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Effects of Beverage Solvents on Disintegration Time and Dissolution Rate of Metronidazole Tablets

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ABSTRACT: Drug Disintegration time refers to the period within which a mechanical break-up of compressed tablet dissolve upon exposure to physiological fluids within a short period of time into tiny granules upon ingestion, while drug dissolution rate becomes a key tool in understanding the importance for its bioavailability and therapeutic effectiveness. Hence, the objective of this paper was to assess the impact of seven different solvents, which includes five non-alcoholic beverages (Exotic juice, soft drink, coffee, milk, and milo), one alcoholic beverage (beer), one dilute acid (0.1 M HCl) and a control distilled water (dil. H_2O) on the disintegration time and dissolution rate of metronidazole tablets. The distilled water was used as control. The results obtained show that the mean disintegration times were 2.28 ± 0.04 (0.1 N HCl), 4.21 ± 0.12 (beer), 3.24 ± 0.05 (coffee), 3.23 ± 0.07 (distilled water), 5.21 ± 0.09 (Exotic juice), 3.17 ± 0.06 (Fanta), and 16.16 ± 0.11 (milk). The mean dissolution rates on the other hand were 98.87 ± 0.12, 78.09 ± 0.09, 84.27 ± 0.11, 86.52 ± 0.40, 67.98 ± 0.09, 92.70 ± 0.50, and 44.94 ± 0.22 respectively. Metronidazole tablets disintegrated and dissolved more in 0.1 N HCL than in other mediums and less in milk. From this study, although the disintegration time and dissolution rate of metronidazole were not greatly affected by the different beverages except for Exotic juice, and the mixture of milk and Milo, care should be taken when replacing water with any beverage in ingesting tablets.

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The importance of oral dosage forms cannot be over-emphasized. The oral route is the most common route of drug administration. In adults, the oral route is the predominant route of administering solid dosage forms (Hummer *et al*., 2023). Oral solid dosage forms (OSDFs) which include capsules and tablets, are the most widely used. OSDFs are not without some shortcomings; however, the advantages outweigh their shortcomings. These advantages include self-administration, dose accuracy, compactness, ease of manufacture, and long shelf life (Avbunudiogba *et al*., 2013; Almukainzi *et al.*, 2018; Almukainzi *et al.*, 2021). The disintegration rate, dissolution rate, and invariably the bioavailability of OSDF depend on many factors, one of which is the physiological state of the gastrointestinal tract (GIT). The ease of

