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EVALUATION OF METRONIDAZOLE TABLETS FORMULATED WITH DIFFERENT DISINTEGRANTS USING MOISTURE ACTIVATED DRY GRANULATION (MADG)

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Abstract:

Introduction: *Metronidazole is a synthetic oral nitroimidazole antibiotic used in the treatment of infections caused by anaerobic bacteria and protozoa. It also has amebicidal and antiprotozoal properties.*

Aim*: The purpose of the study was to formulate and evaluate metronidazole tablets formulated with polymers (PVP and PEG) and maize starch as disintegrant using moisture activated dry granulation (MADG).*

Method*: Twenty-four (24) batches of metronidazole granules and tablets were prepared by moisture activated dry granulation. Metronidazole (200 mg), lactose and gelatin (1,2,4 and 8 %) were mixed, followed by continuous mixing. Prior to compression, micro-crystalline cellulose, disintegrants and magnesium stearate were added. The dried granules were passed via 1.0 mm sieve after which they were labelled and stored in an air tight container. All other batches were also similarly prepared.*

Result*: The result showed that the mean weight of the tablets ranged from 0.33 ± 0.01 to 0.35 ± 0.04 g. Tablet hardness ranged from 5.00 ± 0.85 to 6.36 ± 1.43. The results showed that batch 11 tablets had higher crushing strength than batch 24 with a significant difference. Table 2 shows the hardness test results and clearly indicates that the results of all the samples significantly differ from each other ($p < 0.05$). The tablet friability test ranged from 0.21 ± 0.17 for batch 24 and 0.60 ± 0.16 for batch 11. The formulated tablets showed average disintegration time ranges from 0.52 ± 0.01 to 14.03 ± 0.03. According to USP, the disintegration time must be in the range of 15 min for uncoated tablets, and 30 mins for film coated tablets*

Conclusion: The study established that polyethylene glycol and polyvinyl pyrrolidone polymers had better dissolution profile than maize starch which has the best disintegration properties.

Keywords*: Metronidazole, Moisture activated dry granulation, Disintegrants, Polymers.*

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INTRODUCTION:

Metronidazole is a synthetic oral nitroimidazole antibiotic used in the treatment of infections caused by anaerobic bacteria and protozoa [1]. It also has amebicidal and antiprotozoal properties. It is more soluble in alcohol and water. Its mechanism of action is based on the prevention of nucleic acid synthesis by destroying microbial cell DNA [2]. Metronidazole exists in different forms such as white-to-white, circular, biconvex and film coated tablets. The drug has a molecular formular of $C_6H_9N_3O_3$, a molecular weight of 171.15 g/mol, a melting point of 159-163 ^oC and a biological half-life of 8 h.

Oral delivery of the drug is the most preferred route of drug administration due to the ease of administration, patient compliance and flexibility in the formulations [3, 4]. Two major factors determine the clinical effectiveness of tablet formulations. They are the ability of the drug to be present in the labelled amount and its availability to the body [5]. An oral tablet is meant to deliver the drug to the human body via the gastro-intestinal system in order to produce a therapeutic effect [6-8]. It had been reported that in many situations, the bioavailability of drugs from different manufacturers did not give the same therapeutic response [9]. Medicines with poor quality do not meet official standards for strength, quality, purity, packaging and labeling. Serious health implications is usually associated with counterfeit and substandard drugs [10].

Metronidazole is administered via different routes like rectal, topical, intravenous, oral and vaginal with different bioavailability percentages ranging from 80 % (oral), 60-80 % (rectal), and 20-25 % (vaginal) [11]. Adverse drug reactions associated with metronidazole include nausea, diarrhea, weight loss, abdominal pain, vomiting, headache, dizziness and metallic taste in the mouth [11].

Moisture activated dry granulation (MADG) is a process where granules are created with water and a granulating binder, but are not heat dried or milled. There are two stages associated with the MADG. The agglomeration and moisture distribution [12]. MADG was developed in response to the difficulties experienced with wet granulation in terms of endpoint, drying and milling. Wet granulation endpoint is very sensitive to granulation time and shear. The wet granules need to be dried to a narrow range of moisture contents, which is difficult. The dried granules need to be milled, but the milled granules often have either too many fines or too many coarse particles.

