

Formulation, Optimization and Evaluation of Micronutrient Mini-Tablets for Management of Nutritional Deficiency Disorders

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Abstract—Nutritional deficiency and malnutrition affect populations across every life stage, from childhood to old age, and micronutrients including calcium, iron, iodine, zinc, copper, potassium, sodium and magnesium are essential for oxygen transport, neural function, growth and tissue repair. Commercial supplements are typically formulated at fixed, high doses unsuited to dose personalization, particularly for pediatric and geriatric patients. This study developed patient-compliant, dose-flexible dosage forms, comprising individual 50 mg mineral mini-tablets and a combined 315 mg micronutrient tablet, by direct compression of seven micronutrient salts. A Quality-by-Design framework employing a three-factor Central Composite Design optimized binder, lubricant and glidant/diluent levels against friability and hardness as Critical Quality Attributes, using Design Expert software to generate ANOVA-validated polynomial models and a design space. Formulations were evaluated for pre-compression parameters (angle of repose, bulk and tapped density, Carr's index, Hausner's ratio) and post-compression parameters (hardness, friability, weight variation, appearance), with mineral content confirmed by Atomic Absorption Spectroscopy. Quadratic models for friability ($R^2 = 0.9491$) and hardness ($R^2 = 0.9332$) were statistically significant ($p < 0.0001$) with non-significant lack-of-fit; the point-predicted optimum, 4 mg binder, 5 mg lubricant and 3.5 mg diluent, was validated experimentally with 98.01% and 96.72% accuracy for friability and hardness, respectively. All formulations showed satisfactory flow, acceptable hardness (4.6–5.6 kg/cm²), low friability (under 1%), and mineral content within expected ranges on assay (AAS $r^2 \geq 0.999$). The optimised formulations together offer a scientifically validated, patient-compliant and commercially scalable platform for dose-flexible correction of nutritional deficiencies across all age groups.

Index Terms—Micronutrients; Mini-tablets; Direct compression; Quality by Design; Central Composite Design; Nutritional deficiency; Malnutrition; Atomic Absorption Spectroscopy

I. INTRODUCTION

Good health is founded on sound nutrition, and an even, well-balanced diet combined with regular physical activity is essential for optimal wellbeing and development at every stage of life (Brenner et al., 2021). A balanced diet must supply an adequate and varied proportion of both macronutrients (carbohydrates, proteins and fats) and micronutrients (vitamins and minerals); the human diet requires at least seventeen minerals and thirteen vitamins to prevent nutritional disorders. The quantity of each nutrient required varies with age, illness, pregnancy and lactation, body size, and lifestyle factors such as alcohol intake and smoking (Beauman et al., 2005).

1.1 Micronutrients and Nutritional Deficiency

Micronutrients — principally calcium, chloride, chromium, cobalt, iodine, iron, manganese, magnesium, potassium, phosphorus, selenium and zinc — participate in essentially every biological process governing human growth, development and maintenance, despite being required only in trace amounts. Global regulatory and health bodies have defined age- and sex-specific Recommended Dietary Allowances (RDA) for each of these nutrients. When intake falls persistently below the RDA, a spectrum of nutritional-deficiency disorders can result, ranging from generalised malnutrition to specific conditions such as iron-deficiency anaemia, iodine-deficiency

disorders, zinc deficiency and osteoporosis-related mineral deficiencies (Varghese and Stein, 2019).

Nutrition has been recognised by the World Health Assembly as central to the Sustainable Development Goals 2030, and combating malnutrition — both under-nutrition and the ‘double burden’ of coexisting under- and over-nutrition — remains a global public-health priority (World Health Organization, 2018). In India, national surveys have shown that stunting and iron-deficiency anaemia, though declining, remain highly prevalent, while overweight and obesity are simultaneously rising across age and socio-economic groups (Varghese and Stein, 2019). Because nutritional status among women and children is closely inter-linked, and because poor maternal nutrition compromises both individual health and national productivity, national nutrition policy has historically emphasised macronutrient sufficiency, leaving micronutrient correction comparatively under-addressed at the level of dosage-form design (Madsen and Gitlin, 2007; Gupta and Gupta, 2014).

1.2 Limitations of Existing Dosage Forms

A range of nutritional-supplement formulations — tablets, syrups, suspensions, effervescent powders and chewables — are commercially available to correct nutritional deficiency and malnutrition. However, most marketed products are formulated at a single, fixed high dose intended for a broad age range, and are therefore poorly matched to the wide inter-individual variation in nutrient requirement dictated by age, sex, physiological state and severity of deficiency (Deshpande and Giri, 2013; Emerson and Cavazzuti, 2015). High-dose, large-volume formulations are additionally difficult for paediatric and geriatric patients to swallow, contributing to poor compliance (Szczepanska and Kotlowska, 2019). There is thus a clear need for a dosage-form platform that permits dose individualisation — allowing the clinician or care-giver to titrate the number of dosage units administered according to RDA or deficiency status — while remaining easy to swallow, stable, and inexpensive to manufacture at scale.

1.3 Mini-Tablets as a Patient-Compliant Platform

Mini-tablets — compressed tablets typically 2–4 mm in diameter — have emerged as an attractive multiparticulate alternative to conventional single-unit tablets and capsules. Their small size and near-

spherical geometry improve swallowability across all age groups, including infants and the elderly, and multiple mini-tablets (of the same or different actives) can be combined and encapsulated or sachet-packed to build a required dose, giving considerable flexibility for dose personalisation (Nishida and James, 2004). Because they are manufactured by conventional tableting technology, mini-tablets are readily scalable for commercial production, and their comparatively uniform size and narrow particle-size distribution support content uniformity and ease of downstream processing, such as capsule filling (Lean et al., 2019).

1.4 Rationale and Objectives of the Present Work

Building on this rationale, the present work was designed around the following considerations:

- Nutritional requirements can be addressed individually as per RDA or measured deficiency status.
- Different micronutrients can be delivered together, in a single dosage form, when combination therapy is indicated.
- Mini-tablets are a highly patient-compliant dosage form for both children and adults.
- The optimal particle size and uniform size distribution of mini-tablets facilitate accurate capsule filling.
- Dose can be personalised simply by varying the number of mini-tablets administered.
- The platform offers strong potential for commercial scale-up and for new product development.