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disintegration and dissolution of OSDF into the gastric environment is an important factor in drug bioavailability (Almukainzi *et al.,* 2021). For a drug to be absorbed from the GIT, it must first of all be in solution. The rate of drug dissolution/release can under certain conditions be the rate-controlling step in the appearance of a drug in the systemic circulation. Thus, physiological factors that influence the dissolution and release from dosage form are also considered wherever applicable. It will be assumed that the drug is in solution in appropriate gastrointestinal (GI) fluids for a proper understanding of how various physiological factors can influence drug absorption. One important property of the GI fluids is pH, which varies along the length of the tract (Venkateswarlu 2010; Avbunudiogba *et al*., 20). There is considerable inter-subject variation in gastrointestinal pH depending on factors such as the general health of the individual, and the presence of localized disease conditions (e.g. gastric and duodenal ulcers) along the GIT. Other factors are types and amount of food ingested, drug therapy, etc. In the case of drug therapy, anticholinergic drugs inhibit or reduce gastric secretion and oral administration of antacids usually elevates gastric pH for a short period of time. The gastric fluids are highly acidic, usually ranging from pH 1 to pH 3.5. It is more acidic at night and fluctuates during the day, primarily in response to food ingestion. Food ingestion generally increases pH and then slowly decreases over the next several hours (Venkateswarlu, 2010). When moving from the stomach to the small intestine, there is an abrupt change in pH. Pancreatic secretions contain a high concentration of bicarbonate which neutralizes gastric fluid entering the duodenum and thus regulates the pH of fluids in the upper intestinal region. This neutralization of gastric fluids in the duodenum is important to prevent the inactivation of pancreatic enzymes, damage to the intestinal epithelium, and prevent precipitation of bile acid, which is poorly soluble in acid pH. The pH of intestinal fluids increases from 5.7 in the pylorus to 7.7 in the proximal jejunum. In the large intestine, the pH is 8 (Ibezim, 2005; Venkateswarlu, 2010; Nagaich *et al.,* 2010). The rate of dissolution of a drug from a dosage form depends on the solubility of the drug in GI fluids. GI fluid pH decides the solubility of the drug since most of the drugs are either weak acids or bases. Weak acidic drugs dissolve most readily in alkaline media and therefore will have a greater rate of dissolution in the intestinal fluids compared to gastric fluids. Basic drugs will dissolve most readily in acidic solutions and thus the dissolution rate will be greater in gastric fluids compared to the intestinal fluids (Venkateswarlu, 2010; Abuhelwa *et al.,* 2017). Numerous factors such as the general health of the individual, the presence of localized disease conditions along the GIT, types and amount of food ingested, and drug therapy, affect the pH of the GI fluids and invariably drug disintegration, dissolution, absorption and bioavailability (Venkateswarlu, 2010; Abuhelwa *et al.,* 2017). Of these numerous factors, the type and amount of food ingested play a major role in altering the pH of the GI fluids. There is hardly a day that humans and animals fail to ingest one form of food or the other. Ingested food could increase, decrease, or normalize the pH of the GI fluids (Kohl *et al., 2014;* Abuhelwa *et al.,* 2017). Tablets/capsules ought to be administered with a full glass of water; however, it has been observed that many patients do not follow this recommendation. Many patients take their medications with liquid beverages other than water (Almukainzi *et al.,* 2021). Thus, the aim of the present study is to assess the effect of commonly consumed beverages on the disintegration and dissolution of metronidazole tablets. Metronidazole is classified as a nitro imidazole anti-infective agent that has specific activity against a number of obligate anaerobic organisms and protozoa. Metronidazole occurs as a pale-yellow, crystalline powder. It has a bitter slightly saline taste with a little odour. It is slightly soluble in water and alcohol, freely soluble in dichloromethane, and soluble in acetone (Nawab *et al*., 2016; Avbunudiogba and Oghenekevwe, 2021). In 1959 the drug metronidazole was first used to treat an infection caused by *Trichomonas vaginalis*; later, other new therapeutic properties were discovered. Today, Metronidazole is used to treat many infections caused by *Clostridia*, *Rosacea*, *Bacteroides*, *Fusobacteria* and oral and dental infections, joint and bone infections, endocarditis, gynaecologic infections, septicaemia, respiratory tract infections (Ceruelos *et al*., 2019; Avbunudiogba and Oghenekevwe, 2021). Metronidazole as a drug is commonly referred to as "an old warhorse" and ranks among the essential medicines as defined by the World Health Organisation, WHO (Leitsch, 2017; Avbunudiogba and Oghenekevwe, 2021). Unlike most other antimicrobial agents, it has a pleiotropic mode of action and reacts with a large number of molecules. It needs to be reduced at its nitro-group at low oxygen concentration in order to become toxic, explaining why it is exclusively harmful to anaerobic and microaerophilic microbes. Generally, resistance of pathogens to metronidazole is low up to this day (Leitsch, 2017). Hence, the objective of this paper was to assess the impact of seven different solvents, which includes five non-alcoholic beverages (Exotic juice, soft drink, coffee, milk, milo), one alcoholic beverage (beer), one dilute acid (0.1 M HCl) and a control distilled water (dil. H_2O) on the disintegration time and dissolution rate of metronidazole tablets.

MATERIALS AND METHODS

Materials: Commercial metronidazole tablets (obtained from a pharmacy in Abraka town, Delta State, Nigeria), pure metronidazole powder (Dongxiang Zhejiang, China), distilled water prepared in Industrial Pharmacy Laboratory, Faculty of Pharmacy, Delta State University, Abraka, Nigeria; hydrochloric acid (BDH Chemical, Poole England), Fanta drink (Nigeria Bottling Company Limited, Lagos Nigeria), bullet energy drink (Sun mark Limited), Chi exotic pineapple and coconut nectar (Chi limited, Lagos Nigeria), Peak skimmed milk (Friesland Campinas WAMCO, Nigeria), Nestle milo (Nestle, Nigeria PLC), Nescafe classic pure instant coffee (Good Foods), Goldberg premium lager beer (Nigeria Breweries, PLC)

Methods: Physical evaluation of the commercial tablets was carried out to ascertain if they met the official standards.

Weight variability test: Twenty randomly selected tablets were weighed using an analytical balance (Shimasu analytical balance, Model: ATY224, Philippines); the average weight of the tablets was determined according to the method described by Nagashree 2015; Avbunudiogba and Aumade, 2022.

