METRONIDAZOLE FAST DISSOLVING TABLETS BY DIRECT COMPRESSION: A STUDY BY RESPONSE SURFACE ANALYSIS UTILIZING CENTRAL COMPOSITE DESIGN

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ABSTRACT
The present study aimed to formulate and optimise Metronidazole fast-dissolving tablets (FDTs) using the direct compression technique and a Central Composite Design (CCD). The objective was to achieve rapid disintegration, enhanced dissolution, and acceptable physicochemical properties. Preformulation studies confirmed the purity, identity, and suitable physicochemical characteristics of Metronidazole, with good solubility in 0.1 N HCl supporting its selection as the dissolution medium. Thirteen formulations (METF1–METF13) were developed using varying concentrations of cross-carboxymethylcellulose sodium (CCS) and sucralose. All formulations complied with pharmacopoeial limits for weight variation, hardness, and friability. The tablets exhibited rapid disintegration (72–115 s), acceptable wetting time (35–61 s), uniform drug content, and fast drug release, with several formulations achieving more than 90% dissolution within 30–60 minutes. Drug release kinetics predominantly followed zero-order and Higuchi models, indicating diffusion-controlled release with Fickian behaviour. Statistical analysis (ANOVA) confirmed the significance of the quadratic models ($p < 0.05$), with CCS significantly influencing disintegration and dissolution, while sucralose mainly affected wetting time. The optimised formulation containing 72.5 mg CCS and 214 mg sucralose showed close agreement between predicted and experimental responses. ATR and DSC studies confirmed drug–excipient compatibility and formulation stability. The study concludes that CCD-based optimisation is an effective approach for developing Metronidazole FDTs with potential for improved patient compliance and future scale-up.

Keywords:
Metronidazole, Fast dissolving tablets, Central Composite Design, Cross carmellose sodium, Direct compression, Response surface methodology
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INTRODUCTION

Pharmaceutical dosage forms play a crucial role in determining the safety, efficacy, stability, and patient acceptability of drug therapy. A dosage form is the physical form in which a drug is administered to achieve the desired therapeutic effect, and its design significantly influences drug bioavailability and clinical performance. Advances in pharmaceutical research have shifted focus not only toward the discovery of new drug molecules but also toward the development of improved drug delivery systems that enhance therapeutic outcomes and patient compliance.

Among various routes of administration, the oral route remains the most preferred due to its convenience, safety, cost-effectiveness, and high patient acceptance. Conventional oral dosage forms such as tablets and capsules dominate the pharmaceutical market; however, they present several limitations, including difficulty in swallowing, delayed onset of action, dependence on water, and reduced compliance in pediatric, geriatric, and dysphagic patients. These challenges have driven the development of novel oral drug delivery systems that can provide rapid drug release and improved ease of administration.

Fast dissolving tablets (FDTs), also known as orally disintegrating tablets, have emerged as an effective alternative to conventional tablets. These dosage forms are designed to disintegrate rapidly in

the oral cavity without the need for water, resulting in faster onset of action and improved patient compliance. The rapid disintegration of FDTs is primarily achieved through the incorporation of superdisintegrants, which promote tablet breakup through mechanisms such as swelling, wicking, and deformation recovery. Due to their ease of administration and reduced risk of choking, FDTs are particularly beneficial for pediatric, geriatric, and mentally compromised patients.

Metronidazole is a widely used antimicrobial agent effective against anaerobic bacterial and protozoal infections. Despite its therapeutic importance, its conventional tablet formulation is associated with drawbacks such as bitter taste, delayed disintegration, and swallowing difficulty. Formulating Metronidazole as a fast dissolving tablet can overcome these limitations by enhancing patient acceptability, ensuring rapid drug release, and improving therapeutic response.

Direct compression is one of the most commonly employed techniques for the preparation of FDTs due to its simplicity, cost-effectiveness, and suitability for large-scale production. However, successful formulation requires careful selection and optimization of excipients and processing parameters. Modern pharmaceutical research increasingly employs statistical optimization techniques such as Response Surface Methodology (RSM) and Central Composite Design (CCD) to systematically evaluate the influence of formulation variables and to develop robust, reproducible, and optimized dosage forms in accordance with Quality by Design (QbD) principles.

Therefore, the present study focuses on the formulation and optimisation of fast dissolving tablets of Metronidazole using suitable superdisintegrants and statistical design tools, to improve drug release, patient compliance, and overall therapeutic efficacy.

MATERIALS AND EXPERIMENTAL METHODS

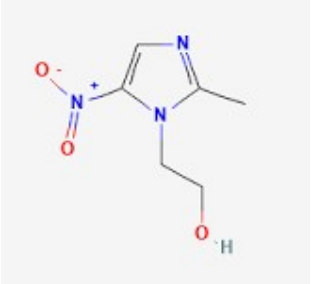

Figure 1: Chemical structure of Metronidazole

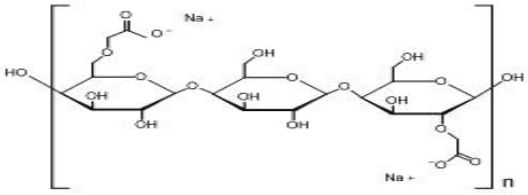

Figure 2: Chemical structure of Cross carmellose sodium

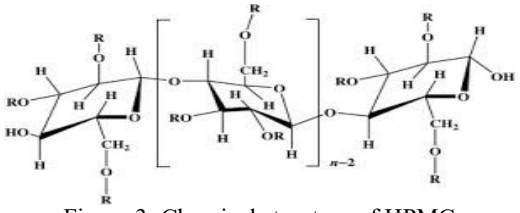

Figure 3: Chemical structure of HPMC

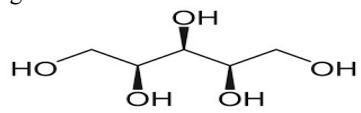

Figure 4: Chemical structure of Mannitol

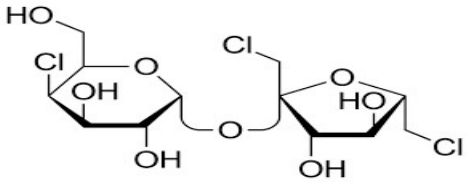

Figure 5: Chemical structure of Sucralose

Preformulation Study of Metronidazole

Appearance

Metronidazole appeared as a white, amorphous powder.