Accordingly, the objective of the present study was to develop, statistically optimise using a Quality-by-Design (QbD)/Central Composite Design (CCD) approach, and comprehensively evaluate (i) individual 50 mg mineral mini-tablets of seven micronutrients — magnesium, iodine, iron, zinc, copper, potassium and sodium — and (ii) a fixed-dose combination 315 mg micronutrient tablet containing all seven minerals, each prepared by the direct-compression method, so as to provide a patient-compliant, dose-flexible therapeutic option for the correction of nutritional deficiency and malnutrition across all phases of life.

II. REVIEW OF LITERATURE

The physiological role of trace elements, the epidemiology of nutritional deficiency, and the

pharmaceutical technology of mini-tablet formulation have each been the subject of substantial prior investigation, summarised below.

2.1 Micronutrients in Human Physiology and Disease
Chitturi et al. (2015) reported that trace elements act as cofactors for numerous enzymes and as stabilising centres for enzyme and protein structures, mediating vital biochemical reactions at the cellular, biochemical and molecular level; both deficiency and excess of these elements can precipitate disease. Hussain et al. (2016) similarly noted that trace elements, required in amounts of ≤ 100 mg/day, are integral to normal biological structures and function, and that imbalance in their optimal circulating levels has been associated with a range of chronic and degenerative conditions, including certain malignancies, prompting increasing analytical interest in their diagnostic and prognostic value. Fraga et al. (2005) and Ames et al. (2001) further established the mechanistic links between micronutrient insufficiency, oxidative stress and impaired cellular repair, underscoring the biological rationale for targeted micronutrient supplementation.

2.2 Epidemiology of Nutritional Deficiency

Varghese and Stein (2019), analysing National Family Health Survey-4 (2015–2016) data covering 655,156 women aged 15–49 years and 145,653 children aged 6–59 months across 36 Indian states and 640 districts, demonstrated a persistent double burden of malnutrition — the coexistence of anaemia, underweight and stunting alongside rising overweight — with significant state- and district-level excess prevalence not fully explained by household wealth. These findings reinforce the continued, widespread need for accessible and dose-flexible micronutrient-correction strategies suitable for large-scale public-health deployment.

2.3 Mini-Tablet and Multiparticulate Dosage-Form Development

Several groups have reported the successful development of mini-tablets for both paediatric and adult use. Vemula et al. (2018) developed mini-tablets of isradipine by direct granulation and, following evaluation of angle of repose, bulk and tapped density, Carr's index and Hausner's ratio, selected an optimal formulation on the basis of superior physicochemical performance. Opeyemi et al. (2018) formulated and evaluated a multiparticulate mini-tablet system of

naproxen sodium, confirming drug–excipient compatibility by FTIR and demonstrating that direct-compression mini-tablets prepared with hydroxypropyl methylcellulose (HPMC K4M) and PVP K30 met pharmacopoeial pre- and post-compression limits while achieving sustained drug release over ten hours. Rohera et al. (2017), Iurian et al. (2020) and Spomer et al. (2014) have separately confirmed the acceptability and swallowability advantages of mini-tablets in paediatric populations, supporting their selection as a platform for micronutrient delivery in the present study.

2.4 Quality by Design and Central Composite Design in Tablet Optimisation

The application of Quality-by-Design principles, using response-surface methodologies such as the Central Composite Design, has become well established for the systematic optimisation of tablet Critical Quality Attributes. Beg et al. (2019) and Kotłowska et al. (2019, 2020) applied CCD/Box–Behnken designs to optimise binder, lubricant and diluent levels against hardness, friability and disintegration time, generating validated second-order polynomial models with high R^2 and non-significant lack-of-fit — an approach mirrored in the design strategy adopted here. Park et al. (2019), Mitra et al. (2017) and Cooper et al. (2016) have likewise demonstrated that formulation-by-design approaches materially reduce the number of experimental trials required to identify a robust design space, while improving the mechanistic understanding of factor interactions on tablet performance. Sivakumar et al. (2006), Politis et al. (2017) and Planins et al. (2014) have reported complementary work on direct-compression excipient selection (microcrystalline cellulose, PVP K30, magnesium stearate, talc) for achieving acceptable flow and compressibility of poorly compressible mineral salts, directly informing the excipient choices used in the present mini-tablet and micronutrient-tablet formulations.

Collectively, the literature confirms (i) the well-established biological necessity of micronutrients and the continuing public-health burden of their deficiency, (ii) the suitability of mini-tablets as a patient-compliant, dose-flexible multiparticulate platform, and (iii) the utility of CCD-based Quality-by-Design methodology for the rational optimisation

of directly compressed tablet formulations — together providing the scientific basis for the present study.

III. MATERIALS AND METHODS

3.1 Materials

Magnesium sulphate, potassium iodide, ferrous sulphate, cupric sulphate, potassium chloride and sodium chloride were procured from LOBA Chemie, Mumbai; zinc sulphate heptahydrate and potassium chloride were procured from SRL, Mumbai. Polyvinylpyrrolidone (PVP K30), microcrystalline cellulose (MCC), magnesium stearate, stearic acid, lactose and talc (LOBA Chemie, Mumbai) were used as binder, diluent/filler, lubricants and glidant respectively. Food-grade colour and flavour were obtained from IFF, Mumbai. All chemicals used were of analytical or pharmacopoeial grade.

3.2 Instrumentation

Table 1. Major instruments used in the study.

S.No.	Instrument	Manufacturer
1	Automatic tablet punching machine	Chronomach, Ahmedabad
2	Digital weighing balance	Mettler Toledo, USA
3	Friabilator	Gupta Instruments Pvt. Ltd.
4	Hardness tester (Monsanto type)	Amar Enterprises, Ambala Cantt.
5	Hot air oven	Gupta Scientific Industries, Ambala
6	Magnetic stirrer	Amar Enterprises, Ambala Cantt.
7	pH meter	Amar Enterprises,

S.No.	Instrument	Manufacturer
		Ambala Cantt.
8	Purified water system	Millipore, India
9	Sieve shaker	Amar Enterprises, Ambala Cantt.
10	Atomic Absorption Spectrophotometer (AAS)	Shimadzu Corp., Japan
11	FT-IR Spectrophotometer	Perkin Elmer, USA

Design Expert Version 12 (Stat-Ease Inc.) was used for Formulation-by-Design (QbD) studies and statistical analysis; Microsoft Excel 2019 and Microsoft Office 2019 were used for calculations and documentation.