Tablet thickness and diameter: The thickness and diameter were determined using multiple digital device (Veego Instrument Corporation Model VDIGITABOI, Mumbai, India). A Sample of tablets (10) was selected at random, weighed, and the mean values recorded.

Hardness test: This test was carried out using a multiple digital tablet hardness test apparatus (Veego Instrument Corporation Model VDIGITABOI, Mumbai, India). A sample (10) of tablets was randomly selected. Each tablet was placed inside the apparatus and the force was applied until the integrity of the tablet failed. Oral tablets normally have a hardness of 4-10 kgF; Hypodermic and chewable tablets are much softer (3 kgF) and sustained-release tablets are much harder (10-20 kgF) (Nelson, 2006).

Tablet friability test: Ten (10) tablets randomly selected were used for this test. The tablets were dedusted and weighed. The weighed tablets were placed in the drum of the friabilator (Erweka tablet friability test apparatus, model TA3, Germany) and rotated at 25 rpm for 4 min. The tablets were then removed from the friability machine, dedusted, and reweighed. The friability result was calculated from the formula:

$$Friability\ \% = \frac{W_0 - W}{W_0} * 100 \ldots. \ (Eqn\ 1)$$

Where W_0 is the initial weight of the selected tablets, W is the final weight of the tablets

Disintegration test: The time it took for each of the six tablets to break up was determined in a BP disintegration tester (Manesty tablet disintegration apparatus, model TD29T176, England) using the British Pharmacopoeia (2002) method for the determination of disintegration time for uncoated tablets. The disintegration medium was 900 mL of 0.1 N HCl maintained at 37 ± 2°C. The mean disintegration time was calculated. The time at which no particle remained in the tube (except tablet coating), was recorded as the disintegration time for each tablet.

The above procedure was repeated using the different beverages in their original purchased forms (without dilution) and distilled water as the disintegration media in place of 0.1 N HCl. Temperature was maintained at 37 ± 2°C.

Preparation of calibration curve of metronidazole: A sample of Metronidazole powder (100 mg) was weighed and transferred into a 100 mL volumetric flask. A sample of 0.1 N HCl (10 mL) was added to it and shaken for a few min. Further, the volume was made up to 100 mL using 0.1 N HCl (stock solution). This stock solution was then filtered and different concentrations (125, 62.5, 31.25, 15.625, 7.8125, and 3.906 µg/ml) were prepared from it. The absorbance of prepared solutions was measured using a UV-Visible spectrophotometer at a wavelength of maximum absorption (330 nm).

Dissolution test: In vitro dissolution was performed by using the British Pharmacopoeia dissolution test type I apparatus (Copley Scientific). The dissolution study was done according to the method described by Nawab *et al*., 2016. One (1) tablet of Metronidazole 400 mg formulation was placed in the basket with 900 mL of 0.1 N HCl as the dissolution medium, and the apparatus was assembled.

The temperature was maintained at 37 ± 0.5°C and rotation speed of 100 rpm. The operation was carried out for 45 min and then the sample solution was withdrawn and filtered. The filtered samples were analysed using a UV Spectrophotometer at a wavelength of 330 nm.

The above procedure was then repeated using 600 mL of 0.1 N HCl and 300 mL of vehicle (beverage) as the dissolution medium.

RESULTS AND DISCUSSION

The details of the selected metronidazole tablets (Emgyl®) are presented in Table 1. The brand complied with NAFDAC (National Agency for Food and Drug Administration and Control) requirements and guidelines. The product complied with the inclusion of the NAFDAC registration number, manufacture date, expiring date, batch number, and country of origin.

Post-compression parameter: The results of the physicotechnical evaluation of the test drug are presented in Table 2. The weight variability of 0.5540 ± 0.02 g was obtained and falls within the Pharmacopeia standard. The mean tablets' thickness and diameter are 5.6 ± 0.08 mm and 11.12 ± 0.04 mm respectively. A hardness value of 7.57 ± 0.4 KgF was observed, while a mean percentage friability of 75± 0.01% was recorded. A standard hardness value of 4 to 10 kgF is acceptable for conventional tablets. On the other hand, British Pharmacopeia specifies a percentage friability of not more than 1% for uncoated tablets.