Bulk Density Bulk density was determined by pouring 5 g of powder into a 10 mL graduated cylinder.

[{Bulk density} = \frac{M}{V} = \frac{5}{6.5}]

Bulk density = 0.76 ± 0.02 g/cm³

Tapped Density The cylinder was tapped until a constant volume was achieved.

[{Tapped density} = \frac{5}{5.2}]

Tapped density = 0.96 ± 0.05 g/cm³

Carr's Index[{Carr's index} = \frac{dt - db}{dt} \times 100]

Carr's index = 20.83%

Hausner's Ratio

[{Hausner's ratio} = \frac{dt}{db}]

Hausner's ratio = 1.26

Angle of Repose (Fixed Funnel Method)

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where h = 3.5 cm and r = 2.6 cm.

Angle of repose = 53.39°

Melting Point Melting point was determined using the capillary method with a G Lab MeltingPoint Apparatus (Mumbai, India).

Melting point = 158°C

Calibration Curve

Preparation of 0.1 N HCl0.1 N HCl was prepared by diluting concentrated hydrochloric acid with distilled water.

Preparation of Phosphate Buffer (pH 6.8) Potassium dihydrogen phosphate and disodium hydrogen phosphate were dissolved in distilled water and volume was adjusted to 1000 mL.

Preparation of Phosphate Buffer (pH 7.4) Disodium hydrogen phosphate, potassium dihydrogen phosphate, and sodium chloride were dissolved and volume made up to 1000 mL.

Preparation of Stock Solution100 mg of Metronidazole was dissolved in 100 mL of solvent to obtain Stock A (1000 µg/mL). Stock B (100 µg/mL) was prepared by diluting 10 mL of Stock A to 100 mL. Aliquots of Stock B were further diluted to obtain required concentrations for calibration.

Table1: Absorbance value of Metronidazole in 0.1 N HCl

Concentration (µg/ml)	Absorbance
2	0.212
4	0.344
6	0.528
8	0.624
10	0.888
12	0.926

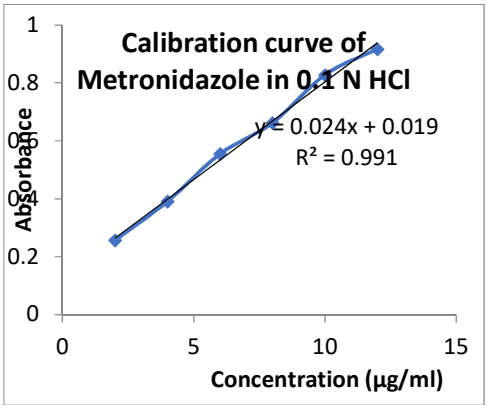

Fig 6: Calibration curve of Metronidazole in 0.1 N HCl

Table2: Absorbance value of Metronidazole in phosphate buffer 6.8

Concentration (µg/ml)	Absorbance
2	0.209
4	0.376
6	0.439
8	0.573
10	0.626
12	0.776

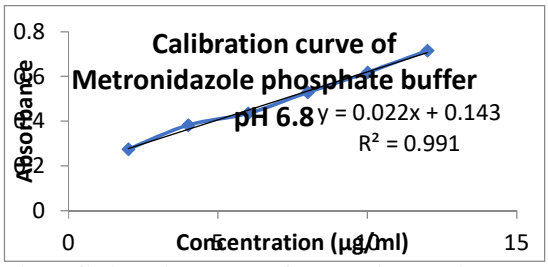

Fig 7: Calibration curve of Metronidazole in phosphate buffer 6.8

Table 3: Absorbance value of Metronidazole in phosphate buffer 7.4

Concentration (µg/ml)	Absorbance
2	0.218
4	0.346
6	0.454
8	0.529
10	0.628
12	0.763
14	0.988

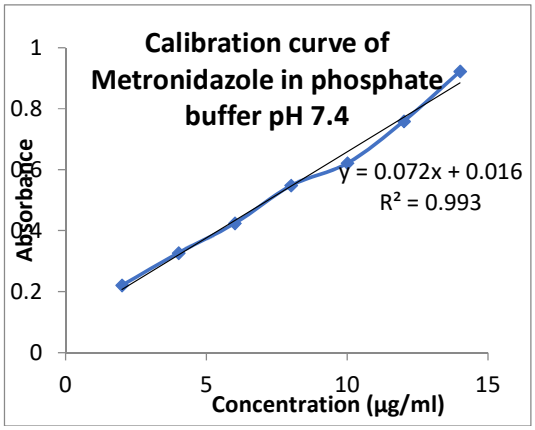

Fig8: Calibration curve of Metronidazole in phosphate buffer 7.4

Table 4: Absorbance value of Metronidazole in distill water

Concentration (µg/ml)	Absorbance
2	0.237
4	0.228
6	0.439
8	0.552
10	0.637
12	0.746
16	0.961

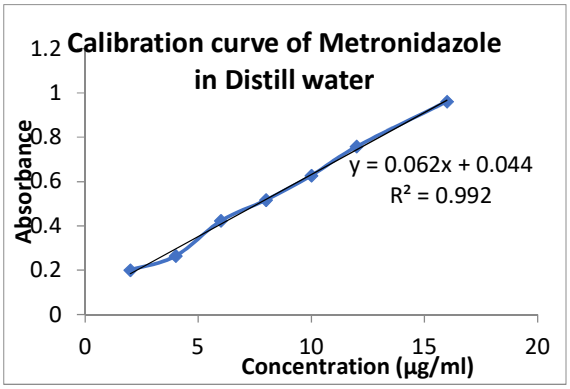

Fig 9: Calibration curve of Metronidazole in distill water

Table 5: Absorbance value of Metronidazole in ethanol

Concentration (µg/ml)	Absorbance
2	0.246
4	0.391
6	0.435
8	0.621
10	0.838
12	0.992