3.3 Calibration of Glassware and Instruments

Prior to use, the thermometer, measuring cylinders, analytical balance, sieves, AAS, FT-IR and pH meter were calibrated against pharmacopoeial standards. The thermometer was calibrated against the melting point of benzoic acid (IP, 2014); measuring cylinders were calibrated gravimetrically against the known density of water; the analytical balance was calibrated using certified external weight standards; sieve aperture size was verified microscopically per IP (2007); the AAS was calibrated using copper standard solutions (0.5–2.5 µg/mL) with acceptance of correlation coefficient ≥ 0.9900 ; the FT-IR was calibrated for resolution performance and wavenumber accuracy using a polystyrene film reference per IP (2014); and the pH meter was calibrated using standard buffers of pH 4.01 and 6.87.

3.4 Pre-formulation Studies

Pre-formulation characterisation was carried out on each micronutrient salt to establish identity, purity and processing behaviour prior to tablet development, comprising:

- Organoleptic evaluation (colour, odour, taste) by visual/sensory inspection.
- Solubility analysis in water and common solvents.

- FT-IR spectroscopy for identification: samples (2% w/w) were blended with dry KBr, compressed into a disc at 10,000 psi, and scanned 32 times at a resolution of 2 cm^{-1} over $500\text{--}4000\text{ cm}^{-1}$.
- Atomic Absorption Spectroscopy (AAS) for elemental confirmation and quantification, exploiting the characteristic absorption wavelength of each element in atomic (flame) form.

3.5 Formulation Development by Direct Compression
Both the individual mini-tablets and the combination micronutrient tablet were prepared by direct compression, selected because several of the mineral salts (e.g., potassium chloride) possess inherently free-flowing, cohesive properties suitable for compression without prior granulation. For the remaining, less compressible salts, standard direct-compression excipients were incorporated: microcrystalline cellulose and lactose as diluent/filler, PVP K30 as dry binder, magnesium stearate and stearic acid as lubricants, and talc as glidant, together with food-grade colour and flavour.

3.5.1 Preparation Procedure

- Required quantities of magnesium stearate, stearic acid, lactose, talc, PVP K30 and MCC were accurately weighed.
- The active micronutrient salt, together with colour and flavour, was weighed and blended with the excipients.
- The blend was mixed thoroughly for a fixed time to ensure homogeneity.
- The mixed powder was passed through sieve no. 10 to achieve a uniform particle size.
- The resulting free-flowing blend was compressed directly on an automatic tablet-punching machine to yield 50 mg mini-tablets (individual minerals) or a 315 mg combination tablet (all seven minerals).

3.6 Experimental Design: Optimisation by Central Composite Design (CCD)

A three-factor Central Composite Design (CCD), comprising 20 experimental runs, was employed to optimise the mini-tablet formulation. The amount of binder (A), amount of lubricant (B) and amount of glidant/diluent (C) were selected as independent (input) variables, and friability (Y1, %) and hardness (Y2, kg/cm^2) were selected as dependent responses

(Critical Quality Attributes). High, mid and low levels of each factor are given in Table 2.

Table 2. High, mid and low levels of the factors selected for CCD optimisation.

Factor	Low	Mid	High
A: Amount of binder (mg)	2	8	14
B: Amount of lubricant (mg)	2	5	8
C: Amount of glidant/diluent (mg)	1	3.5	6

The response for each Critical Quality Attribute was fitted to a second-order polynomial equation of the general form:

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_1^2 + \beta_4X_2^2 + \beta_5X_1X_2 \dots (\text{Eq. 1})$$

where Y is the predicted response, β_0 the intercept, X_1 and X_2 the coded factor levels, X_1X_2 the interaction term, and X_1^2 , X_2^2 the quadratic terms, with $\beta_1\text{--}\beta_5$ the corresponding regression coefficients. Model adequacy was assessed by ANOVA (R^2 , adjusted R^2 , predicted R^2 , Adequate Precision and model F-/p-values), and by the lack-of-fit F-test. Two- and three-dimensional response-surface plots were generated using Design Expert (Version 12) to visualise factor–response relationships, and an overlay plot was constructed to define the design space. The Point Prediction feature of the software was then used to identify the optimum factor combination, which was validated experimentally in triplicate.

3.7 Characterisation of Mini-Tablets and Micronutrient Tablet

3.7.1 Pre-compression (In-Process Quality Control) Parameters

- Particle size — determined by sieve analysis (100 g sample, mechanical shaking for 10 min).
- Angle of repose (θ) — determined by the fixed-funnel method: $\theta = \tan^{-1}(h/r)$, where h is the height and r the radius of the powder cone (Eq. 2).
- Bulk density (ρ_b) — $\rho_b = M/V_0$, where M is powder mass and V_0 the un-tapped (poured) volume (Eq. 3).

- Tapped density (ρ_{tap}) — $\rho_{\text{tap}} = M/V_f$, where V_f is the volume after mechanical tapping (500–1250 taps) to a constant volume (Eq. 4).
- Carr's compressibility index — Compressibility Index (%) = $[(\rho_{\text{tap}} - \rho_b)/\rho_{\text{tap}}] \times 100$ (Eq. 5).
- Hausner's ratio — Hausner's Ratio = ρ_{tap}/ρ_b (Eq. 6).

3.7.2 Post-compression (Finished Product Quality Control) Parameters

- Weight variation — 20 tablets of each formulation were individually weighed and evaluated against IP weight-variation limits ($\pm 10\%$ for ≤ 80 mg, $\pm 7.5\%$ for > 80 mg but < 250 mg, and $\pm 5\%$ for ≥ 250 mg).
- Friability — assessed using a Roche-type friabilator (25 rpm, 100 revolutions, 6-inch drop height); $F(\%) = (1 - W_0/W) \times 100$, where W_0 and W are tablet weights before and after the test (Eq. 7).
- Hardness — measured on 6 tablets per batch using a Monsanto-type hardness tester (kg/cm^2).
- Appearance — assessed visually and graded qualitatively (very good, good, fair, poor, very poor).
- Content confirmation — the micronutrient content of each tablet type was quantified by Atomic

Absorption Spectroscopy against a validated calibration curve for each analyte.