During agglomeration, a major portion of the formulation containing the drug is agglomerated. The drug is blended with filler and binder in the powder form, which constitutes approximately 50-80 % of the formula weight. In moisture distribution stage, a small amount of water is sprayed as small droplets onto the blend. Water moistens the blend and causes the binder to become tacky, which causes particles, to form moist agglomerates. This process does not create large granules, which would need milling, and because very little water is used in the process, the endpoint is not sensitive to blending [13].

MATERIALS AND METHODS:

2.0 Materials

Metronidazole was obtained from Evans Pharmaceutical Company, England. Gelatin was obtained from May and Baker, Lagos. Magnesium stearate and lactose was procured from Ludwigshafen, Germany. All other reagents and solvents used were analytical grade.

Methods

2.1 **Preparation of metronidazole granules and tablets using moisture activated dry granulation.**

Twenty-four (24) batches of metronidazole granules and tablets were prepared by moisture activated dry granulation according to the formula in Table 1 [14]. Metronidazole (200 mg), lactose and gelatin (1, 2, 4 and 8 %) were mixed, followed by continuous mixing. Prior to compression, micro-crystalline cellulose, disintegrants and magnesium stearate were added. The dried granules were passed via 1.0 mm sieve after which they were labelled and stored in an air tight container. All other batches were also similarly prepared.

Table 1: Formula used in the preparation of 24 batches of metronidazole

Ingredients	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Metronidazole	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Lactose (g)	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Gelatin (g)	0.35	0.0035	0.00035	0.00035	0.00035	0.00035	0.0070	0.0070	0.0070	0.070	0.070	0.070	0.014	0.014	0.014	0.014	0.014	0.014	0.028	0.028	0.028	0.028	0.028	0.028
PVP (g)	0.35	0.007	-	-	-	-	0.035	0.070	-	-	-	-	0.035	0.070	-	-	-	-	0.035	0.070	-	-	-	-
PEG (g)	-	-	0.035	0.070	-	-	-	-	0.035	0.070	-	-	-	-	0.035	0.070	-	-	-	-	0.035	0.070	-	-
Maize starch	-	-	-	-	0.0108	0.035	-	-	-	-	0.018	0.035	-	-	-	-	0.0108	0.035	-	-	-	-	0.0108	0.035
Magnesium stearate	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Microcrystalline cellulose	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01

2.2 Evaluation of granule properties.

2.2.1. Determination of angle of repose

A plastic funnel in ring-supported by a retort stand. A sheet of paper was placed below the funnel assembly. A sheet of fibre board was placed below the funnel orifice making sure it fits tightly. 30.0 g quantity of the powder was transferred into the funnel. The fibre sheet was drawn away and the timer simultaneously started. The timer was stopped when all of the powder had passed through the funnel. The height of the heap was measured using a graduated ruler. A pencil was used to outline the base of the contour. The angle of the conical heap so formed was determined from equation 8. The powder was returned to the funnel and the experiment was repeated thrice [15]:

$$\text{Tan } \Theta = \frac{\text{height of powder heap, (h)}}{\text{radius of powder heap, (r)}} \quad - \quad - \quad - \quad - \quad - \quad - \quad -1$$

2.2.2. Bulk density

A weighed quantity of powder (20.0 g) was placed in a 100-ml graduated cylinder. The cylinder was gently dropped onto a wooden surface three times from a height of one inch at 2 sec interval. The volume

assumed after the treatment was taken as the bulk volume. The experiment was repeated thrice [16]:

Bulk density (g/ml) = $\frac{mass}{bulk\ volume}$ - - - - - - - - -2

2.2.3 Tapped density

A weighed quantity (20.0 g) of the powder was placed in a 100-ml graduated cylinder. The cylinder was tapped up to 500 times on the wooden surface or to a constant volume. The final volume attained represents the tapped volume. The experiment was repeated thrice [16]:

Tapped density (g/ml) = $\frac{mass}{tapped\ volume}$ - - - - - -3

2.2.4 Hausners quotient

The Hausner ratio (HR), defined as the ratio of tapped to bulk densities. It is a common technique widely used to describe the packing behavior of powders when they are subjected to tapping [103]:

Hausner ratio = $\frac{\text{tapped density}}{\text{bulk density}}$ - - - - - - - -4

2.2.5 Determination of percentage fines.

The granules were shaken through a 0.1 mm sieve and the fine particles were obtained. The weight of the fines were measured and expressed as the percentage of total weight of granules.