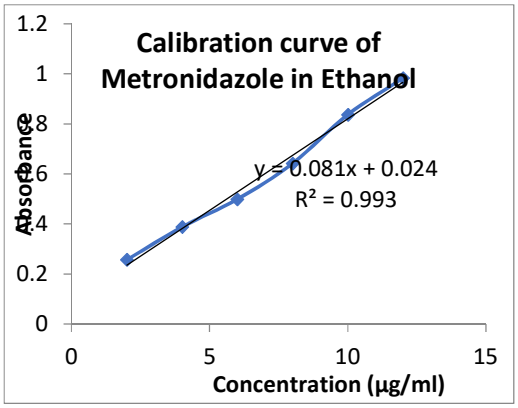

Fig 10: Calibration curve of Metronidazole in ethanol

Solubility determination: The solubility of drug in various solvents such as 0.1 N HCl, Distill water, Phosphate buffer 6.8, 7.4 and ethanol was determined by saturated solubility method. In this method excess of Metronidazole was added in a total of 2ml of each of the above mentioned solvents and this solution was shaken on rotary flask shaker at room temperature for 24 hr. The filtered supernatants were further diluted with solvent mentioned above and analyzed UV spectrophotometrically (277) for their drug content. From these results, the solubility of Metronidazole in the respective volatile solvent was calculated. All experiments were carried out in triplicate.

Table 6: Solubility of Metronidazole in different solvents

Solvent	Solubility (mg/ml)
0.1 N HCl	55.28±5.8
Distill water	11.1±3.06
Phosphate buffer 6.8	0.06±0.02
Phosphate buffer 7.4	0.08±0.001
Ethanol	0.6±0.01

Dissolution study of drug:

10 mg of Metronidazole was filled in Capsule-1 and subjected to dissolution by USP basket type-1 dissolution apparatus (EDT-08Lx Dissolution apparatus, Electrolab, Mumbai). Temp maintained 37±0.5°C and stirring speed fixed to 50 RPM. Specific time interval samples collected and subjected to absorbance determination and converted to concentration with help of calibration curve.

Table7: Dissolution study of pure Metronidazole

Time (Minute)	Percentage cumulative drug release				
	Ethanol	0.1 N HCl	Phosphate buffer 6.8	Phosphate buffer 7.4	Distill water
0	0	0	0	0	0
5	11.48±1.2	65.34±2.8	8.13±1.5	8.44±2.1	27.36±1.3
30	46.27±5.7	99.87±4.4	30.28±2.7	36.81±5.2	52.72±3.2
60	65.33±3.9		45.44±3.8	54.27±3.8	82.94±4.6
120	82.79±6.2		72.83±2.9	77.65±4.4	99.67±5.2
180	99.15±7.1		89.93±3.4	99.87±2.8	
240			99.21±5.2		

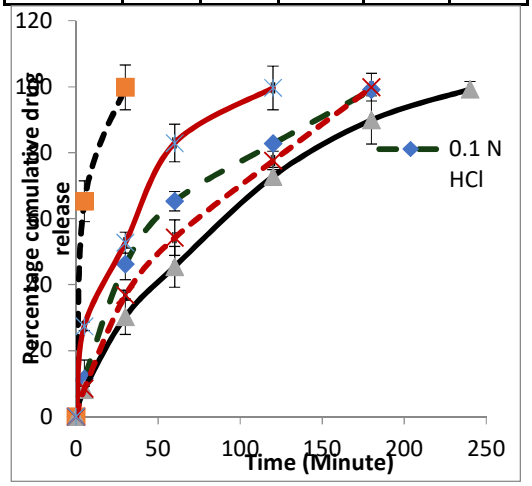

Fig 11: Dissolution study of pure drug

ATR study of Drug and Excipients

Attenuated total reflection (ATR) is a sampling technique used in conjunction with infrared spectroscopy which enables samples to be examined directly in the solid or liquid state without further preparation. ATR spectroscopy is

particularly useful for online monitoring of polymer composition. Its ability to fingerprint chemical components allows IR to determine the constituents of a chemical process. The study was conducted by ***ATR Bruker Opus 7.0, Germany***

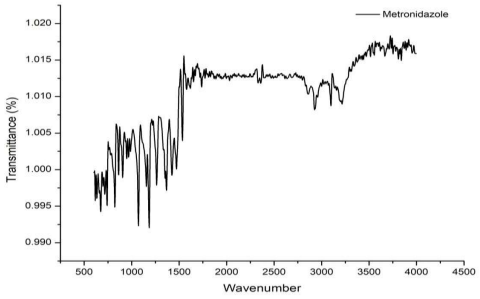

Fig 12: ATR spectra of pure Metronidazole

The IR spectrum of metronidazole shows characteristic peaks for its functional groups: strong broad bands around 3400.65 cm^{-1} for the O-H stretch, sharp bands around 1543.32 cm^{-1} and 1365 cm^{-1} for the nitro (NO_2) group, and peaks in the 1424 cm^{-1} region for C=N and C=C stretches of the imidazole ring, with C-H stretches (aliphatic/aromatic) appearing around 2971.76 cm^{-1}. These bands confirm the presence of hydroxyl, nitro, and imidazole moieties, allowing identification and structural analysis (Fig 16).

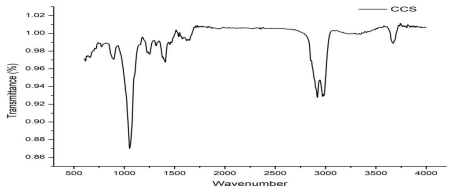

Fig13: ATR spectra of Cross carmellose sodium

The IR spectrum of cross carmellose sodium, a cross-linked polymer of carboxymethyl cellulose sodium, exhibits several characteristic absorption bands consistent with its chemical structure. A prominent feature is a broad and strong peak around 3421.66 cm^{-1}, which is attributed to the O-H stretching vibrations of the hydroxyl groups and adsorbed moisture. A C-H stretching peak appears around 2998.55 cm^{-1}. The spectrum also features strong bands related to the carboxylate functional groups (COO^-), specifically an asymmetric C=O stretching vibration around 1435.63 cm^{-1}. Additionally, C-O stretching vibrations within the pyranose ring structure of the cellulose backbone are typically observed in the fingerprint region, around 1112 cm^{-1} and 985.09 cm^{-1}.