IV. RESULTS AND DISCUSSION

4.1 Calibration and Pre-formulation Results

All glassware and instruments used in the study were confirmed to be within pharmacopoeial acceptance limits prior to use: the thermometer read a mean melting point of 121°C against a benzoic-acid standard of $122 \pm 2^\circ\text{C}$; the 10 mL and 50 mL measuring cylinders read within 2–3% of nominal volume; the analytical balance agreed with certified weights to within ± 0.03 g across the 2–50 g range; the FT-IR met IP (2014) resolution-performance and wavenumber-accuracy specifications (observed wavenumber error $\leq 1.52 \text{ cm}^{-1}$ across thirteen polystyrene reference bands); and the pH meter read 4.06 and 6.82 against standard buffers of 4.01 and 6.87, respectively, all within the ± 0.2 acceptance window. All seven micronutrient salts were confirmed, on organoleptic and solubility testing, to be freely soluble, odourless to characteristic-odoured white/off-white crystalline solids consistent with their respective pharmacopoeial monographs, and FT-IR spectra showed characteristic absorption bands consistent with each salt's expected functional groups, confirming identity and purity prior to formulation.

4.2 Central Composite Design: Optimisation of Mini-Tablet Formulation

The 20-run CCD matrix, with the amount of binder, lubricant and glidant/diluent as factors and friability and hardness as responses, is summarised in Table 3.

Table 3. Central Composite Design matrix and observed responses for mini-tablet optimisation.

Run	A: Binder (mg)	B: Lubricant (mg)	C: Glidant/Diluent (mg)	Friability (%)	Hardness (kg/cm^2)
1	8	5	3.5	0.788	5.54
2	14	8	6	0.45	6.04
3	2	2	1	1.00	6.06
4	8	5	3.5	0.755	5.76
5	8	5	7.7	0.77	5.25
6	8	5	0	0.98	5.54
7	18.09	5	3.5	0.628	5.80
8	8	5	3.5	0.77	5.98
9	8	5	3.5	0.712	5.90

Run	A: Binder (mg)	B: Lubricant (mg)	C: Glidant/Diluent (mg)	Friability (%)	Hardness (kg/cm ²)
10	14	8	1	0.61	5.52
11	8	0	3.5	1.05	5.45
12	8	10.05	3.5	0.98	4.90
13	8	5	3.5	0.79	5.90
14	0	5	3.5	1.25	5.20
15	14	2	1	0.96	5.56
16	2	2	6	1.06	5.40
17	14	2	6	0.66	5.23
18	2	8	1	1.09	4.80
19	2	8	6	1.11	4.49
20	8	5	3.5	0.69	5.65

Multiple linear regression analysis of the CCD data gave statistically significant second-order polynomial models for both responses (Table 4), and the fit statistics are summarised in Table 5.

Table 4. ANOVA and lack-of-fit statistics for the CCD-derived models.

Fit statistic	Friability	Hardness
R ²	0.9491	0.9332
Adjusted R ²	0.9034	0.8731
Predicted R ²	0.6716	0.8028
Adequate precision	16.235	13.592
Model F-value	20.73	15.59
Model p-value	<0.0001	<0.0001
Lack-of-fit F-value	0.082 (n.s.)	0.880 (n.s.)

Both models showed high R² and adjusted R² values, adequate precision ratios well above the desirable minimum of 4 (16.235 and 13.592), and highly significant model F-values ($p < 0.0001$) with non-significant lack-of-fit ($p > 0.1$), confirming that the quadratic models adequately described the design space and could be used for prediction with confidence.

Table 5. Polynomial regression coefficients for friability and hardness models.

Coefficient	Friability (%)	Hardness (kg/cm ²)
Intercept	0.75	5.78
A – Binder	−0.19	0.16
B – Lubricant	−0.039	−0.14
C – Glidant/diluent	−0.054	−0.066

Coefficient	Friability (%)	Hardness (kg/cm ²)
AB	-0.088	0.32
AC	-0.068	0.099
BC	0.012	0.20
A ²	0.048	-0.080
B ²	0.075	-0.19
C ²	0.026	-0.12

(A) Friability response surface

(B) Hardness response surface

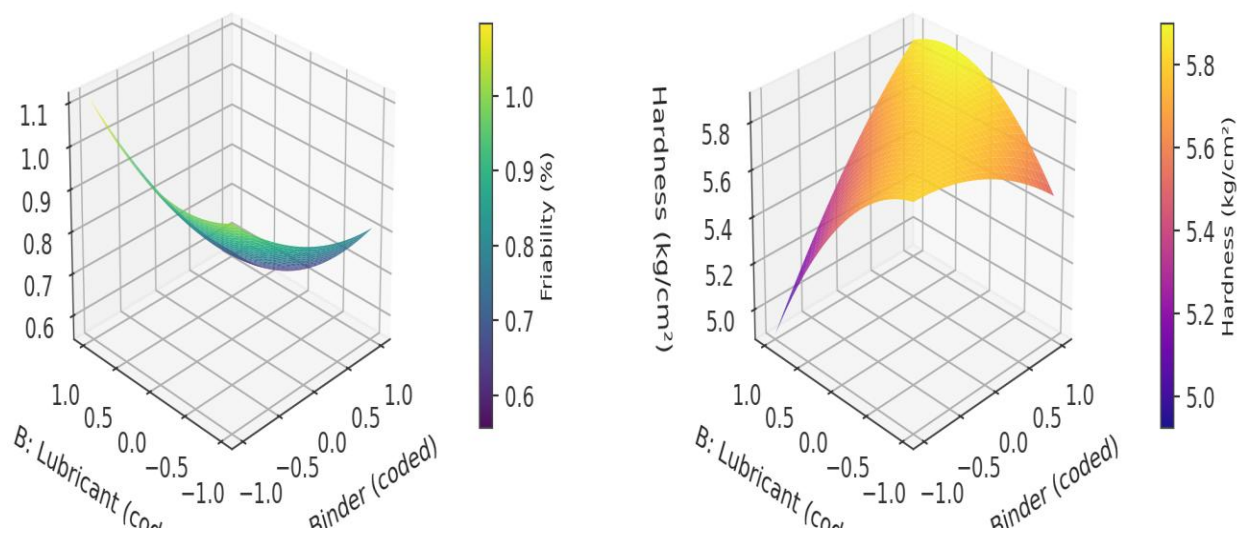


Fig. 1. Three-dimensional response-surface plots showing the effect of binder (A) and lubricant (B) levels on (A) friability and (B) hardness, with glidant/diluent (C) held at its mid (coded) level.