Table 1: Product (metronidazole) details

S/N	Product details	
1	Manufacturer	Emzor Pharmaceutical Industries Ltd. Isolo, Lagos, Nigeria
2	Generic name	Metronidazole BP 400 mg
3	Country of origin	Nigeria
4	Batch No	1610C
5	NAFDAC No	04-7953
6	Manufacturing date	05/2023
7	Expiry date	05/2026
8	Appearance & shape	Yellow coloured, biconcave & circular in shape, and smooth

Table 2: Physicomechanical properties of the tablets

Weight Uniformity (g) ±SD	Thickness (mm) ±SD	Diameter (mm) ± SD	Hardness (kgF) ± SD	Friability (%) ± SD
0.5540 ± 0.0165	5.6 ± 0.0775	11.12 ± 0.0414	7.57 ± 0.4116	0.75± 0.01

Table 3: Disintegration time in the various beverages

Dissolution medium (Beverages)	Disintegration time (min) ± SD
0.1N HCL	2.28 ± 0.04
Beer	4.21 ± 0.12
Coffee	3.24 ± 0.05
Distilled Water	3.23 ± 0.07
Exotic Juice	5.21 ± 0.11
Fanta	3.17 ± 0.06
Milk & Milo	16.16 ± 0.11

Disintegration and dissolution: The results of disintegration and dissolution in the various mediums under investigation are presented in Table 3 and Figure 1. The test drug disintegrated within 6 min in all the mediums except in milk and Milo whose mean disintegration time is 16.16 ± 0.11 min. On the other hand, over 70% of the drug was released within 45 min in 0.1 N HCl, beer, coffee, distilled water, and Fanta. The mean percentage drug released in Exotic juice is 67.98 ± 0.09% and 44.94 ± 0.22% in a mixture of milk and Milo in 45 min.

Weight Uniformity: A weight uniformity test for tablets is required to ensure that the drug content in each tablet is distributed in a narrow range around the label strength because a slight variation in the weight of the tablet reflects a variation in the content of the active ingredient. As observed from Table 2, the weight variability of 0.5540 ± 0.0165 for the metronidazole tablets was within the acceptable range of pharmacopeia standards. These variations are expected not to have a significant impact on the disintegration time of the tablets. Thus, the weight variations of the tablets will not have any effect on their disintegration time and drug release.

Hardness: Hardness values greater than or equal to 4 kgF are considered optimal and acceptable as such tablets can withstand transportation and handling and be able to disintegrate and release the adequate quantity of drug for the required therapeutic effect. One of the basic physicomechanical parameters that can affect the disintegration time of tablets and invariably drug release rate is hardness (Kitazawa *et al*., 1975). An overly hard tablet would increase disintegration time.

Friability: The friability test evaluates the ability of a tablet to withstand chipping and abrasion in the process of packaging, handling, and transportation. Weight loss due to friability was found to be less than 1% indicating that the brand is mechanically stable and will not undergo any wear or tear during transportation (Naveedand and Qamar, 2014). According to the British Pharmacopoeia maximum loss of not more than 1% of the mass of the tablets tested is required (BP, 2002).

Disintegration: Disintegration refers to the physical break up of a compressed tablet into small granules or particles upon ingestion and thus it is characterized by the breakdown of the inter-particulate bonds, which were formed during the compaction of the tablet. The results above reveal rapid disintegration of the drug in all the beverages except the mixture of milk and Milo which exceeded the limit. The disintegration times of the tablets in the beverages were not significantly increased except in the milk and Milo. Therefore, almost all of the test beverages did not significantly influence the disintegration times of metronidazole tablets. In the mixture of milk and Millo metronidazole tablet had the longest disintegration time (16.60 min). This may have a major clinical impact because the

disintegration time was more than 15 min (BP-specified disintegration time limit for uncoated tablets), and also the average gastric emptying time when fluid is taken with a dosage form in the absence of food (Venkateswarlu, 2010). The mechanism of disintegration could be due to liquid uptake or penetration of liquid into the tablet matrix to cause swelling and eventual rupture of the tablet. A liquid's viscosity, contact angle, and surface tension have been shown to influence the penetration rate of the liquid into a tablet and consequently, the disintegration time of the tablet (Parojcic *et al.*, 2007). For example, it has been shown in this study that disintegration is delayed in the mixture of milk and Milo. This may be due to poor penetration rate for the mixture of milk and Milo, which may be a reflection of its relatively high viscosity. If the test media are grouped into low viscosity (water and 0.1 N HCl), medium viscosity (Fanta, beer, and coffee), and high viscosity (Exotic juice, milk, and Milo) beverages, it would be expected that their penetration rate into the tablets will follow this order with the low viscosity beverages accounting for faster disintegration times followed by the medium viscosity and high viscosity beverages, in that order. This was more or less the case

