Section A-Research paper

Evaluation and Characterization of metronidazole matrix tablet formulation

Mrs. Namita S. Girhepunje[1], Dr. Nitin G. Dumore[1], Mrs. Monali N. Dumore[2], Shital N. Shende[1], Aarti K. Thakre[1], Mansi R. Barai[1], Manjusha H. Charde[1]

[1]Dadasheb Balpande College of Diploma in Pharmacy, Nagpur, Maharashtra-440037, India

[2]Dadasaheb Balpande College of Pharmacy, Nagpur, Maharashtra-440037, India

Corresponding author
Dr. Nitin G. Dumore
Principal
Dadasaheb Balpande College of diploma in Pharmacy,
Nagpur, Maharashtra-440037, India
Email ID: nitingdumore@gmail.com
Contact no. 8888406985

ABSRACT

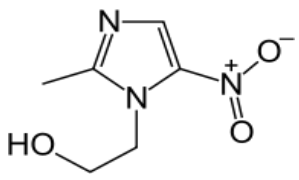
In order to treat the pathogenic bacterium, new medications must constantly be created. In this study, imidazole tablet physicochemical properties were investigated while various heterocyclic compounds were converted into 5-nitroimidazole derivatives. The nitroimidazole antibiotic drug metronidazole, technically known as 2-(2-methyl-5-nitro-1Himidazol-1-yl) ethanol, is used mostly for anaerobic bacteria and protozoa. Antibiotic, amebicide, and antiprotozoal all describe metronidazole. It is the medication of choice for mild-to-moderate Clostridium difficile infection initial episodes. In paper shows the results of quality control tests on four different Metronidazole generic products and four different brand-name products. The results are summarised as an average value for tablet hardness, weight uniformity, friability percentage, average time of disintegration test, and percentage of Metronidazole content in each sample product. Medicinal chemistry focuses on the development, identification, and interpretation of the chemical mechanisms underlying the biological activity of substances, using Manihot ultilissima starch, metronidazole tablets were made with good compact (9–10 Kgf hardness) and minimal friability.

Key words:- Metronidazole, UV Spectrophotometer, Thin layer chromatography (TLC), FTIR.

INTRODUCTION

Medical chemistry focuses on the development, identification, and interpretation of the chemical mechanisms underlying the biological activity of substances.[1] Determining how medications work at the molecular level is the intellectual objective of a medicinal chemist.[2]

Antiprotozoal drugs are medicines that are used to treat a variety of diseases caused by protozoa. Some commonly used antiprotozoal drugs are metronidazole (Flagyl), eflornithine (Ornidyl), furazolidone (Furoxone), hydroxyl chloroquine (Plaquenil), iodoquinol (Diquinol, Yodoquinol, Yodoxin), and pentamidine (Pentam 300).[3] As a supplement to other medications, metronidazole is recommended for the treatment of Helicobacter pylori eradication therapy in peptic ulcer disease. [5,6] Using thin layer chromatography (TLC), the purity of each synthesised derivative was examined. Shimadzu Fourier Transform Infrared Spectrophotometer (FTIR- 8400s) and KBr pellets were used to record the IR spectra of the 5-nitroimidazole derivatives. The Micro Mass Quattro II triple quadruple Mass Spectrometer was used to obtain the mass spectra. The agar diffusion technique was employed in our procedure to test and evaluate novel compounds' antibacterial activity Fourier Transform Infrared Spectrophotometer (FTIR- 8400s) and KBr pellets were used to record the IR spectra of the 5-nitroimidazole derivatives. The Micro Mass Quattro II triple quadruple Mass Spectrometer was used to obtain the mass spectra. The agar diffusion technique was employed in our procedure to test and evaluate novel compounds' antibacterial activity In order to defend against the harmful effects of protozoal infections, the immune system is essential. An imidazole derivative with a nitro group is 5-nitroimidazole. [7,8] The class of nitroimidazole antibiotics, which have been used to treat anaerobic bacterial and parasite diseases, consists of a number of nitroimidazole derivatives. The solubility of pharmaceuticals is drastically altered by the addition of organic co-solvent [9]. The main treatment for Clostridium difficile infection, which is the main cause of pseudomembranous colitis, is metronidazole. It is given orally, three times each day, for seven to fourteen days (or even longer), at dosages of 250 to 500 mg[10,11]. Metronidazole can help control colonic (but not small bowel) Crohn's disease and is also used to treat Crohn's patients with perianal fistulas. The impact of the starch polymer concentrations on the solubility of metronidazole was examined using a two-way analysis of variance (ANOVA) in design without repeated values and a 6 3 contingency table. The water attraction and solubility of APIs have been found to be improved by reduced particle size, increased surface area, improved wettability of the surface area, and improved interparticulate spacing. [12]