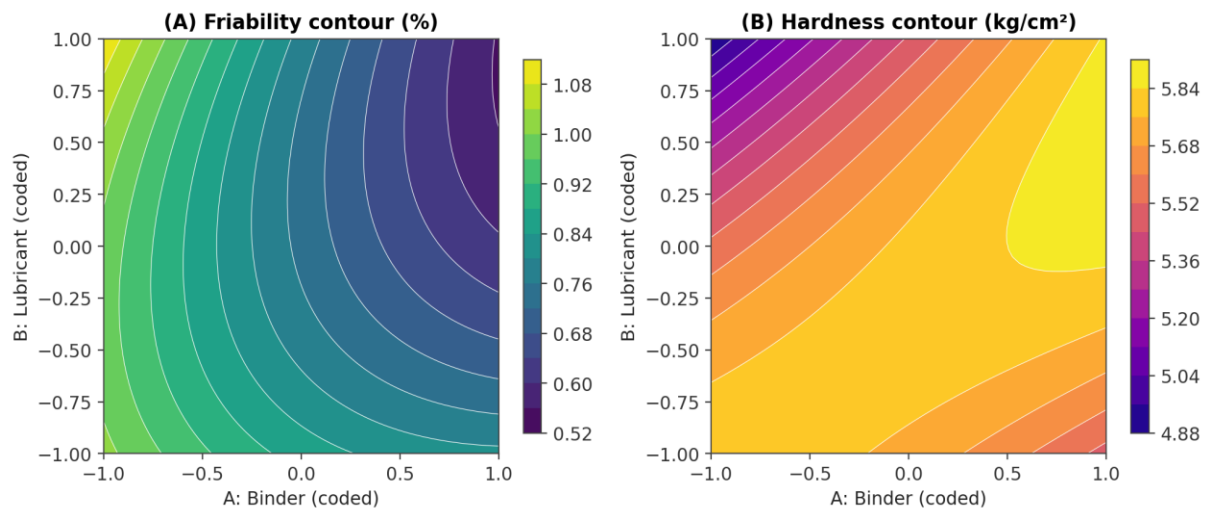


Fig. 2. Two-dimensional contour plots corresponding to the response surfaces in Fig. 1 for (A) friability and (B) hardness.

The response surface and contour plots showed a negative effect of lubricant level and a positive effect of binder level on friability, with clear factor–factor interaction reflected in the non-parallel contour lines. At lower binder concentration, increasing lubricant level produced a gradual rise in hardness, whereas at the higher lubricant level a steep fall in friability was observed as the amount of lubricant was increased from its lower to higher setting, consistent with the expected lubricating/anti-friction action of magnesium

stearate and stearic acid at the granule surface. An overlay plot combining the acceptable ranges for both friability and hardness was used to delineate the design space, from which the Point Prediction feature of Design Expert identified an optimum composition of 4 mg binder, 5 mg lubricant and 3.5 mg glidant/diluent, predicted to give a friability of 0.95% and a hardness of 6.0 kg/cm². Laboratory confirmation of this optimum (Table 6, Fig. 3) showed excellent agreement between predicted and observed values.

Table 6. Validation of the optimised CCD model by laboratory confirmation runs.

Response	Predicted value	Observed value	Accuracy (%)
Friability (%)	0.95	0.49	98.01
Hardness (kg/cm ²)	6.0	5.56	96.72

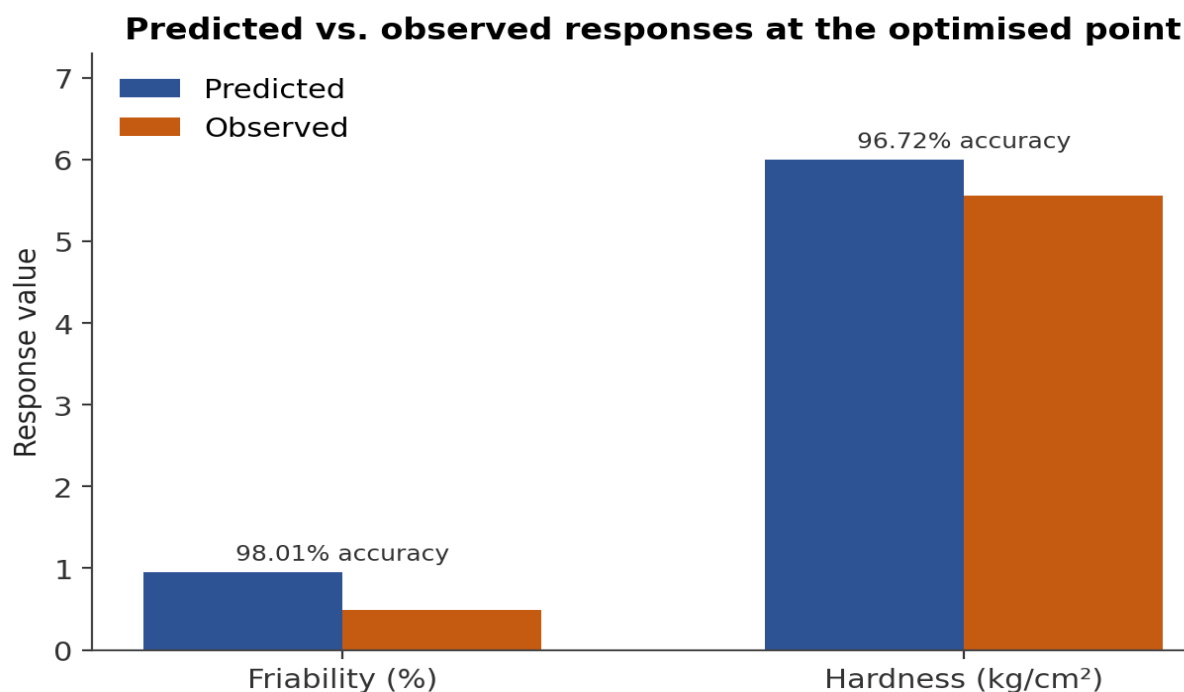


Fig. 3. Predicted versus observed friability and hardness at the optimised formulation point.