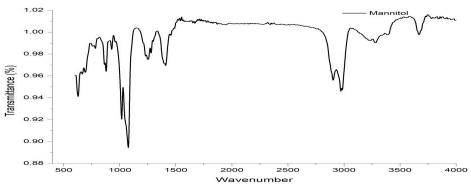

Fig 14: ATR spectra of Mannitol

The charatectisc peak at 3400.26 cm^{-1} indicated presence of O-H stretching. C-H stretching observed at 2996.71 cm^{-1} by C-H vibration. A sharp C-O bending appeared at 1025.22 cm^{-1}. Similarly other CH vibrations noted at 954.28 cm^{-1} and 733.97 cm^{-1}.

Fig 15: ATR spectra of Hydroxy propyl methyl cellulose (HPMC)

The IR spectrum of HPMC (Hydroxypropyl Methylcellulose) shows key peaks indicating its polymeric structure, notably a broad band around 3426.67 cm^{-1} for O-H stretching, C-H stretches around 2984.11 cm^{-1}, and strong C-O bond vibrations (C-O-C and C-O) at 1030.76 cm^{-1}, characteristic of cellulose derivatives, confirming the presence of hydroxyl and ether linkages within its anhydro-glucose ring structure,

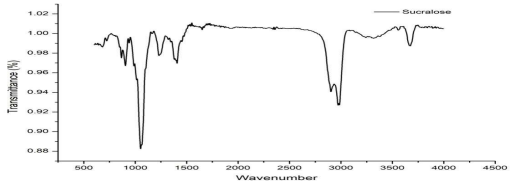

Fig 16: ATR spectra of Sucralose

Hydroxyl Group (O-H) & C-O Stretches: Broad absorption appeared at around 3574.61 (O-H stretch, often from water) and intense bands between 1004.27 cm^{-1} C-O-C ether & C-O alcohol stretches) are typical for sugars, with specific strong peaks at 1025, 1001 for sucralose Strong absorption band for CO around 1624 cm^{-1} appeared.

Differential Scanning Calorimetry (DSC) study

DSC is a thermal analysis apparatus measuring how physical properties of a sample change, along with temperature against time. In other words, the device is a thermal analysis instrument that determines the temperature and heat flow associated with material transitions as a function of time and temperature. DSC was carriedout by **DSC-60, Shimadzu, USA**.

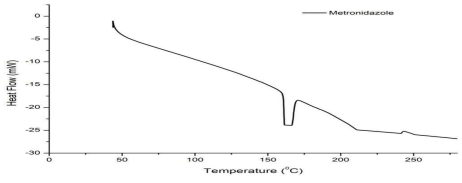

Figure 17: DSC of Metronidazole

It observed (Figure 23) a sharp endothermal peak at 156.22 °C with heat of energy of -147.21 mJ; which is as per the literature study.

Method of preparation of Metronidazole Fast Dissolving Tablet (FDT)

Metronidazole fast-dissolving tablets were prepared by the direct compression technique. Accurately weighed quantities of Metronidazole, Spray dried lactose, Cross povidone and mannitol were used.

All those ingredients are weighed accurately by Precision balance and passed through sieve number 60. Mixing and blending took place in a clean and dry mortar and pestle. Finally the obtained powder was then blended with a small amount (2mg) of magnesium stearate (lubricant) and talc (glidant; 2mg) to improve flow and compression properties.

Finally, the blend was compressed into tablets using a rotary tablet compression machine (Cadmach Mini Press 12 mm Punch) fitted with flat-faced punches. Final weight of the tablet was made to 400 mg with help of diluent.

Formulations suggested by Central composite Design (CCD)

Study type: Response surface

Sub type: Randomized

Design type: Central composite design

Design model: Quadratic

Process order: Polynomial and Quadratic

Block: No block

Table 8: Factors considered and their quantity:

Factor	Name	Units	Type	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	Crosscarmellose sodium	mg	Numeric	18.93	231.07	-1 ↔ 50.000	+1 ↔ 200.000	125.00	61.24
B	Sucralose	mg	Numeric	-39.71	299.71	-1 ↔ 10.000	+1 ↔ 250.000	130.00	97.98

A two-level three-factorial CCD was used in the present study to evaluate the effects of selected independent variables on the responses. Three independent factors such as Spray dried lactose (A), Cross povidone (B) considered. The responses recorded in the experiment are disintegration time, wetting time and dissolution. Mathematical fitting and analysis were performed by the *polynomial equation*. The optimized formula was solved by graphical optimization technique along with a numerical method using the confidence interval value of alpha 0.05. For the two level two-factor CCD, a total of 13 experimental runs as provided in table 2.

Table 9: Formulation Table

	Factor 1	Factor 2	Response 1	Response 2	Response 3
Run	A:Crosscarmellose sodium	B:Sucralose	Disintegration time	Wetting time	Dissolution
	mg	mg	Sec	Sec	%
METF1	125	130	96	35	87.91
METF 2	231.066	130	115	44	82.93
METF 3	125	130	105	41	73.25
METF 4	125	130	98	39	69.86
METF 5	50	250	87	51	78.47
METF 6	50	10	95	48	89.14
METF 7	200	250	107	52	90.48
METF 8	18.934	130	87	44	79.07
METF 9	125	-39.7056	85	39	69.63
METF 10	125	130	92	40	82.77
METF 11	200	10	112	59	81.72
METF 12	125	299.706	72	61	79.76
METF 13	125	130	87	51	84.35

Characterization of FDT

Initially a tablet was taken and crushed in a mortar and pestle. In a 100 mL volumetric flask, the crushed FDT (Equivalent amount of 150 mg of drug) was placed, and the minimum amount of ethanol was added and thoroughly mixed. Approximately 10 minutes were spent sonicating (Ultrasonicator, CPX3800-E, Branson) the dispersion. 0.1 N HCl was added to the resultant mixture and the volume was adjusted to the desired level. The dispersion was bath sonicated for an additional 5 minutes, until it became transparent. The resulting mixture was subsequently filtered using a 0.45 µm pore size Whatman membrane filter. To quantify drug content, the filtrate was

analyzed with a UV-Visible spectrophotometer (Shimadzu UV-1800, Japan) at 277 nm. Using the following formulas, the percent drug loading (DL) were estimated and can be found in **Table 2**

Drug loading:

$$DL\ (\%) = \frac{\text{Drug content in FDT}}{\text{Total weight of FDT}} \times 100 \quad \text{.....(Equation 1)}$$

Table 10: Drug loading of formulations METF1-METF13.

