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Review article

DISSOLUTION PROFILE OF METRONIDAZOLE TABLET IN DIVERSE FATTY DISSOLUTION MEDIUMS.

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Abstract:

Objective: The aim of the study was to confirm the interaction of food with metronidazole 400 mg tablet with diverse dissolution medium like milk, oil and gastric fluid to observe the effects of physiological changes in terms of absorbance.

Study design: experimental study.

Place and duration: Jinnah University for Women, over six months

Method: The brand Flagyl (Metronidazole) 400 mg were purchased from the local pharmacies of Karachi (Pakistan) for the evaluation of dissolution profile in diverse medium.

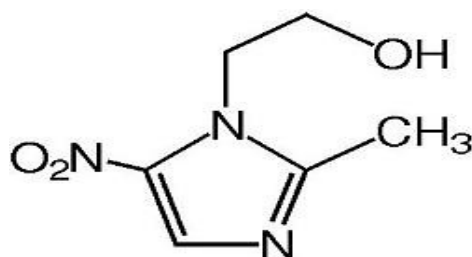
Results: The outcomes related to this research study are clearly showing that all the results come out within the specified limits of BP/USP which is not less 85 %. The results of one way Anova test between the groups and within the groups showing significant difference i.e. p value < 0.05 . Multiple comparisons also performed by Tukey HSD and LSD test of standards with diverse dissolution mediums showing a significant difference between the medium i.e. p value < 0.05 .

Conclusions: We concluded from our study that metronidazole is not contraindicated with milk, oil with gastric fluid.

Keywords: Metronidazole, milk, oil, in vitro dissolution, one-way Anova.

INTRODUCTION:

Metronidazole (5-nitroimidazole) selectively acts against to anaerobic microorganisms, including microbes and protozoa. It is typically bactericidal at small fixations ¹. Metronidazole is the drugs of decision of different sponging contaminations, pseudo membranous colitis, anaerobic sicknesses, pores and skin break out rosaceous, Helicobacter pylori and Crohn's sickness and utilized as part of medical practice for a long time ². (Figure 1)



Chemical structure

Figure 1: Chemical structure of metronidazole

Absorption is fast through oral route in small digestive tract. Liver metabolism via oxidation

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Competing Interests:

The authors declare no competing interests

Additional information is available at the end of the article.

and conjugation with glucuronic acid³. It disposes of in urine 7-8 hours of half-life length.⁴ Drug dissolution is a uniform technique significantly measuring drug discharge from a finished product. The principle capability of the dissolution test is probably mentioned as takes after: Maximization of beneficial activity for the product to improve the assessment of drug release⁵. Estimation of 'bioequivalence', means they are same in term of all intents and purposes from distinct batches of items as of one or exclusive producers⁶.

Dissolution Media:

Simulate gastric fluid contains HCl, NaCl, pepsin, water and has a pH of 1.2. Most research of gastric pH indicates that the common gastric pH normally lies in the 1.5–1.9. For susceptible acids and impartial compounds, this small distinction makes clearly no difference within the dissolution characteristics, but for terribly poorly soluble susceptible bases, the dissolution results in compendia SGF are possibly to overestimate the in vivo dissolution fee. in addition deviations from gastric physiology are the pepsin concentration, which may be very excessive compared to that discovered in gastric juice aspirated below fasted state conditions and the surface anxiety of approximately 70 mN/m that does not don't forget the much lower common surface tension of human gastric fluid⁷. For the evaluation of olive oil markers different methods were applied and different solvents were used which include hexane.⁸ Olive oil has been shown, in vitro, to be capable with potent biological activities. Previously reported that olive oil dose-dependently absorbed in humans after ingestion^{9, 10}. Milk is a white fluid and low viscosity with slightly sweet in taste commonly used as food^{11, 12}. Regardless of the fact that the medium addresses a number of the traits of gastric juice, there are some functions that might be maximized.¹³

METHODOLOGY:

Experimental study conducted in Jinnah University for Women over six month of period to evaluate interaction of milk and edible oil and gastric fluid with metronidazole by using Anova Test, Tukey HSD and LSD tests and details of methodology step by step as follow;

Material and reagents:

Flagyl 400 mg tablet product information:

Metronidazole B.P generic were used for the experimental work which is manufactured by Sanofi Aventis Pakistan limited. The physical appearance of this product was light yellow colored circular shaped film coated tablet and having a packaging with PVC printed aluminum foil.

Instruments and reagents

Reference standard of Metronidazole and other reagents /chemicals such as chlorhydric acid –HCl (Merck); potassium chloride -KCl (Merck) was provided by JUW. Instrument and apparatus were used from the industrial pharmacy laboratory of JUW (Jinnah University for women Karachi, Pakistan). The UV spectrophotometer 1800, by shimadzu(Japan), Galvano scientific 11 pH meter (Pakistan), The dissolution tester containing eight-basket UDA-80 USP Standard (Veeco, India) were utilized for the experimental work¹.

Collection of Samples:

Flagyl 400 mg tablet normally available advertised logo (production date now not exceed more than 4 months in the past from the shopping time) was collected with blister packing. The pattern was well checked for their production batch wide variety, license wide variety, production date and expiring dates earlier than amassing.

Preparation of Reference Sample:

Hundred and one gm of widespread metronidazole which include 0.1 HCl solutions of 40 ml turned into moved to the volumetric flask and delivered mark to one hundred ml, now dilute 2.2 ml in 50 volumetric flask¹⁴(table 1, 2).