Percentage weight = $\frac{\text{weight of fines}}{\text{Total weight of granules}}\ x\ 100$ - - - - - 5

2.3 **Tablet compression**

The dried and screened granules were separated into fine and coarse particles. The fines were then lubricated with 1 % w/w concentrations of magnesium stearate and mixed with the coarse particles. The granules were compressed into tablets using F-3 Manesty single punch tableting machine fitted with 9.5 mm flat faced tooling. Compression pressure was maintained at 47 to 55 N [16].

2.4 Evaluation of tablets

2.4.1 Hardness test

Ten (10) tablets were randomly selected from each batch. Using the Monsanto tester, the pointer was fixed at 0 Kgf. One tablet was held and placed with the tester holder and the screw adjusted until the pressure applied cracked the tablet. The hardness of each tablet was determined and recorded [17].

2.4.2 Uniformity of weight

Twenty (20) tablets were randomly selected from each batch. Using the analytical balance (120-5DM, S.Mettler, Germany), the 20 tablets were weighed together. The mean tablet weight was then calculated. Subsequently the tablets were weighed individually and the weights of the tablets recorded. The variations of individual tablet weights from the mean weight were determined, and the percentage deviations calculated [17]:

Percentage deviation = $\frac{\text{Deviation}}{\text{Mean weight}}$ x 100 - - - - - - 6

2.4.3 Tablet friability

Ten (10) tablets were selected at random from each batch. Subsequently, they were dedusted and accurately weighed together in an analytical balance. The dedusted tablets were then placed into the friabilator which was set to rotate at 25 rpm for 4 min. Then the tablets were removed, dedusted and re-weighed. The mean loss in weight and percent friability was then calculated. The friability test was repeated 3 times. The mean and standard deviation were then calculated [ ]:

Friability test = $\frac{\text{initial weight} - \text{final weight}}{\text{initial weight}}$ x 100 - - - 7

2.4.4 **Disintegration test**

Six (6) tablets were selected at random from each batch using the Erweka disintegrating unit and distilled water as the disintegrating medium maintained at 37 ± 1.0 °C. One tablet was placed into each tube of the disintegrating unit. The time taken for each tablet to completely break down to particles and pass through the wire mesh was recorded. The mean disintegration time and standard deviation from each batch was calculated [17].

2.4.5. **Dissolution studies**

The *in-vitro* drug release studies were carried out using tablet dissolution test apparatus (Erweka DT-D, Heusens-tamm, Germany) [18]. Initially, 900 ml of 0.1 N HCl at (pH 1.2) was used as the dissolution medium for 2 h at 50 rpm, maintained at 37 ± 1.0 °C. Samples were withdrawn at 5, 10, 20, 40, 60, 80, 100 and 120 min intervals and replaced with fresh equal volumes of the dissolution media maintained at the same temperature. From the Beer's calibration curve, the concentration of each drug released over time was calculated. The percentage amount of metronidazole released for each batch was plotted against time [18].

Data analysis

All the measurements were repeated at least thrice and the data obtained analyzed by Student *t*-test and One-Way Analysis of Variance (ANOVA). Statistical analysis was performed using Statistical Product and Services Solution software (SPSS, version 22.0 Inc., Chicago IL, USA) and Excel Microsoft Office version 2012. The results were presented as mean ± SD, and

statistical differences between means considered significant at ($p < 0.05$).

