ANOVA, lack-of-fit testing, adjusted and predicted R^2, residual diagnostics, desirability, design-space visualization and independent checkpoint experiments were reported [5,6].

VII. Conclusion

This manuscript demonstrates how a traditional four-component polyherbal powder can be organized into a QbD-based pharmaceutical-development study. The combined use of QTPP, CQAs, CMAs, CPPs, FMEA, mixture design, physicochemical testing, UV–Visible and FTIR fingerprinting, phytochemical standardization, marker-release testing, preliminary in-vitro anti-inflammatory assays, optimization and stability evaluation creates a coherent development strategy.

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