Chemical (IUPAC) name: 2-(2-methyl-5-nitro-1H-imidazol-1-yl) ethanol

Metronidazole calibration curve preparation in 0.1 N HCl

Making a solution of 0.1N HCl

9.8 ml of concentrated HCl must be diluted with distilled water to a volume of 1000 ml in order to create 0.1N HCl.

Making a basic stock solution

Metronidazole was used to make the stock solution (100 g/ml), which was made by accurately dissolving 10 mg of the medication in a tiny amount of methanol. The volume was then made up to 100 ml using 0.1N HCl to create a standard stock solution. [13]

Calculation of max

With the use of 0.1N HCl, a calibration curve for metronidazole was created, and the max was discovered to be 274.6 nm.

calibration curve creation

A variety of dilutions of the metronidazole stock solution were created, ranging from 2 to 10 g/ml. At a wavelength of 274.6 nm, the absorbance of these solutions was measured, and a calibration curve was constructed using a UV-Visible spectrophotometer (Shimadzu UV-1800). The greatest absorption of metronidazole was observed at 274 and 277 nm, respectively. [14]

Drug content:

Ten tablets of each formulation were weighed and powdered. The quantities of powder equivalent to 50 mg of Metronidazole was transferred and in to a 100-ml of volumetric flask and extracted with 0.1 N HCl solution and kept aside for 2 hours than it was filtered suitable dilution were made and absorbance was measured by the using UV spectrophotometer at 276nm[11]. [15]

FTIR spectrum of Metronidazole

For the identification of pure drugs and a compatibility analysis of drug excipients, FTIR spectroscopy was used. The spectra of the pure drug in figure were obtained from an FTIR spectrophotometer in the 4000-500 cm-1 range. The spectra of the drug with excipients in figure no. 3 exhibited peaks that were close to or nearly identical to those of the pure drug, i.e. for C-H, C=C, and C=N stretching. This shows that there has been no alteration or interaction between the medicine and excipients. [16]

Formulation	**Hardness (kg/cm^3)**	**Friability (%)**	**Drug content (%)**
F1	5	0.197	92
F2	5	0.265	90
F3	5.8	0.294	85
F4	6	0.186	82
F5	5.8	0.301	87

Table 1. Formula for kneading metronidazole with different polymer and tabletting.

Variant Factor	**MTZ (mg)**	**X (mg)**	**Y (mg)**	**Starch paste**	**Starch (mg)**	**MCC (mg)**	**Mg/St (mg)**	**w/e (1:1) ml**	**CP (NM)**
Ax	200	50	0	10	160	20	1	5	45
Bx	200	100	0	10	110	20	1	5	45
Cx	200	200	0	10	10	20	1	5	45
Ay	200	0	50	10	160	20	1	5	45
By	200	0	100	10	110	20	1	5	45
Cy	200	0	200	10	10	20	1	5	45

Key:

MTZ = metronidazole.

w/e = water/ethanol.

x = corn starch.

y = *Manihot ultilissima* starch.

MCC = microcrystalline cellulose.

Mg/St = magnesium stearate.

Ax = 4:1 (MTZ: corn starch).

Bx = 2:1 (MTZ: corn starch).

Cx = 1:1 (MTZ: corn starch).

Ay = 4:1 (MTZ: *Manihot ultilissima* starch).

By = 2:1 (MTZ: *Manihot ultilissima* starch).

Cy = 1:1 (MTZ: *Manihot ultilissima* starch).

CP(NM) = compressed pressure in Newton Meter.

Utilising Manihot utilissima starch and a variety of processing methods, the formulation of metronidazole tablets is improved.

The standard calibration curve for metronidazole in 0.1 N HCl.