4.3 Pre- and Post-compression Characterisation of Optimised Mini-Tablets

Granules for all seven optimised mini-tablet formulations exhibited good to fair flow, with angle of repose ranging from 21° to 24°, Carr's compressibility index between 15.3% and 16.5%, and Hausner's ratio between 1.6 and 1.8 — all within limits generally considered acceptable for direct-compression

manufacture (Table 7, Fig. 4). The corresponding compressed mini-tablets showed hardness of 5.5–5.6 kg/cm², friability well below the pharmacopoeial ceiling of 1% w/w, and average weight within the IP weight-variation tolerance for tablets of this size range; all batches were judged to have good visual appearance (Table 8, Fig. 5).

Table 7. Pre-compression (in-process) characterisation of granules for each mini-tablet formulation.

Mineral (50 mg mini-tablet)	Angle of repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner's ratio
Magnesium sulphate	23 ± 0.5	0.85 ± 0.02	0.736 ± 0.03	15.47 ± 1.1	1.8 ± 0.1
Potassium iodide	24 ± 0.5	0.83 ± 0.02	0.740 ± 0.03	16.44 ± 1.1	1.6 ± 0.1
Ferrous sulphate	23 ± 0.5	0.86 ± 0.02	0.730 ± 0.03	15.54 ± 1.1	1.7 ± 0.1
Zinc sulphate heptahydrate	21 ± 0.5	0.81 ± 0.02	0.690 ± 0.03	16.44 ± 1.1	1.8 ± 0.1
Cupric sulphate	22 ± 0.5	0.86 ± 0.02	0.741 ± 0.03	15.55 ± 1.1	1.7 ± 0.1
Potassium chloride	21 ± 0.5	0.83 ± 0.02	0.740 ± 0.03	16.34 ± 1.1	1.6 ± 0.1
Sodium chloride	23 ± 0.5	0.86 ± 0.02	0.741 ± 0.03	16.54 ± 1.1	1.8 ± 0.1

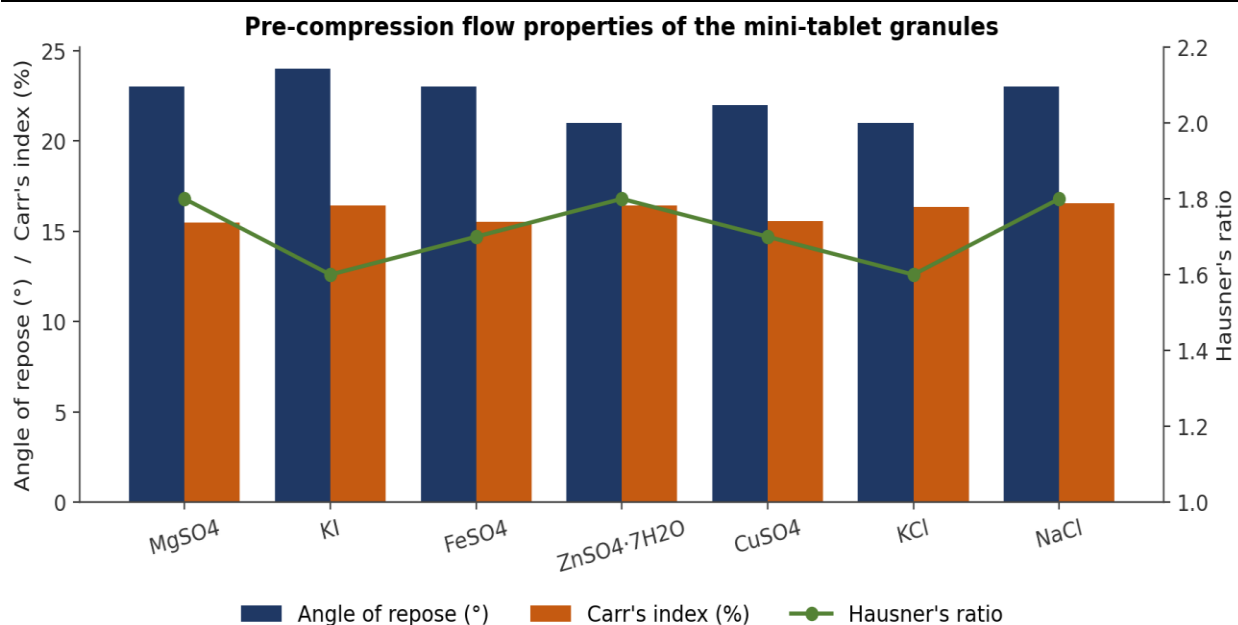


Fig. 4. Angle of repose, Carr's index and Hausner's ratio for the seven mini-tablet granule blends.

Table 8. Post-compression (finished-product) characterisation of each mini-tablet formulation.

Mineral (50 mg mini-tablet)	Hardness (kg/cm ²)	Friability (%)	Average weight (mg)	Appearance
Magnesium sulphate	5.5 ± 0.5	0.45 ± 0.03	50 ± 5	Good
Potassium iodide	5.6 ± 0.5	0.47 ± 0.03	51 ± 5	Good
Ferrous sulphate	5.6 ± 0.5	0.46 ± 0.03	50 ± 5	Good
Zinc sulphate heptahydrate	5.5 ± 0.5	0.47 ± 0.03	50 ± 5	Good
Cupric sulphate	5.6 ± 0.5	0.49 ± 0.03	50 ± 5	Good
Potassium chloride	5.5 ± 0.5	0.49 ± 0.03	49 ± 5	Good
Sodium chloride	5.6 ± 0.5	0.47 ± 0.03	50 ± 5	Good

4.4 Development and Characterisation of the 315 mg Micronutrient Combination Tablet

Based on the optimised mini-tablet composition, a fixed-dose combination tablet (315 mg) incorporating all seven micronutrients was formulated (Table 9).

