RESEARCH ARTICLE

Formulation and Taste Masking of Metronidazole Oral Disintegrating Tablets by a Novel Approach

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ABSTRACT

The anti-protozoal drug, metronidazole, is developed as an oral disintegrating tablet (ODT) to treat amoebiasis and to bypass hepatic metabolism. The work aimed to prepare, taste-masking oral disintegrating tablets of metronidazole using different proportions of the drug and disintegrants in various ratios by an effervescent method. The ODT was developed by direct compression with various concentrations of super disintegrating agents (1-7%). In this technique, sodium bicarbonate and tartaric acid were used to generate effervescence. The formulated tablets were assessed for physicochemical characteristics. The results of FTIR spectroscopy indicated the stable character of metronidazole. *In vitro* studies revealed that batch F6 was having a 97.65% cumulative amount of drug release at 20th minute compared to other formulations. Due to the effervescent method, there was a significant increase in drug release, seen at the 1:1.5 ratio. Taste evaluation studies were conducted on healthy human volunteers.

Keywords: Effervescent method, Metronidazole, Oral disintegrating tablets, Super disintegrants, Taste masking.

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INTRODUCTION

Because of the easiness of administration and formulation, oral delivery is the foremost widely accepted route.[1,2] But commonly used oral dosage forms are difficult in accepting or chewing, leading to patient's incompatibility.[3,4] An ODT is a compact dosage form that comprises medical substance and disintegrates speedily in seconds without water when positioned on the tongue. This is very suitable for patients traveling or who do not have instant access to water and thus provide better patient compliance. The availability of drugs is also improved due to absorption from mouth, pharynx, and esophagus.[5,6] Good mouthfeel, specifically for pediatrics, a taste-masking method, is employed to avoid the bitter taste of medicaments. Metronidazole is an anti-protozoal drug formulated as an orally disintegrating tablet to treat amoebiasis and to bypass liver metabolism.

MATERIALS AND METHODOLOGY

Metronidazole received as a gift sample from DRL, Hyderabad. Sodium bicarbonate and tartaric acid were procured from Hetero Drugs, Hyderabad. Remaining other chemicals obtained for this work were of analytical grade.

Drug-Excipient Compatibility Studies

The Compatibility studies of the pure drug along with excipients were studied employing a Fourier Transform – Infra-Red (FTIR) spectrophotometer and the spectrum of every sample was noted over 450–4000 cm^{-1}.

Method of Preparation

The pure drug, sodium bicarbonate, tartaric acid, Avicel pH 102, was accurately weighed and blended in a glass mortar for 15 minutes. All the formulations were prepared as per the composition given in Table 1, and finally, tablets were compressed using 9 mm round flat-faced punches.

Evaluation of Oral Disintegrating Tablet (ODT) Formulations

The developed tablets were evaluated for weight uniformity using an electronic balance, thickness using a digital screw gauge, hardness with Monsanto hardness tester, and friability was determined by Roche friabilator, and drug content was determined by dissolving the powder equivalent to one dose in a suitable solvent, and the obtained solution was filtered, and absorbance was measured by means of UV Visible spectrophotometer at 270 nm against blank.[7]

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Table 1: Composition of metronidazole oral disintegrating tablets

Formulation ingredients	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*
Metronidazole	100	100	100	100	100	100	100	100
Super disintegrants (SSG:CP:CCS) 12, 14, and 18%	5	4	15	17	15	11	19	20
Avicel PH102	100	90	48	41	84	10	60	62
Sodium bicarbonate	16	18	39	10	18	60	22	54
Tartaric acid	39	18	39	42	54	90	39	42
Na.stearyl fumarate	5	5	5	5	5	9	5	5
Talc	5	5	4	5	5	5	5	5
Starch	30	60	50	80	19	15	50	12