RESULTS AND DISCUSSION:

The angle of repose is also indicative of flow rate [19]. It is important to note that in tableting, an angle of repose of 25, shows excellent flow, 25-30 shows good flow, 30-40 shows passable, while > 40 shows poor flow. All the batches could be said to possess good flow since the angle of repose was within the ranges of 24 ± 25.0 to 35 ± 32.3 (Table 2). Hausner's ratio and Carr's index are both indirect means of assessing the flow properties of granules. The Hausner's ratio were within the ranges of 1.06 ± 0.02 and 1.26 ± 0.02, while the Carr's index were within the ranges of 6.55 ± 0.13 and 24.00 ± 1.00 [20]. Tapped density is a function of particle size and size distribution. The tapped density of the metronidazole granule ranged from 0.45 ± 0.01 to 0.82 ± 0.02. The size of the particles affects it, as decrease particle size leads to increase tapped density and vice versa [20].

Table 2: Micromeritic and flow properties of metronidazole granules.

Batches	Tapped density (g/cm^3) mean ± SD	Angle of repose (^{o}) mean ± SD	Flow rate (g/s) mean ± SD	Hausners Ratio mean ± SD	Carrs index (%) mean ± SD	Percentage fines. Mean ± SD
1	0.82 ± 0.02	29 ± 27.3	9.33 ± 0.15	1.16 ± 0.01	16.66 ± 1.52	20.23 ± 0.01
2	0.56 ± 0.02	24 ± 25.0	6.90 ± 0.10	1.26 ± 0.02	13.83 ± 0.15	20.50 ± 0.13
3	0.62 ± 0.02	32 ± 30.3	6.21 ± 0.01	1.21 ± 0.02	10.94 ± 0.04	20.74 ± 0.01
4	0.65 ± 0.02	28 ± 28.3	8.13 ± 0.01	1.15 ± 0.02	10.74 ± 0.04	20.17 ± 0.01
5	0.68 ± 0.01	30 ± 30.6	9.76 ± 0.01	1.15 ± 0.01	8.76 ± 0.11	21.07 ± 0.01
6	0.67 ± 0.01	34 ± 31.7	7.25 ± 0.01	1.12 ± 0.01	7.62 ± 0.24	20.24 ± 0.02
7	0.55 ± 0.01	27 ± 26.0	10.06 ± 0.01	1.07 ± 0.01	10.80 ± 0.10	21.44 ± 0.02
8	0.55 ±0.04	30 ± 28.3	8.36 ± 0.01	1.12 ± 0.01	15.74 ± 0.04	22.48 ± 0.04
9	0.62 ± 0.02	30 ± 29.0	7.15 ± 0.01	1.16 ± 0.02	15.62 ± 0.01	24.22 ± 0.04
10	0.64 ± 0.01	31 ± 29.3	6.57 ± 0.21	1.18 ± 0.01	13.83 ± 0.02	23.52 ± 0.03
11	0.61 ± 0.01	31 ± 29.6	8.06 ± 0.02	1.15 ± 0.01	7.92 ± 0.02	22.46 ± 0.23
12	0.62 ± 0.02	33 ± 31.3	7.15 ± 0.01	1.07 ± 0.01	6.55 ± 0.13	24.29 ± 0.03
13	0.53 ± 0.02	27 ± 27.0	7.65 ± 0.03	1.06 ± 0.02	21.55 ± 0.05	23.23 ± 0.01
14	0.52 ± 0.02	27 ± 26.7	10.35 ± 0.03	1.26 ± 0.02	24.00 ± 1.00	21.45 ± 0.02
15	0.57 ± 0.02	32 ± 29.3	8.04 ± 0.01	1.31 ± 0.01	23.64 ± 0.13	20.11 ± 0.02
16	0.56 ± 0.01	30 ± 27.7	7.10 ± 0.01	1.30 ± 0.01	17.53 ± 0.03	20.82 ± 0.02
17	0.48 ± 0.01	33 ± 30.0	6.24 ± 0.02	1.20 ± 0.01	14.30 ± 0.01	25.02 ± 0.04
18	0.52 ± 0.02	27 ± 27.0	9.62 ± 0.03	1.16 ± 0.01	12.66 ± 0.57	24.76 ± 0.58
19	0.46 ± 0.01	32 ± 28.7	8.21 ± 0.01	1.26 ± 0.01	19.48 ± 0.01	21.03 ± 0.05
20	0.45 ± 0.01	30 ± 28.0	8.36 ± 0.01	1.24 ± 0.01	21.66 ± 2.08	21.68 ± 0.04
21	0.48 ± 0.01	29 ± 28.7	9.12 ± 0.02	1.25 ± 0.01	14.31 ± 0.03	22.12 ± 0.09
22	0.47 ± 0.01	35 ± 32.3	10.11 ± 0.01	1.25 ± 0.01	14.54 ± 0.04	23.07 ± 0.77
23	0.52 ± 0.02	34 ± 32.3	9.22 ± 0.03	1.18 ± 0.01	21.47 ± 0.08	23.12 ± 0.81
24	0.53 ± 0.01	30 ± 30.7	7.05 ± 0.01	1.17 ± 0.01	18.84 ± 0.03	24.25 ± 0.36