0.1N HCl was used to generate the metronidazole calibration curve. The regression coefficient R2 = 0.999 revealed that the graph's slope was 0.04 and its intercept was 0.04, respectively. [17]

Standard Calibration Curve

With an R2 value of 0.9991, the metronidazole standard calibration curve in 0.1 N HCl shown in Figure 1 demonstrated excellent linearity. The graph's regression equation was y = 0.0388x 0.0029. [18]

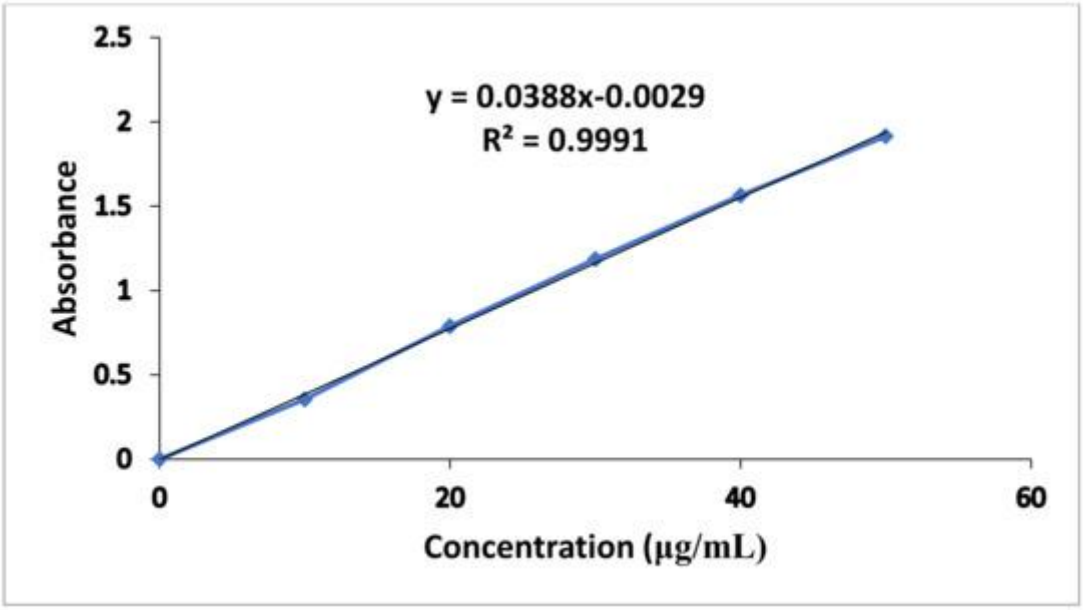


Figure 1 . Metronidazole Standard Calibration Curve in 0.1 N HCl.

Where "y" represents slope while "x" reflects unknown concentration of drug.

Solubility Studies

The above table shows experiments on the solubility of metronidazole in a variety of solvents, including water, 0.1 N HCl, and phosphate buffer (pH 4.5, 6.8, and 7.4) maintained at 25 ℃ and

37 °C. The table clearly shows that metronidazole had a higher solubility in water than in the other solvents, where it had a lower solubility profile. [19]

Imidazoles are two-nitrogen, five-membered rings with a complicated side chain connected to one of the nitrogen atoms. Chemically speaking, metronidazole (MET), an antiprotozoal, is 2-methyl-5-nitroimidazole-1-ethanol.1 Metronidazole has prodrug properties. Pyruvate-ferredoxin oxidoreductase, a redox enzyme, converts it in anaerobic organisms. By chemically reducing the nitro group of metronidazole, ferredoxin (or a ferredoxin-related metabolic activity) disrupts the DNA helical shape, which prevents the formation of nucleic acids.2 A thorough review of the literature reveals that a number of analytical techniques, including UV spectrophotometry, HPLC, amperometry, Supercritical Fluid Chromatography, HPTLC, chemiluminescence, voltammetry, polarography, and GC-FID, have been reported for the estimation of metronidazole in both single and combination form. 1[20]

Metronidazole has the chemical formula (2-Methyl-5-nitroimidazole-1-ethanol), the molecular weight 171.2 g/mole, and the molecular formula $C_6H_9N_3O_3$. Physically, it is a white to pale-yellow crystalline powder with a faint smell, bitter and salty taste, melting point of 158–160°C, and solubility in diluted acid but only to a limited extent in water. [21,22]

Quality control tests of selected product:

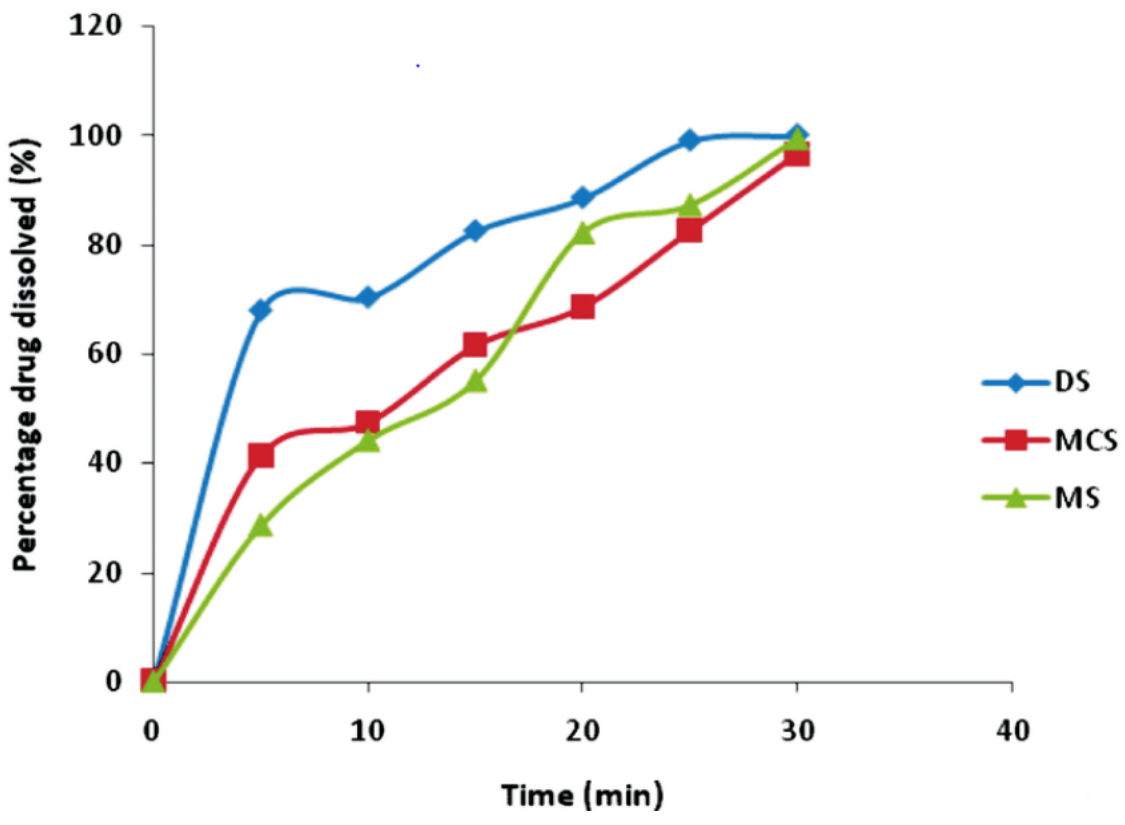
The results of official and unofficial quality control tests that were conducted on brand-name and four different generic products of metronidazole are shown in table , which summarises the results as an average value for tablet hardness, weight uniformity, percent of friability, the average time of disintegration test, as well as percent of Metronidazole content in each sample products. By calculating the percentage of medicine released at a given time using the equation for the Metronidazole calibration curve (each number represents mean SD, n = 6), Figure 3 illustrates the release profiles of various brands of Metronidazole tablets. [23,24]

Quality control tests that performed on brand and four different generic products of Metronidazole are presented in table no. which summarized the result as an average value for tablet hardness, weight uniformity, percent of friability, the average time of disintegration test in addition to percent of Metronidazole content in each sample products. Figure shows the release profiles of different brands of Metronidazole tablets by measuring the percent of drug released at a specific time by applying the equation of Metronidazole calibration curve (each value represent mean ± SD, n = 6).

Table 2: Results of official and unofficial quality control tests on generic and four brands of metronidazole tablets.