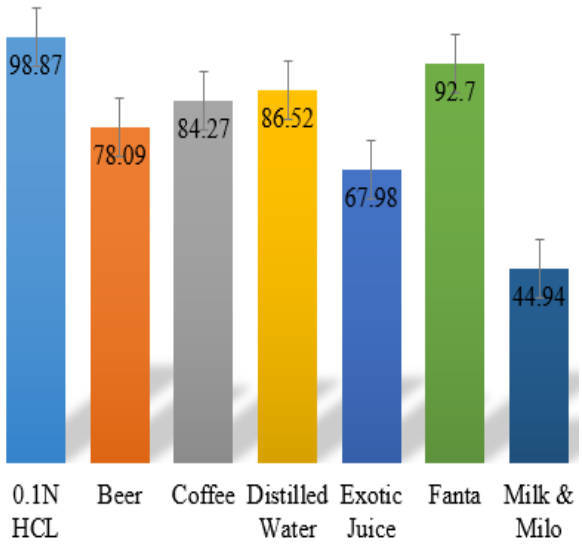

Fig 1: Percentage of drug release at 45 min in the various mediums

Dissolution test: The British Pharmacopoeia specification is that not less than 70% of the stated amount of uncoated tablets should be in solution within 45 min. The test drug (metronidazole tablets) fulfilled this requirement in all the mediums with the exception of Exotic juice, milk, and Milo. The brand (Emgyl®) released at least 78% of its content within 45 min 0.1 N HCL, Coffee, Fanta, Beer, and Distilled Water. In Exotic juice, and milk & Milo, Metronidazole (400 mg) tablets had a poor drug release of 67.98%, and 44.94% respectively after 45 min. Thus, systemic bioavailability of the drug will be low in addition to low therapeutic efficacy when Exotic juice or milk is used to administer metronidazole tablets. For solid dosage form, before absorption dissolution inside the body in the gastric medium is an important one that would be helpful to ease their rate of absorption, distribution, metabolism, and excretion and at last to have a profound effect on therapeutic activity related to pharmaceutical agents. Maximum and rapid dissolution in GI fluid leads to high and rapid absorption of the drug from GI which in turn promotes maximal and prompt action of the drug. Thus, there is a general consensus that dissolution is the primary step in the therapeutic outcome of a drug. However, the rate of dissolution of any agent never remains the same in different vehicles (Nawab *et al*., 2016; Amukainzi, 2021). The rate of drug release is controlled by an increase or decrease in the drug solubility and concentration of the drug in the matrix system. Also, dissolution depends on the surrounding medium. Food intake exerts a complex influence on the bioavailability of drugs. It may interfere not only with tablet disintegration, drug dissolution, and drug transit through the gastrointestinal tract, but may also affect the metabolic transformation of drugs in the gastrointestinal wall and in the liver. Different food components can have different effects, and food may interact in opposite ways, even with drugs that are chemically related. Therefore, the net effect of food on drug bioavailability can be predicted only by direct clinical studies of the drug in question. Food and its components and contaminants may have both short and long-term effects on both the absorption and biotransformation processes influencing the systemic availability of drugs.

Conclusion: Disintegration is an important first step or process that is needed for the release of the drug content in a formulated oral dosage form into the GIT before dissolution. This study has been able to establish the negative effect of food beverages on dissolution and disintegration of metronidazole tablets. The results also imply that carbonated drinks, alcoholic drinks, and beverages should be avoided and may not be used in the administration of the solid dosage forms due to their impact on the disintegration time and dissolution rate.

REFERENCES

Abuhelwa, AY; Williams, DB; Upton, RN; Foster, DJR (2017). Food, gastrointestinal pH and models of oral drug absorption. *Eur. J. Pharm. Biopharm*. 112: 234-248. DOI: 10.1016/j.ejpb.2016.11.034

Almukainzi, M (2021). Assessment of oral dosage forms administration manner and acceptability. *Pharmacia.* 68(2): 393-400. https://doi.org/10.3897/pharmacia.68.e65604

Almukainzi, M; Alobaid, R; Aldosary, M; Aldalbahi, Y; Bashiri, M (2021). Investigation of the effects of different beverages on the disintegration time of over-the-counter medications in Saudi Arabia. *Saudi Pharm. J.* 29(7): 699-705. DOI: 10.1016/j.jsps.2021.04.032

Almukainzi, M; Araujo, G; Lobenberg, R (2018). Orally disintegrating dosage form. *J Pharm Invest.* 49(2): 229-243.