Table 3: Physiochemical properties of metronidazole tablets.

Batches	Weight uniformity mean ± SD	Friability mean ± SD	Hardness mean ± SD	Disintegration mean ± SD
1	0.33 ± 0.01	0.90 ± 0.17	5.30 ± 0.85	1.39 ± 0.08
2	0.34 ± 0.01	0.60 ± 0.21	5.85 ± 1.35	0.63 ± 0.04
3	0.34 ± 0.01	0.69 ± 0.17	5.00 ± 0.85	0.62 ± 0.53
4	0.34 ± 0.01	0.69 ± 0.28	5.40 ± 1.59	0.57 ± 0.08
5	0.33 ± 0.01	0.73 ± 0.22	5.20 ± 1.01	0.52 ± 0.06
6	0.34 ± 0.01	0.60 ± 0.09	5.75 ± 1.23	0.47 ±0.01
7	0.33 ± 0.01	0.57 ± 0.09	5.60 ± 0.57	5.23 ± 0.01
8	0.33 ± 0.01	0.45 ± 0.13	5.70 ± 1.34	2.27 ± 0.01
9	0.32 ± 0.01	0.52 ± 0.29	5.70 ± 1.34	1.32 ± 0.01
10	0.34 ± 0.01	0.53 ± 0.29	6.35 ± 1.16	1.07 ± 0.02
11	0.34 ± 0.01	0.60 ± 0.16	6.36 ± 1.43	1.13 ± 0.01
12	0.34 ± 0.01	0.42 ± 0.21	6.00 ±1.16	1.08 ± 0.01
13	0.35 ± 0.02	0.39 ± 0.16	5.60 ± 1.17	8.21 ± 0.02
14	0.34 ± 0.01	0.36 ± 0.16	5.70 ± 1.27	7.55 ± 0.04
15	0.34 ± 0.01	0.34 ± 0.15	5.30 ± 1.01	14.07 ± 0.04
16	0.34 ± 0.01	0.50 ± 0.25	5.55 ± 1.19	0.54 ± 0.02
17	0.34 ± 0.01	0.44 ± 0.20	5.80 ± 1.23	0.67 ± 0.01
18	0.34 ± 0.01	0.19 ± 0.11	5.50 ± 1.52	14.03 ± 0.03
19	0.34 ± 0.02	0.22 ± 0.18	6.05 ± 0.89	2.53 ± 0.04
20	0.34 ± 0.02	0.29 ± 0.15	6.04 ± 0.89	1.14 ± 0.03
21	0.33 ± 0.02	0.26 ± 0.15	5.50 ± 1.52	2.20 ± 0.01
22	0.34 ± 0.02	0.26 ± 0.17	5.50 ± 1.53	2.20 ± 0.01
23	0.34 ± 0.02	0.21 ± 0.17	6.03 ± 0.89	1.14 ± 0.03
24	0.34 ± 0.02	0.21 ± 0.17	5.40 ± 1.53	1.14 ± 0.03

Table 3 shows the results of the weight uniformity test carried out on the metronidazole tablets. The result showed that the mean weight of the tablets ranged from 0.33 ± 0.01 to 0.35 ± 0.04 g. The weight uniformity test was performed on the tablets to determine its compliance with USP specifications. All the tablets passed the weight uniformity test as the percentage of weight deviation was within the USP limits of ± 5 % of average weight. The BP stipulates that tablets with an average weight of 250 mg or more should have percentage deviation not greater than 5 % [21]. According to Mizanur *et al*, the metronidazole tablets meat the USP specification [22].