Run	Drug loading
METF1	98.21 ±4.2
METF 2	98.46±2.9
METF 3	99.37±3.6
METF 4	95.18±4.4
METF 5	98.66±5.2
METF 6	99.25±1.7
METF 7	99.61±1.8
METF 8	97.64±3.4
METF 9	99.42±2.2
METF 10	99.27± 7.3
METF 11	98.48±5.5
METF 12	9751±4.1
METF 13	98.63±2.7

***In-vitro* drug release:** In vitro drug release of Metronidazole from the FDT was performed by USP Type II dissolution testing apparatus. The drug release studies of the Metronidazole solution is carried out in 900 ml of 0.1 N HCl maintained at 37±0.5° with a RPM maintained at 50 with constant heating equipment (IKA Auto Temp Regulator, Germany). A sample of 2 ml solution of solvent was pipette out and collected in 10 ml Volumetric flask. Aliquot were withdrawn at the regular interval and replaced with same volume of fresh buffer. The aliquots were diluted with fresh media. Amount of drug underwent dissolution was measured by using U.V. spectrophotometer at the wavelength 277 nm against 0.1 N HCl as the blank. The information can be found in **Table 4 and 5.**

Table 11: In-vitro drug release data of METF1-METF7

Time (Min)	METF 1	METF F2	METF F3	METF F4	METF F5	METF F6	METF F7
0	0	0	0	0	0	0	0
5	47.83± 1.2	41.64± 2.3	29.11± 3.3	27.19± 1.6	30.15± 1.8	40.47± 2.8	40.28± 3.3
10	55.85± 3.6	48.59± 3.6	32.59± 1.9	31.68± 2.8	39.28± 3.7	46.55± 1.9	49.86± 1.7
15	70.96± 4.4	70.46± 2.7	46.78± 2.8	48.75± 3.7	45.37± 2.8	64.35± 3.9	62.14± 4.5
20	86.25± 1,8	79.69± 1.9	62.08± 3.6	62.05± 2.8	60.42± 2.4	82.71± 1.9	7904±5 .2
30	87.91± 2.7	82.93± 4.5	73.25± 2.9	69.86± 4.2	78.47± 3.3	89.14± 4.6	90.48± 1.9
40	99.15± 5.2	87.11± 2.9	76.18± 5.5	74.13± 1.8		93.18± 5.2	96.43± 4.4
60	99.78± 1.9	89.88± 2.7	77.81± 1.6	79.47± 4.2		97.74± 1.8	97.11± 6.2

Table 12: In-vitro drug release data of METF8-METF13

Time (Min)	METF F8	METF F9	METF F10	METF F11	METF F12	METF F13
0	0	0	0	0	0	0
5	23.96±1.2	29.46±1.2	45.12±2.9	50.64±1.9	35.14±1.8	29.73±1.8
10	29.06±3.2	31.92±4.2	58.36±3.7	60.95±2.5	40.52±2.5	38.63±4.5
15	50.11±3.5	34.14±5.2	75.85±6.1	80.08±3.3	57.68±6.3	56.27±5.2
20	65.72±4.7	62.36±3.5	80.92±5.5	81.11±6.2	73.09±3.6	89.93±3.7
30	79.07±5.3	69.63±1.8	94.77±2.8	90.72±1.8	79.76±1.8	98.35±6.1
40	77.51±1.9	72.85±5.2	98.16±3.7	99.58±2.7	81.15±3.3	
60	81.53±2.8	76.24±4.7	99.86±1.9		83.58±6.2	

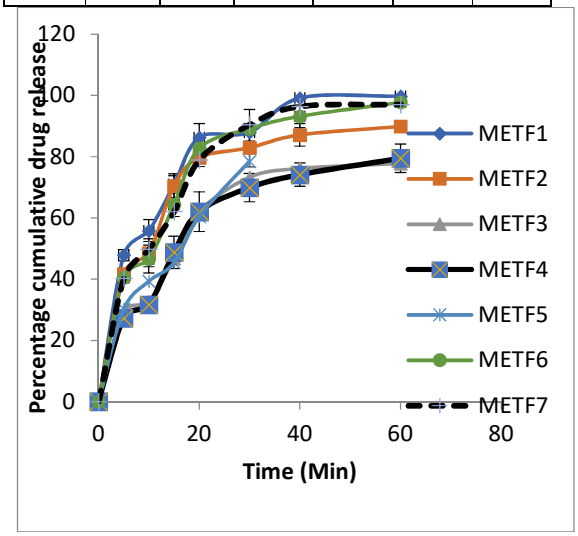

Fig 18: Figure shows In-vitro drug release data of FDT METF1-METF7

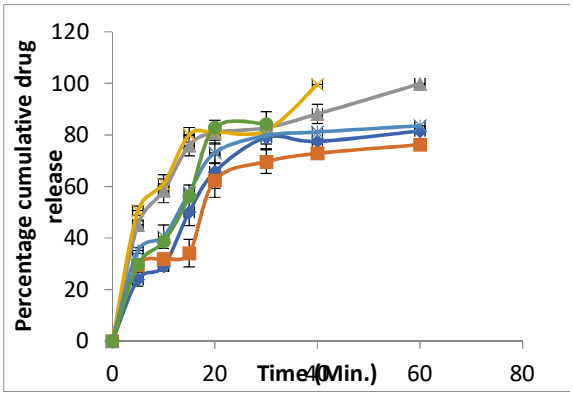

Fig 19: Figure shows In-vitro drug release data of FDT METF8-METF13

The in vitro dissolution of CCD-optimized FDTs (METF1–METF13) showed rapid drug release, with most formulations achieving 90–99% release within 30–60 min. This burst release is typical of fast-dissolving tablets, where rapid wetting and disintegration dominate early dissolution.