Table 9. Composition of the 315 mg micronutrient combination tablet.

Ingredient	Amount
Magnesium sulphate	14 mg
Potassium iodide	2.61 mg
Ferrous sulphate	2.72 mg
Zinc sulphate heptahydrate	4.40 mg
Cupric sulphate	2.51 mg
Potassium chloride	5.73 mg
Sodium chloride	5.10 mg
PVP K30 (binder)	30 mg
Microcrystalline cellulose (diluent)	30 mg
Magnesium stearate (lubricant)	22.5 mg
Stearic acid (lubricant)	22.5 mg

Ingredient	Amount
Lactose (diluent)	150 mg
Talc (glidant)	20 mg
Colour	1 mg
Flavour	1 mg

Granules for the combination tablet showed an angle of repose of $31^\circ \pm 0.5$, bulk density 0.75 ± 0.02 g/mL, tapped density 0.516 ± 0.03 g/mL, Carr's index $15.04 \pm 1.1\%$, and Hausner's ratio 1.5 ± 0.1 — flow properties that, while somewhat poorer than the individual mini-tablet granules (reflecting the higher total powder load and mineral-salt fraction), remained within a workable range for direct compression. The compressed 315 mg tablets showed a hardness of 4.6 ± 0.5 kg/cm², friability of $0.79 \pm 0.03\%$, and average weight of 314 ± 5 mg, all within acceptable pharmacopoeial limits, with good visual appearance (Fig. 5).

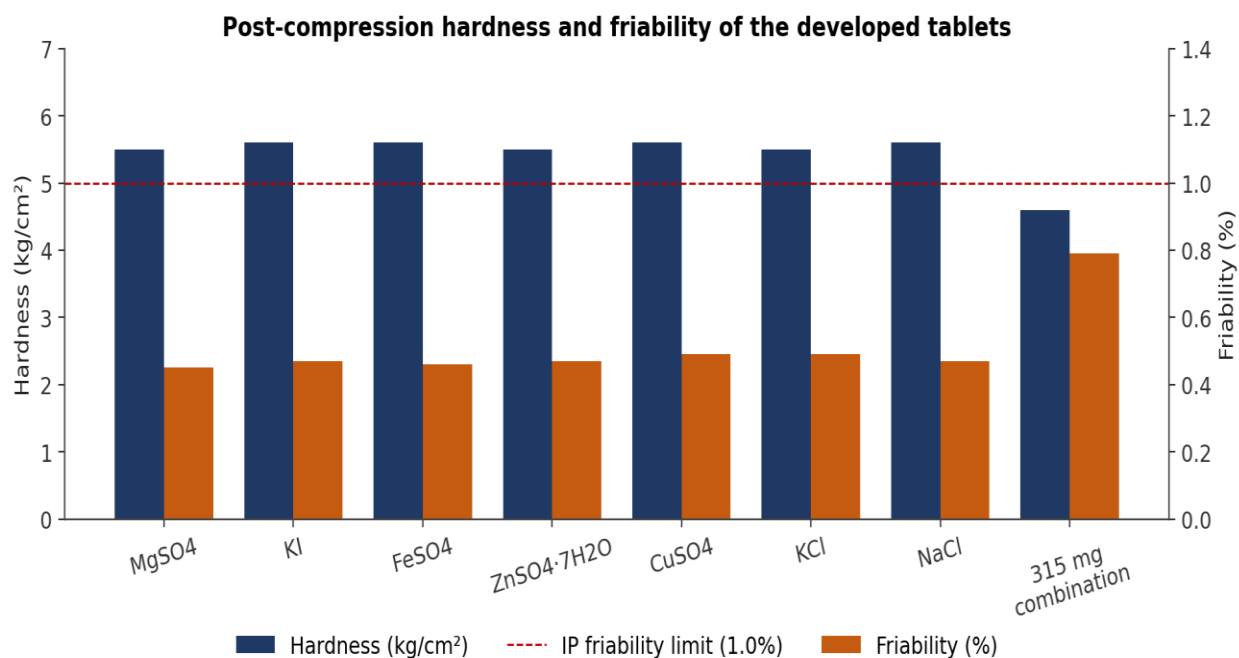


Fig. 5. Post-compression hardness and friability of the seven mini-tablet formulations compared with the 315 mg combination tablet, relative to the Indian Pharmacopoeial friability limit (1.0% w/w).

4.5 Content Confirmation by Atomic Absorption Spectroscopy

The mineral content of the combination tablet was confirmed by AAS against individually validated calibration curves for each of the seven micronutrients (Table 10); all seven calibration curves showed excellent linearity ($r^2 \geq 0.9991$).

Table 10. AAS calibration parameters for the seven micronutrients.

Micronutrient	Regression equation	r^2
Magnesium sulphate	$y = 0.0742x + 0.0105$	0.9991
Potassium iodide	$y = 1.576x + 0.0025$	0.9996
Ferrous sulphate	$y = 0.1134x + 0.0057$	0.9992
Zinc sulphate heptahydrate	$y = 0.1594x + 0.0053$	0.9995
Cupric sulphate	$y = 0.5072x + 0.0044$	0.9995

Micronutrient	Regression equation	r^2
Potassium chloride	$y = 0.9268x + 0.0071$	0.9996
Sodium chloride	$y = 1.63x - 0.004$	0.9991

Table 11. AAS-determined micronutrient content of the 315 mg combination tablet against the expected amount.