The hardness was carried out using the Mosanto hardness tester. The result of the hardness test of metronidazole tablets are shown in Table 3. Tablet hardness ranged from 5.00 ± 0.85 to 6.36 ± 1.43. The results showed that batch 11 tablets had higher crushing strength than batch 24 with a significant difference. Table 3 shows the hardness test results and clearly indicates that the results of all the samples significantly differ from each other ($p < 0.05$). Tablet hardness is an important parameter in drug availability because it affects the dissolution rates of drugs and friability. The tablet formulations were within the ranges of 4 to 8 Kgf [23].

Friability test is used to determine the resistance of tablets to abrasion [23]. It is an important parameter in tablet handling, packaging and transportation. It is used to determine the physical strength of compressed and uncoated tablets upon exposure to mechanical shock and attrition. According to Rahman *et al*, all the brands met the friability specification [24]. The results of the friability test are shown in Table 3. The tablet friability test ranged from 0.21 ± 0.17 for batch 24 and 0.60 ± 0.16 for batch 11.

Disintegration test was carried out under USP specifications [23]. The formulated tablets showed

average disintegration time ranges from 0.52 ± 0.01 to 14.03 ± 0.03. According to USP, the disintegration time must be in the range of 15 min for uncoated tablets, and 30 mins for film coated tablets [23]. According to Rahman *et al*, all the brands met the requirement as the disintegration time was found to be between the ranges of 7.25 ± 0.69 to 17.0 ± 0.63 mins [24]. All the tablets passed the disintegration test.

Dissolution of a drug tablet is an important step which leads to the absorption of the drug in the body. The disintegration process breaks the intact tablets into smaller particles thus increasing the surface area thereby increasing absorption. According to BP specification, at 45 min, not less than 70 % of the prescribed or stated amount of the active ingredient should have been released at the completion of dissolution test. The dissolution profile, shows that none of the formulations released all its drug content within the 120 min test period. For film coated metronidazole tablets, drug release should not be less than 85 % of labelled amount in 60 min [23]. According to Rahman *et al*, their brand Metro-04 had maximum drug release within the 60 min (98.87 %), while brand Metro-02 had minimum drug release (85.34 %) within the same time interval [24].