Avbunudiogba, JA; Arhewoh, MI; Imonije, JO (2020). Determination of Aspirin Stability in oil in water Emulsion prepared using different oils and gums. *NIJOPHASR*. 9(3): 40-45. https://www.nijophasr.net/index.php/nijophasr/article/view/358

Avbunudiogba, JA; Aumade, D (2022). Formulation and evaluation of controlled release theophylline tablets using *Grewia species* gum as binder. *Res. J. Pharm. Tech.* 15(6): 2697-2702. DOI: 10.52711/0974-360X.2022.00451

Avbunudiogba, JA; Erebor, J; Cash-Torunarigha, OE; Iwuagwu MA (2013). The evaluation of some commercially available brands of piroxicam capsules in the Nigerian market. *Int. J. Pharm. Chem. Biol. Sci.* 3(3):876-880

Avbunudiogba, JA; Oghenekevwe, O (2021). Formulation and evaluation of conventional metronidazole tablets using natural gum extracted from *Grewia species*. *J. Pharm. Res. Int.* 33(37A): 128-137. DOI: 10.9734/jpri/2021/v33i37A31988

British Pharmacopoeia (2002). Her Majesty's stationary office, London. Pages 160, 411, 2366 and A236

Ceruelos, AH; Romero-Quezada, LC; Ledezma, JCR; Contreras, LL (2019). Therapeutic uses of metronidazole and its side effects: An update. *Eur. Rev. Med. Pharmacol. Sci.* 23(1): 397-401. DOI: 10.26355/eurrev_201901_16788

Hummler, H; Page, S; Stillhart, C; Meilicke, L; Grimm, M *et al* (2023). Influences of solid oral dosage form characteristics on swallowability, visual perception, and handling in older adults. *Pharmaceutics*. 15(4): 1315. DOI: 10.3390/pharmaceutics15041315

Ibezim, EC (2005). Effects of dissolution medium, pH, and temperature on the *in-vitro* release properties of metronidazole tablets. *JOPHAS*. 2(2): 209-213. DOI: 10.4314/jophas.v2i2.34979

Kitazawa, S; Johno, I; Ito, Y; Teramura, S; Okada, J (1975). Effects of hardness on the disintegration time and the dissolution rate of uncoated caffeine tablets. *J. Pharm. Pharmacol.* 27(10): 765-770. doi: http://doi.org/10.1111/j.2042-7158.1975.tb09397.x

Kohl, K; Stengel, A; Samuni-Blank, M; Dearing, MD (2014). Effects of anatomy and diet on gastrointestinal pH in rodents. *J. Exp. Zool. A. Ecol. Genet. Physiol.* 321(5): 241-242. DOI: 10.1002/jez.1786

Leitsch, D (2017). A Review on Metronidazole: An old warhorse in antimicrobial chemotherapy. *Parasitology*. 146(9): 1167-1178. DOI: 10.1017/S0031182017002025

Nagaich, U; Chaudhary, V; Tonpay, SD; Karki, R (2010). Design and Evaluation of a metronidazole central core matrix tablet. *J. Adv. Pharm. Technol. Res*. 1(1): 88-96

Nagashree, K (2015). Solid dosage forms: Tablets research and reviews. *J. Pharm. Anal.* 4: 60-71

Naveedand, S; Qamar, F (2014). Comparative study of metronidazole formulations. *DHR- Int. J. Pharm. Sci*. 5(2):111-116

Nawab, A; Ghayas, S; Alam, S; Farooq, N (2016). Dissolution profile of metronidazole film-coated tablet 400 mg (Flagyl®) in the presence of different juices: An *In-Vitro* study. *Int. Res. J. Pharm.* 1: 52-57. DOI:10.7897/2230-8407.0719

Nelson, E (2006). A note on tablet hardness. *JAPhA.* 45(5): 354-355. Doi: 10.1002/jps.3030450526

Parojcic, J; Vasiljevic, D; Ibric, S; Zorica, D (2007). Tablet disintegration and drug dissolution in viscous media: Paracetamol IR tablets. *Int. J. Pharm.* 355(1-2): 93-99 https://doi.org/10.1016/j.ijpharm.2007.11.058

Venkateswarlu, V (2010). Biopharmaceutics and Pharmacokinetics. 2nd edn, Hyderabad, PharmaMed Press; Pp 5-95.