Total weight of the tablet 300 mg

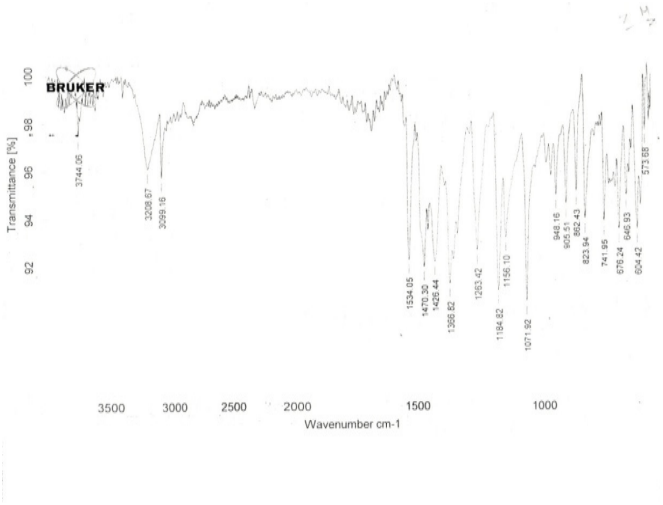


Figure 1: FT-IR spectrum of pure drug metronidazole

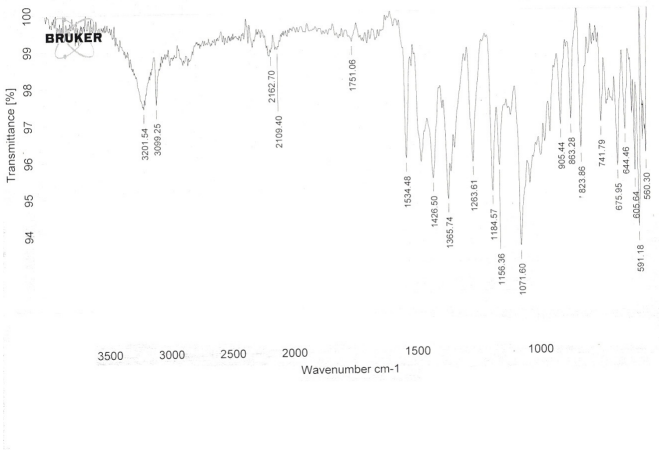


Figure 2: FT-IR spectrum of metronidazole + microcrystalline cellulose

In vitro Dispersion Time

The time essential for the tablet to disperse completely was studied by immersing it in a beaker containing phosphate buffer (10 mL). The tests were carried out in triplicates, and dispersion time was recorded (n = 3) to check for reproducibility.[8]

In vitro Release Studies

The dissolution study was performed by using the USP-II apparatus; 5 mL of samples were collected, diluted, and analyzed for an active ingredient with the aid of UV visible spectrophotometer at 270 nm.[8]

Stability Studies

The stability studies were carried at different environmental conditions by placing them in a stability chamber at varying temperatures and relative humidity as per ICH guidelines for 2 months and periodically characterized for their physicochemical and release pattern.[9,10]

Taste Masking Studies

The experiment was approved by the Institutional Human Ethics Committee, Vaagdevi College of Pharmacy, with an approval number (IHEC/VGOPC/45/2014). On healthy volunteers after taking their consent, taste evaluation studies were performed. The volunteers were distributed into two groups, each containing four, one group is evaluated for taste and another group for mouthfeel. Each individual has received all formulations for taste masking evaluation.

RESULTS AND DISCUSSION

Drug Excipient Compatibility Studies

The obtained principle peaks were measured as distinctive peaks of metronidazole. The peaks were not affected by the excipients indicating the stability. This shows that there is no interference between active pharmaceutical ingredients and excipients. The spectra were shown in Figures 1 and 2.

Characterization of Oral Disintegrating Tablets (ODTs)

Metronidazole ODTs were developed by the effervescent technique using various concentrations of super disintegrants. Super disintegrants were used for preparing ODTs for the enhancement of solubility of the drug. The concentration of super disintegrants was optimized. F1–F8 formulations were prepared, as mentioned in Table 1. The physical parameters of the tablets were assessed, and the data were recorded in Table 2. All the batches were checked for weight variation and were free from tablet defects. The average tablet weight of ODT was 297.3 ± 1.90, and all the formulations complied with the standards of IP. The thickness of the formulations was found to be 4.8 ± 0.08 mm and found to comply with the standards of IP. It is also known that ODTs with more hardness will

Table 2: Evaluation of post-compression parameters

F. code	*Disintegration time (sec)*	*Weight variation (mg)*	*Hardness (kg/cm^2)*	*Thickness (mm)*	*Drug content (%)*
F1	44.90 ± 0.92	277 ± 1.15	3.6 ± 0.15	3.7 ± 0.16	96 ± 1.51
F2	39.25 ± 0.60	282 ± 0.75	3.3 ± 0.11	3.5 ± 0.26	97.33 ± 1.15
F3	34.16 ± 0.75	287 ± 1.51	2.9 ± 0.07	3.7 ± 0.08	88 ± 0.75
F4	32.25 ± 0.76	284 ± 2.86	2.7 ± 0.15	4 ± 0.08	86 ± 1.51
F5	24.89 ± 0.68	286.3 ± 1.90	2.6 ± 0.15	4.2 ± 0.08	82.33 ± 1.15
F6	19.05 ± 0.83	297.3 ± 1.90	3.6 ± 0.15	4.8 ± 0.08	98 ± 0.75
F7	52.66 ± 1.50	274.3 ± 2.30	3.3 ± 0.19	4.63 ± 0.124	81 ± 1.51
F8	47.22 ± 0.89	296 ± 1.90	2.4 ± 0.31	3.6 ± 0.124	77 ± 1.51