CCS, as a superdisintegrant, primarily enhanced early-stage release (5–20 min) through wicking and swelling. Formulations with shorter disintegration and wetting times exhibited higher early release (e.g., METF1: 47.8% at 5 min, 86.3% at 20 min), whereas lower early release (METF3, METF4) reflected slower initial tablet breakup. The CCS effect was non-linear; higher levels did not always yield better dissolution at 30 min, confirming its stronger influence on early rather than final release.

Sucralose indirectly affected dissolution by altering wettability and porosity. Moderate levels supported faster release, while excessive amounts (e.g., METF12) increased wetting time and reduced dissolution, likely due to unfavorable liquid penetration. Overall, optimal rapid release resulted from a balanced interaction between CCS-driven disintegration and sucralose-assisted wetting.

Table 13: Release kinetics study from all formulations (METF1-METF13) prepared based on suggestion from CCD

Formulation	Zero	First	Higuchi	Hixson-Crowell	Korsemeyerpeppas	
					(R^2)	n
METF1	0.786	0.875	0.976	0.909	0.752	0.334
METF2	0.898	0.932	0.921	0.911	0.815	0.452
METF3	0.912	0.944	0.955	0.874	0.877	0.311
METF4	0.935	0.987	0.887	0.807	0.826	0.457
METF5	0.905	0.92	0.896	0.811	0.888	0.287
METF6	0.93	0.99	0.921	0.913	0.638	0.423
METF7	0.926	0.921	0.946	0.937	0.879	0.346
METF8	0.889	0.896	0.966	0.899	0.12	0.212
METF9	0.823	0.911	0.928	0.918	0.864	0.376
METF10	0.854	0.958	0.985	0.851	0.751	0.425
METF11	0.921	0.972	0.933	0.905	0.845	0.341
METF12	0.957	0.984	0.926	0.924	0.921	0.224
METF13	0.927	0.933	0.945	0.851	0.811	0.377

Drug release kinetics study ascertained by Zero order and First order kinetic study (Table 6). It observed most of formulations obeyed zero order and their R^2 value greater than first order. Which indicate drug release primarily does not depend on drug concentration and polymer concentration.

Whereas release mechanism ascertained by Higuchi, Hixon-Crowell and Korsemeyerpeppas model. It observed that, all formulations followed Higuchi pattern mechanism only. It is known that, Higuchi model describes the release of drugs from insoluble matrix as a square root of time dependent process. Remaining obeyed Hixon crowell release mechanism which indicated change in surface area (erosion dominated) during dissolution.

Characterization of FDTs (Short)

Weight variation: Twenty tablets from each batch were weighed individually using a digital balance, and the average weight and percentage deviation were calculated and compared with pharmacopoeial limits.

Hardness: Tablet hardness was measured using a Monsanto hardness tester. Six tablets were tested individually, and the mean hardness (kg/cm²) was calculated.

Friability: Twenty tablets were weighed and rotated in a Roche friabilator at 25 rpm for 4 min (100 revolutions). Tablets were dedusted and reweighed, and percentage friability was calculated.

Disintegration time: Six tablets were tested using a USP disintegration apparatus in distilled water at 37 ± 0.5 °C. The time required for complete disintegration without residue was recorded.

Wetting time:A tablet was placed on dye-moistened filter paper in a Petri dish, and the time

taken for the dye to appear on the tablet's upper surface was recorded. The test was performed on six tablets, and the mean wetting time was calculated.

Table 14: Characterization table for developed FDT

Formulation	Weight variation (%)	Hardness (Kg/Cm^2)	Friability (%)	Disintegration time (Sec)	Wetting time (Sec)
METF1	1.5	3.5	0.4	96	35
METF2	2.6	4.5	0.4	115	44
METF3	3.0	5.0	0.25	105	41
METF4	2.5	5.5	0.6	98	39
METF5	5.5	6.0	0.4	87	51
METF6	2.5	4.5	0.35	95	48
METF7	4.5	4.0	0.2	107	52
METF8	3.5	6.5	0.35	87	44
METF9	1.8	4.5	0.15	85	39
METF10	2.6	3.5	0.32	92	40
METF11	3.0	3.5	0.44	112	59
METF12	2.8	4.5	0.15	72	61
METF13	1.3	4.0	0.25	87	51

Model Validation:

The study need to validate the suitability of model selection as well as ANOVA analysis of independent variables with relation to Responses. It can be seen in Table 8, model is validated as the p-value less than 0.05. Similarly it can be seen that, A, and B^2 are significantly affecting the Response 1.

Table 15: Model validation study by ANOVA for Quadratic Model (Response 1: Disintegration time)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1366.14	5	273.23	4.71	**0.0333**	significant
A-Croscarmellose sodium	733.41	1	733.41	12.64	**0.0093**	
B-Sucralose	123.13	1	123.13	2.12	0.1885	
AB	2.25	1	2.25	0.0388	0.8495	
A^2	197.26	1	197.26	3.40	0.1077	
B^2	244.21	1	244.21	4.21	**0.0393**	
Residual	406.17	7	58.02			
Lack of Fit	224.97	3	74.99	1.66	0.3119	not significant
Pure Error	181.20	4	45.30			
Cor Total	1772.31	12				

Table 16: Model validation study by ANOVA for Quadratic Model (Response 2: Wetting time)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	395.82	5	79.16	1.48	**0.0359**	significant
A-Croscarmellose sodium	18.00	1	18.00	0.3374	0.5795	
B-Sucralose	91.89	1	91.89	1.72	**0.0208**	
AB	25.00	1	25.00	0.4687	0.5156	
A^2	53.57	1	53.57	1.00	**0.0497**	
B^2	232.00	1	232.00	4.35	0.0755	
Residual	373.41	7	53.34			
Lack of Fit	232.61	3	77.54	2.20	0.2303	not significant
Pure	140.80	4	35.20			

Error						
Cor Total	769.23	12				

In above Table 8, it can be seen from P<0.05 data that B and B^2 are significantly affecting the Response 2.