Micronutrient	Amount found (per tablet)	Expected range
Magnesium sulphate	3.7623 mg	3.5 – 4 mg
Potassium iodide	2.1613 mg	2 – 4 mg
Ferrous sulphate	1.7986 mg	1 – 2 mg
Zinc sulphate heptahydrate	3.511 mg	2 – 4 mg
Cupric sulphate	1.5837 mg	1.4 – 2 mg
Potassium chloride	3.5743 mg	3 – 4 mg
Sodium chloride	2.6768 mg	2.3 – 3 mg

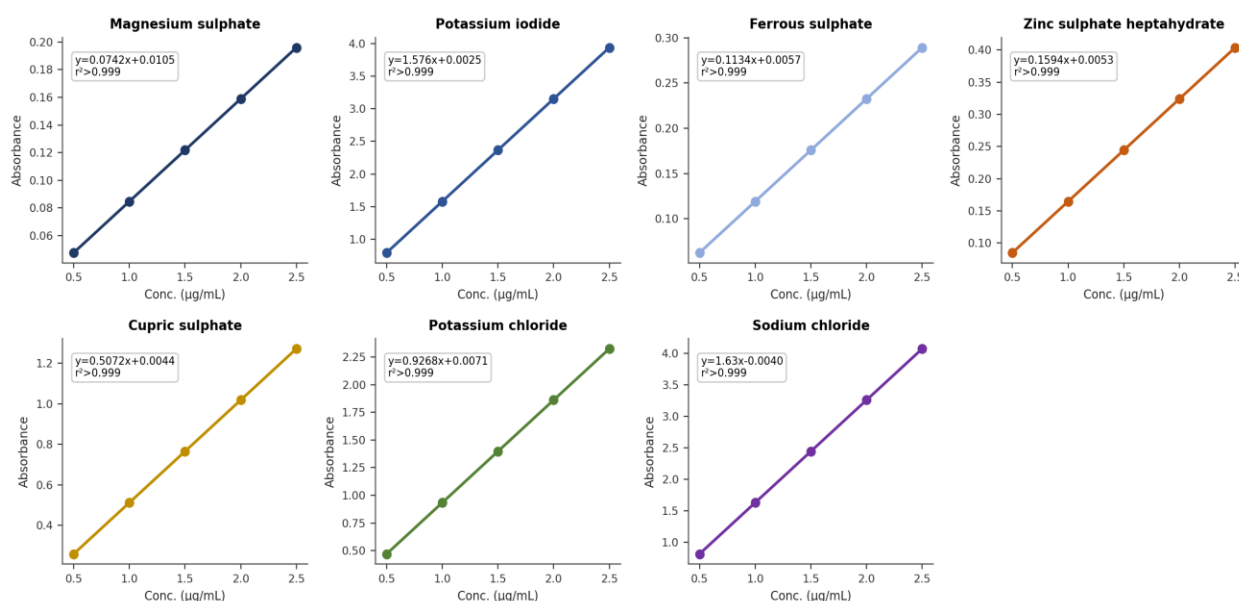


Fig. 6. Atomic Absorption Spectroscopy calibration curves (absorbance vs. concentration) for the seven micronutrients used to confirm tablet content.

For all seven micronutrients, the amount recovered by AAS assay fell within the expected content range, confirming both the accuracy of the formulation process and the suitability of AAS as a rapid, sensitive confirmatory method (detection down to ~1 ppm by flame AAS) for multi-mineral tablet quality control.

4.6 Discussion

Pre-formulation studies confirmed the identity and purity of each micronutrient salt prior to compression, providing assurance that subsequent formulation performance could be attributed to the excipient system and process rather than to raw-material variability. The flow and compressibility results obtained here are consistent with those reported for other directly compressed mini-tablet systems: Vemula et al. (2018) similarly reported acceptable angle-of-repose, Carr's index and Hausner's ratio values for direct-granulation mini-tablets selected on the basis of good physicochemical performance, while Opeyemi et al. (2018) reported that pre-formulation studies of naproxen sodium mini-tablets likewise showed good flow and compaction capacity leading to high-quality mini-tablets meeting pharmacopoeial pre- and post-compression limits.

The CCD-based optimisation approach used here — in which binder, lubricant and glidant/diluent levels were varied systematically and the resulting friability and hardness fitted to significant, non-lack-of-fit quadratic models — allowed the identification of a single optimum composition (4 mg binder, 5 mg lubricant, 3.5 mg glidant/diluent) validated to within 96–98% accuracy of the model's predictions. This confirms that a Quality-by-Design, statistically driven optimisation strategy is both feasible and advantageous for mineral-salt mini-tablet development, where many of the active ingredients (e.g., potassium chloride, sodium chloride) are inherently poor formers of cohesive compacts and are therefore particularly sensitive to small changes in binder and lubricant level.

Unlike single-drug mini-tablet systems reported in the literature, the present study additionally demonstrates that the same optimised excipient ratio can be translated successfully to a fixed-dose combination tablet containing all seven minerals at a substantially higher unit weight (315 mg), without loss of acceptable flow, compressibility, hardness or friability — an important consideration for eventual scale-up and commercial manufacture. The confirmation of

micronutrient content within the expected range by AAS across all seven analytes further supports the robustness of the blending and compression process at combination scale.

Taken together, these findings support the proposed formulations as multifarious therapeutic options capable of delivering micronutrients, alone or in combination, in line with WHO-recommended daily allowances. Because dose can be adjusted simply by varying the number of mini-tablets (or, for the combination tablet, by titrating tablet number), the platform offers considerable flexibility for individualised nutritional correction across all age groups — from paediatric to geriatric populations — and represents a patient-compliant alternative to the large-volume, fixed-dose formulations currently dominating the market.

V. CONCLUSION

Nutritional deficiency and malnutrition remain major global public-health challenges, disproportionately affecting women and children and contributing substantially to impaired physical and cognitive development, chronic ill-health and mortality. Although numerous nutritional-supplement formulations are commercially available, few offer the dose flexibility required to individualise micronutrient correction across the full spectrum of age groups and deficiency severities.

In the present study, seven individual mineral mini-tablets and a 315 mg fixed-dose combination micronutrient tablet were successfully developed by the direct-compression method. A Quality-by-Design framework, implemented through a three-factor Central Composite Design, was used to optimise the amount of binder, lubricant and glidant/diluent against friability and hardness as Critical Quality Attributes, yielding statistically significant, well-fitting polynomial models ($R^2 > 0.93$ for both responses) and an experimentally validated optimum formulation (prediction accuracy 96.7–98.0%). All developed formulations met pharmacopoeial and literature-reported acceptance criteria for flow, compressibility, hardness, friability, weight variation and appearance, and the expected micronutrient content was confirmed by Atomic Absorption Spectroscopy in every case.

The developed mini-tablets and combination tablet thus constitute a scientifically optimised, patient-

compliant, dose-adjustable and commercially scalable platform for delivering micronutrients — singly or in combination — as per individualised or population-level Recommended Dietary Allowances, offering a promising new option for the management of nutritional deficiency and malnutrition across all phases of life.

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