be showing greater disintegration time, hence hardness was determined. The friability was LT 1%, which was acceptable according to Indian Pharmacopeia.

The assay was performed, and the % drug content found to be 98 ± 0.75. No significant change is observed in the tablets and is within the specifications, a sign of good content uniformity.

In vitro Disintegration Time

The disintegration test was executed and recorded for all the formulations. From the evaluation data, it was conveyed that a decrease in the disintegration time exhibited faster drug release (Figure 3) proving to be suitable as ODT. From the observations, it was evident that the water uptake capacity of super disintegrants follows as croscarmellose sodium > sodium starch glycolate > crospovidone.

In vitro Dissolution Study

From Figures 4 and 5, it was absolutely ascertained that the release of drug from different formulations F5, F6, F7, and F8 were found to be 87.65 ± 0.24, 97.65 ± 1.15,

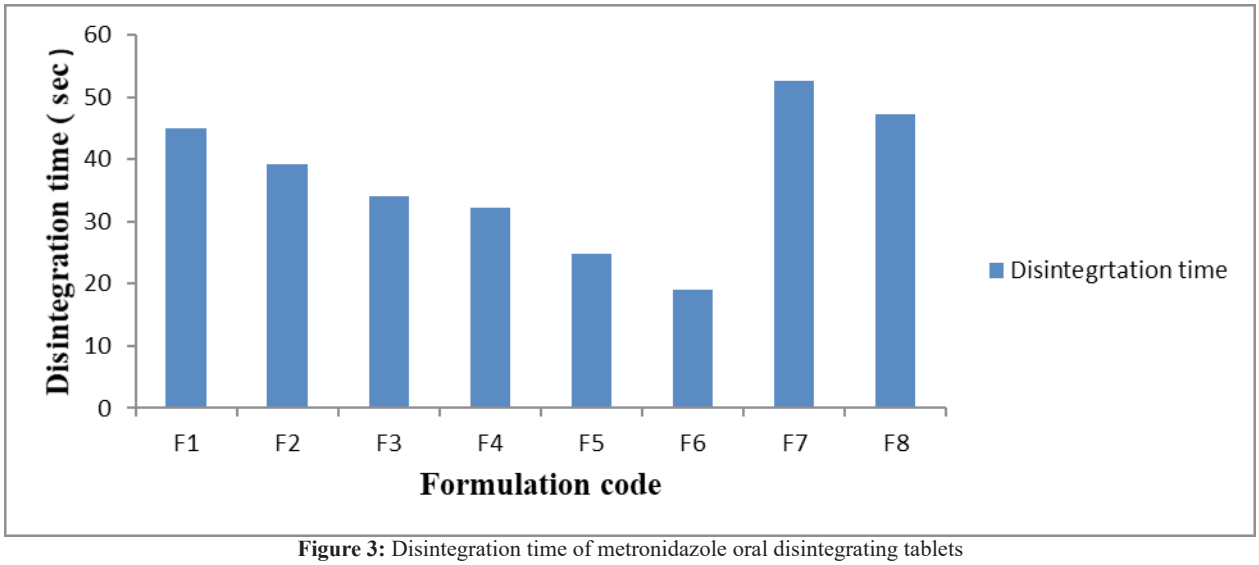
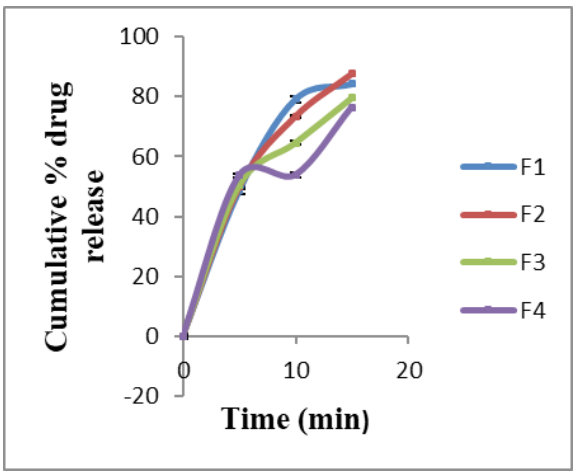
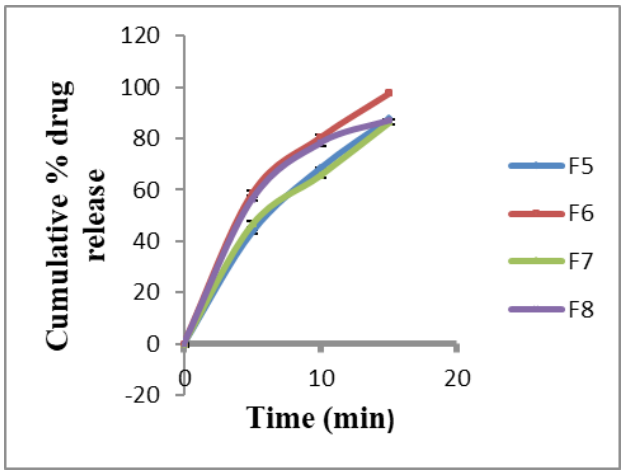