Table17: Model validation study by ANOVA for Quadratic Model (Response 3: Dissolution)

Source	**Sum of Squares**	**Df**	**Mean Square**	**F-value**	**p-value**	
Model	175.69	5	35.14	0.6632	**0.0435**	significant
A-Cross carmellose sodium	12.62	1	12.62	0.2382	**0.0104**	
B-Sucralose	19.27	1	19.27	0.3637	0.5655	
AB	94.38	1	94.38	1.78	**0.0237**	
A^2	42.18	1	42.18	0.7961	**0.0019**	
B^2	3.31	1	3.31	0.0626	0.8097	
Residual	370.86	7	52.98			
Lack of Fit	134.01	3	44.67	0.7544	0.5747	not significant
Pure Error	236.85	4	59.21			
Cor Total	546.55	12				

In above Table 9, it can be seen from P<0.05 data that A and B^2 are significantly affecting the Response 3.

Response surface methodology (RSM):

Response surface methodology (RSM) is a collection of mathematical and statistical techniques for empirical model building. By careful design of experiments, the objective is to optimize a response (output variable) which is influenced by several independent variables (input variables).

Response surface plots such as contour and surface plots are useful for establishing desirable response values and operating conditions. In a contour plot, the response surface is viewed as a two-dimensional plane where all points that have the same response are connected to produce contour lines of constant responses.

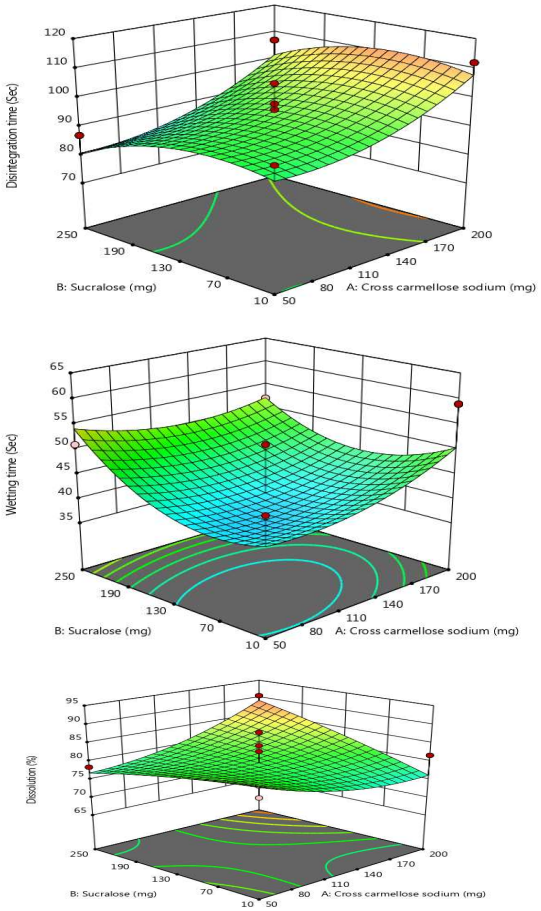

Figure 20: 3D simulation curve of Responses (Sucralose Vs Cross carmellose sodium)

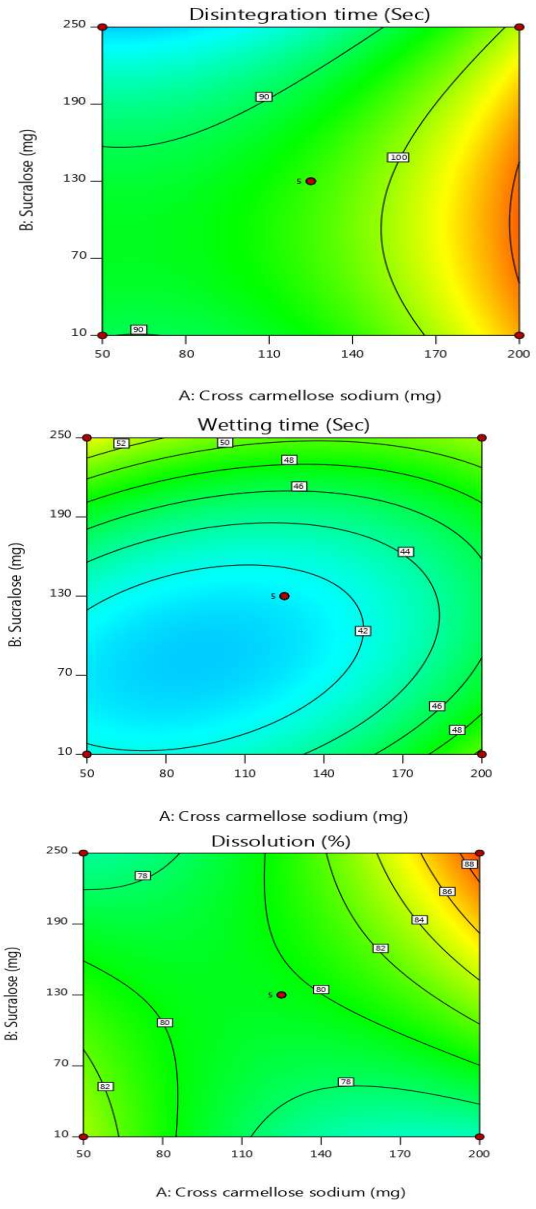

Figure 21: 2D simulation curve of Responses Cross povidone Vs Spray dried lactose

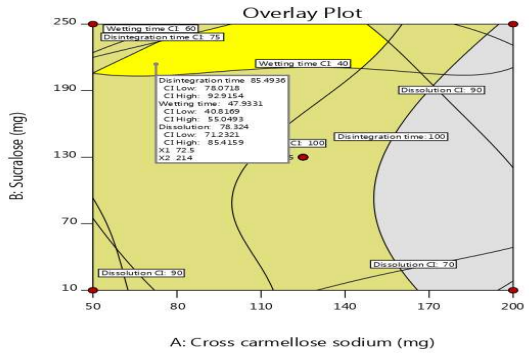

Figure 22: Overlay plot of region highlighting the optimized space and values

The polynomial equation

Polynomial equations were used to describe the effect of formulation variables on tablet responses. The fitted models for disintegration time, wetting time, and dissolution (Equations 1–3) revealed the significance of linear, interaction, and quadratic terms.