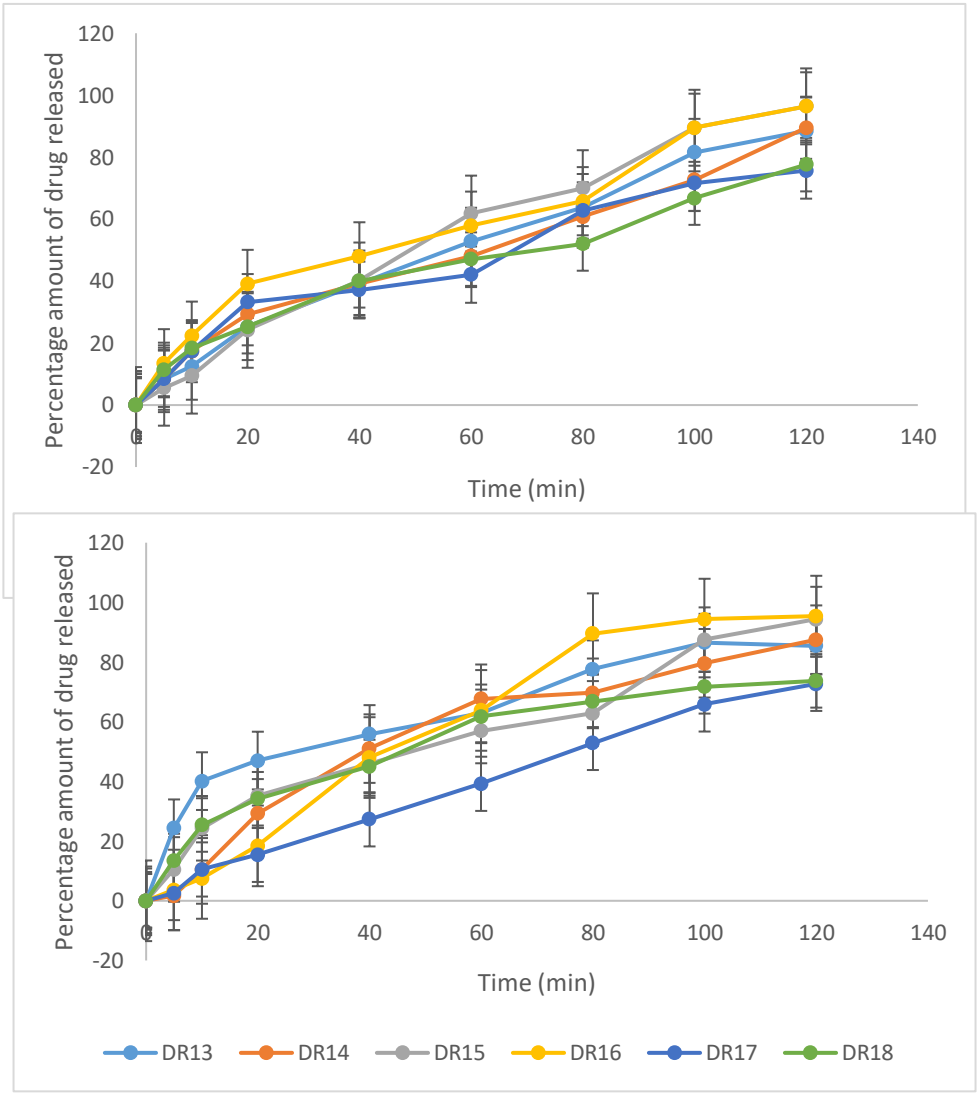

Fig 2: Percentage drug release of tablet containing 4 % binder concentration.

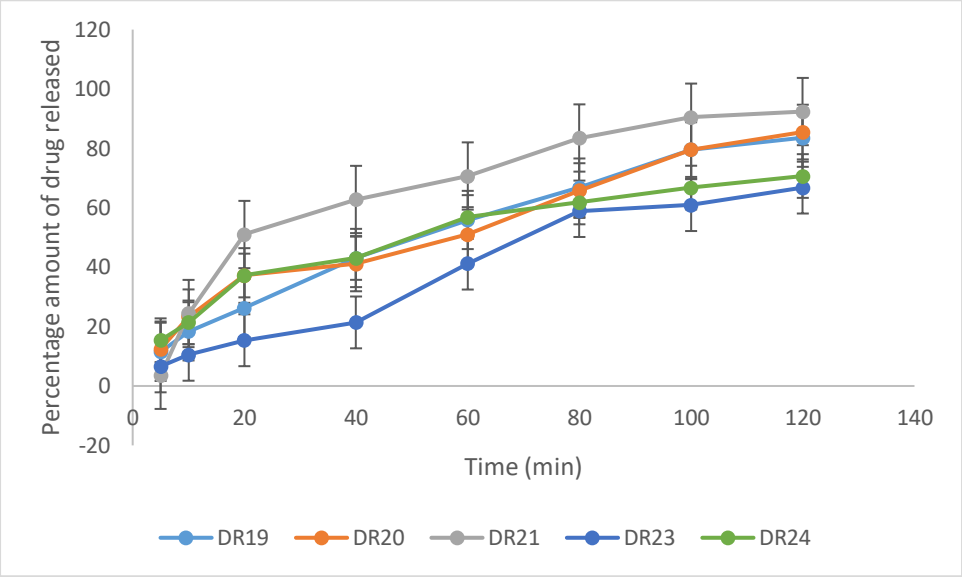

Figure 3: Percentage drug release of tablet batches containing 8 % binder concentration.

CONCLUSION:

Metronidazole was successfully formulated using the moisture activated dry granulation method. The tablet had good granules and tablet properties. The hardness, friability and disintegration time were within the stipulated limits in the compendia.

Conflict of interest.

Authors declared no conflict of interest.

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