Figure 3: Disintegration time of metronidazole oral disintegrating tablets





Figures 4 and 5: Cumulative % release of metronidazole ODT (F1–F4, F5–F8)

Table 3: Cumulative percent release of metronidazole ODT formulations

	Cumulative % drug release		
Time (min)	*5*	*10*	*15*
F1	48.6 ± 0.64	79.2 ± 0.99	84.3 ± 1.03
F2	49.8 ± 0.43	73.4 ± 0.56	87.6 ± 0.45
F3	50.4 ± 0.74	64.6 ± 0.76	79.6 ± 0.65
F4	53.64 ± 0.45	53.87 ± 0.67	76.43 ± 0.76
F5	43.65 ± 0.54	68.54 ± 0.67	87.65 ± 0.24
F6	58.69 ± 0.775	80.52 ± 1.15	97.65 ± 1.15
F7	46.56 ± 0.78	65.76 ± 0.56	86.32 ± 1.53
F8	56.43 ± 0.46	78.34 ± 0.78	86.98 ± 1.54

Table 4: A table indicating the scale of the taste of the formulation

	Taste				*Mouthfeel*			
Formulation	*V1*	*V2*	*V3*	*V4*	*V5*	*V6*	*V7*	*V8*
F1	+	+	+	++	++	+	++	++
F2	++	++	++	++	+++	++	++	++
F3	+	++	++	+	++	+++	+	+++
F4	+	++	++	++	++	+	+	+
F5	++	+	+++	+	++	+++	++	++
F6	+++	+++	+++	+++	+++	+++	++	+++
F7	+	++	+++	+	++	+	++	+
F8	+	+	+++	++	++	+++	+	+++

Taste	*Mouthfeel*	*Result*
Highly bitter	Bad	+
Bitter	Acceptable	++
Acceptable	Pleasant	+++

86.32 ± 1.53, and 86.98 ± 1.54%, respectively, at the end of the 15 minutes (Table 3). Among all the formulations, F6 was found to be the best since it disintegrates within 5 seconds and it revealed 97.65 ± 1.15% drug release within 15 minutes. The rapid release might be because of an easy breakdown due to the super disintegrants mechanism of action.

Stability Studies

Stability study was carried out for 2 months at 2–8°C at 45% RH, 25–30°C at 60% RH, and 45–50°C at 75% RH. The tablets were experimental for physicochemical characteristics and the % drug release proving to be stable both physically and chemically and exposed no significant change in drug content. There was no much difference in physicochemical parameters before and after storage.

80% of volunteers reported that formulation F6 was pleasant and acceptable. The data was tabulated in Table 4.

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CONCLUSION

The ODT of metronidazole was successfully developed by employing the effervescent method considering sodium bicarbonate and tartaric acid and different super disintegrants (sodium starch glycolate, croscarmellose sodium, and crospovidone). Among all the formulations ODT with sodium bicarbonate, tartaric acid (12, 14%) showed responses in the desired range, and the taste masking of the drug is achieved by using sodium bicarbonate, tartaric acid in the ratio of (1:1.5) and the formulation was F6. From the study, it was established that a novel approach of ODT could be developed by using super disintegrants, excipients, and effervescent bases and can be commercialized.

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