For Response 1 (Disintegration time), factor A and the quadratic term B^2 were significant. For Response 2 (Wetting time), factor B and A^2 were significant. For Response 3 (Dissolution), A, the interaction term AB, and A^2 were significant.

These polynomial models indicated that both main and quadratic effects influenced the responses. Optimization was performed using canonical analysis, integrating mathematical and graphical approaches. Based on predefined target ranges from the literature, an optimized formulation was identified, and the design space (yellow region) is shown in Figure 5. The optimized formulation is summarized in Table 11.

Table 18: Optimization formulation table

Factor	Name	Level	Low Level	High Level	Std. Dev.	Coding
A	Cross carmellose sodium	72.50	50.00	200.00	0.0000	Actual
B	Sucralose	214.00	10.00	250.00	0.0000	Actual

As per the information provided in table 10, the optimized FDT was prepared and responses recorded in Table 11 as observed value. The observed value and predicted mean (obtained from response surface simulation) were compared.

Table 19: Point Prediction table of optimized formulation

Response	Predicted Mean	Predicted Median	Observed	Std Dev	SE Mean	95 % CI low for Mean	95 % CI high for Mean	95 % TI low for 99 % Pop	95 % TI high for 99 % Pop
Disintegration time	85.49	85.49	84.5	7.617735	3.918	76.222 54	94.75546	42.80 52	128.175
Wetting time	47.9369	47.9369	42.6	7.303 74	3.756 69	39.05 37	56.82	7.009 36	88.86 44

Dissolution	78.3232	78.3232	80.2	7.278 75	3.743 83	69.4705	87.17 6	37.5358	119.111

ATR study of Optimized formulation

Attenuated total reflection (ATR) is a sampling technique used in conjunction with infrared spectroscopy which enables samples to be examined directly in the solid or liquid state without further preparation. ATR spectroscopy is particularly useful for online monitoring of polymer composition. Its ability to fingerprint chemical components allows IR to determine the constituents of a chemical process. The study was conducted for optimized formulation by ***ATR Bruker Opus 7.0, Germany.***

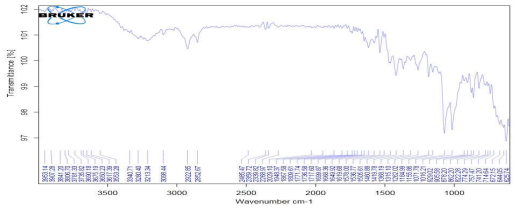

Figure 23: ATR spectra of optimized formulation

Characteristic peaks were identified and characterized accordingly. The presence and absence of characteristic peaks noted from FDT. The IR spectrum of metronidazole optimized tablet shows characteristic peaks for its functional groups: strong broad bands around 3424.61 cm^{-1} for the O-H stretch, sharp bands around 1545.76 cm^{-1} and 1311.08 cm^{-1} for the nitro (NO_2) group, and peaks in the 1420.11 cm^{-1} region for C=N and C=C stretches of the imidazole ring, with C-H stretches (aliphatic/aromatic) appearing around 2965.73 cm^{-1}. These bands confirm the presence of hydroxyl, nitro, and imidazole moieties, allowing identification and structural analysis. This study confirms no major such peak shift took place.

DSC of study of optimized formulation

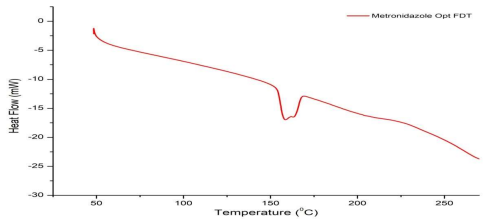

Figure 24: DSC thermogram of Optimized formulation

DSC study (Figure 18) highlighted a sharp endothermal peak at 152.47 °C; which is near to pure drug as recorded earlier value of 156.24°C. This ascertained non significant change in endothermal peak. It also inferred thermal stability of pure drug in FDT formulation. It also observed a broad peak at 202.09 °C. This broadening of peak could be attributed by formation of complex by CCS and drug. It noted there is no such prominent peak appeared for cross povidone and sucralose.

SUMMARY

The present study focused on the formulation and optimization of Metronidazole fast dissolving tablets (FDTs) by direct compression using a Central Composite Design (CCD). The objective was to achieve rapid disintegration, enhanced dissolution, and acceptable tablet properties.

Preformulation studies confirmed the purity, identity, and suitable physicochemical characteristics of Metronidazole, with good solubility in 0.1 N HCl supporting its use as dissolution medium. Thirteen formulations (METF1–METF13) containing varying levels of cross carmellose sodium (CCS) and sucralose were prepared. All formulations complied with pharmacopoeial requirements for weight variation, hardness, and friability.

Disintegration time (72–115 s) and wetting time (35–61 s) indicated rapid tablet performance, while drug content uniformity was within acceptable limits. Dissolution studies showed fast drug release, with several formulations achieving more than 90% release within 30–60 min. Drug release followed mainly zero-order kinetics and Higuchi diffusion, with Fickian diffusion as the predominant mechanism.

ANOVA confirmed the significance of the quadratic models ($p < 0.05$). CCS had a major effect on disintegration and dissolution, whereas sucralose mainly influenced wetting time. The optimized formulation containing 72.5 mg CCS and 214 mg sucralose showed good agreement between predicted and experimental responses, and ATR/DSC studies confirmed drug–excipient compatibility and formulation stability.

CONCLUSION

The study confirmed that Metronidazole fast-dissolving tablets can be successfully formulated by direct compression and optimized using Central Composite Design and Response Surface Methodology. The optimized formulation showed rapid disintegration, acceptable wetting time, uniform drug content, and enhanced in-vitro dissolution, meeting the requirements of FDTs.

Cross carmellose sodium significantly improved disintegration and early drug release, while sucralose mainly influenced wetting behavior and palatability. ANOVA validated the significance and reliability of the developed quadratic models. ATR and DSC studies confirmed drug–excipient compatibility and formulation stability.

Overall, the optimized Metronidazole FDT is promising for improved patient compliance, particularly in pediatric and geriatric patients, and demonstrates the effectiveness of CCD-based optimization for potential scale-up and commercial development.

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