Sample code	Hardness (kg/cm^2) Mean ± SD (n=6)	Friability (%) Mean ± SD (n=10)	Weight Uniformity (mg) Mean ± SD (n=20)	Disintegration Time (min.) Mean ± SD (n=6)	Metronidazole Content (%) Mean ± SD (n=3)
MT-A	13.2 (±0.13)	0.012(±0.02)	687.6(±3.03)	13.4(±0.11)	101.6(±1.55)
MT-B	7.7(±0.5)	0.03(±0.04)	660.4(±19.80)	3.6(±0.465)	95.8(±4.5)
MT-C	9.8(±0.145)	0.025(±0.03)	782.9(±5.60)	14(±0.163)	96.2(±1.74)
MT-D	13.4(±0.16)	0.013(±0.02)	752.3(±14.04)	9(±0.230)	98.2(±2.41)
MT-E	13.7(±0.13)	0.015(±0.023)	967.6(±15.10)	12(±0.141)	99.6(±1.40)

Figure 2: Comparative dissolution profiles of the brand and the different generics of the available Metronidazole tablets in market; (± SD).



Evaluation of immediate release tablet Weight variation :-

Twenty tablets were chosen at random from each batch and weighed one by one. 20 pills' average weight and standard deviation were computed.

Friablity of Tablets:

Friability is related to tablets ability to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of friability test apparatus. Acceptable limit was not more than 1.0% of three samples[10]. Tablet friability was measured using friability tester (Roche friabilator) [25]

$$\% \text{ Friability} = \frac{\text{Intial weight} - \text{final weight} * 100}{\text{Intial weight}}$$

Hardness of Tablets:

hardness of tablet was measured by Monsanto hardness tester. Weight, drug content, hardness and thickness of tablet were representing as mean ± SD.

Thickness of Tablets:

Ten tablets were selected at random from individual formulations and thickness was measured by using Vernier-caliper scale, which permits accurate measurement.

discusses the development and assessment of metronidazole floating tablets that are osmotically regulated. To create in vitro buoyancy, polymers such carbopol, HPMC K4M, guar gum, sodium alginate, and the gas-generating compound sodium bicarbonate were added. Formulation F6 demonstrated a preferable drug release profile after anomalous non-Fickian diffusion for up to 12 hours. NaCl was discovered to boost drug release when it was added to release medium as opposed to media without NaCl. As a result, the finding of this study strongly suggests that the metronidazole floating extended release dosage form has a promising future as an alternative to the standard dosage form for the treatment of H. pylori-induced peptic ulcer disease.

The current study made use of a floating method for metronidazole that had the added benefit of swelling qualities to maintain an extended gastric stay. For the purpose of achieving the goals of the current study, a number of formulations with unique combinations of polymeric admixtures were developed and tested. To determine the drug contents in cumulative drug release, the standard calibration curves were used. A decreased solubility profile was shown by metronidazole at higher pH values, which is consistent with the drug's basic nature, as indicated

by its ionisation constant (pKa), which was 2.62. Additionally, it was discovered that as temperature climbed, the solubility of the drug generally increased as well. As a result, at a higher temperature (37 °C), metronidazole's solubility was also improved in all solvents.

The majority of pharmaceuticals have heats of solution with positive integer values, which might lead to a better solubility profile whenever the system's temperature is raised. This could be the outcome of a heat absorption phenomena. All of the estimated micromechanical property parameters, including the bulk and tapped densities, compressibility index, angle of repose, and Hausner's ratio, were found to be within acceptable bounds and suitable for the direct compression method to create the metronidazole-loaded floating drug delivery system. The bulk and tapped densities were computed in order to obtain the compressibility index and Hausner's ratio. With only minor differences that were statistically insignificant, the values for both types of densities across different formulation batches were essentially identical.

Conclusion:-

In addition to the brand of metronidazole tablet sold in market, the current study was conducted to assess the pharmacological qualities and in-vitro bioavailability of four other generic goods. Several official and unofficial quality-control tests were used to determine whether or not these four brand-name products are pharmaceutically equivalent to the generic counterpart. As they met all of the pharmacopoeial requirements for oral pills, the results showed that nearly all of the tested brands of metronidazole tablets were satisfactory. Brands MT-C and MT-E were shown to be more closely equivalent to the innovator product by displaying highly similar release behaviours, according to the dissolution investigations and derived similarity factor values. As a result, healthcare professionals might be advised to use the tested items.

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Contribution

All authors are equally contributed for the preparation of review Article.

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