Preparation of dissolution medium:

Preparation of Milk:

Packet clean milk of renounced production company olpers become taken 2 hundred ml for the motive of examine. Take 200 ml of milk and seven hundred ml of 0.1 N HCl ml blend nicely before located in dissolution apparatus's basket. Acquire tablets from flagyl four hundred mg method, weighed and positioned in the hampers with 900 ml of milk plus 0.1 N HCl medium was positioned in every vessel and the equipment became assembled. The process within the milk medium turned into completed for sixty (60) mins. After 60 min sample turned into reserved and strained. The released drug turned into assayed by way of the use of UV spectrophotometer at 278 nm ¹.

Preparation Of Olive oil Medium:

Packet fresh olive oil of renounced production company became taken two hundred ml for the cause of study take two hundred ml of olive oil and seven-hundred ml of zero.1 N HCl answer blend properly before located in dissolution basket. Take capsules from flagyl four hundred mg system, measured and located in to baskets with 900 ml of olive oil and 0.1 N HCl vehicle became located in every vessel and the equipment changed into assembled. The procedure within the olive oil vehicle became performed for sixty (60) min. Past 60 min sample turned into reserved and strained. The liberated active was analyzed by the help of UV spectrophotometry at 278 nm

Preparation Of Gastric Medium(0.1 N HCl):

Replicated gastric medium (0.1 N HCl; pH 1.2) was made by 8.5 ml of Hydrochloric acid (36.5% w/v) in 1000 ml distilled water for 0.1N HCl. 400 mg Flagyl tablets were measured and positioned in each vessel of the equipment which contains 0.1 N HCl of 900 ml as dissolution vehicle¹⁴. Turned on the apparatus for operation which becomes finished in 60 minutes, then tested sample become withdrawn from the vessels and filtered with whatmman filter paper. Tested solution was analyzed by utilizing UV spectrophotometer at 278 nm for the drug release ³.

Conditions for % Dissolved Of Metronidazole Tablets (B.P):

The test conditions and specifications of in-vitro dissolution of metronidazole tablets with different dissolution medium such as milk, olive oil and gastric medium contains the volume of medium 900 ml (700:200 i.e 0.1 N HCl : Vehicles) , having the RPM 100, with the specified time i.e 60 minutes. The dissolution test performed in the dissolution equipment of veego international. The spectrophotometric wavelength of this procedure was 278 nm.

Method:

In vitro dissolution study executed via the usage of B.P dissolution check type I apparatus at $37 \pm 0.5^{\circ}\text{C}$ with a degree of agitation 100 rpm/minutes. Randomly selected metronidazole tablet of mentioned manufacturer and placed in the specific medium of simulated gastric fluid and vehicles(900 ml dissolution media) .The dissolution apparatus was operated for 60 minutes , after specified time samples was collected for obtaining the absorbance at 278 nm

of strained quantities of solution, appropriately diluted with 0.1 N HCl, in contrast with a preferred sample containing a recognized strength of USP Metronidazole RS in the equal vehicle/medium. The limit of dissolution is not less 85% dissolved in 60 minutes.

RESULTS

The results of gastric medium were found i.e. sample 01 was 101.12 sample 02 was 101.05 sample 03 was 101.18 sample 04 was 101.25 sample 05 was 100.99 sample 06 was 101.05 but the results in milk medium were found higher than the other fatty medium oil i.e. sample 01 was 114.98 sample 02 was 115.04 sample 03 was 114.85 sample 04 was 114.98 sample 05 was 114.78 sample 06 was 114.91, while the results in olive oil were found in lesser percentages than milk i.e. sample 01 was 106.07 sample 02 was 105.94 sample 03 was 105.74 sample 04 was 106.13 sample 05 was 106.00 sample 06 was 105.87. All the observed results are clearly showing that metronidazole is highly available in milk medium than the oil medium when we compared with the gastric fluids as expressed in table 3. Results and graphical representation are clearly presenting the point that milk is the best medium to be used with metronidazole tablet for the purpose of achieving its prompt and maximum effect. The graphical representation of reference solution verses all the mediums expressed in figure 2 and 3. The descriptive test shows the mean results, standard deviations and upper and lower limits. The mean results of standard, gastric fluid, milk, oil were 1.511500, 1.53183, 1.74117, 1.60533 and 1.610224 and standard deviations were 0.00, 0.001472, 0.001472, 0.002160 and 0.091416 as showing in table 4. *The results of one way ANOVA test between the groups and within the groups showing significant difference i.e. p value < 0.05 as expressed in table 5. Multiple comparisons performed by Tukey HSD and LSD test of standards with different dissolution mediums like gastric fluid, milk and oil showing a significant difference between the medium i.e. p value < 0.05. The results are expressed in table 6.*

Table 1: Reference samples stock concentration

Standard	Stock Concentration $\mu\text{G/ML}$
Metronidazole	44.44

Table 2: Samples stock concentration

Medium	Stock Concentration $\mu\text{g/ml}$
Milk	44.44
Olive oil	44.44
Gastric fluid	44.44

Table 3: Percent dissolved of metronidazole in different dissolution medium.

MEDIUM	SN#	% DISSOLVED	OFFICIAL LIMIT	REMARKS
Milk	1	114.98	NLT 85 %	Pass
	2	115.04		
	3	114.85		
	4	114.98		
	5	114.78		
	6	114.91		
Olive oil	1	106.07	NLT 85 %	Pass
	2	105.94		
	3	105.74		
	4	106.13		
	5	106.00		
	6	105.87		

Gastric fluid	1	101.12	NLT 85 %	Pass
	2	101.05		
	3	101.18		
	4	101.25		
	5	100.99		
	6	101.05		

Table 4: Results of Descriptive Test by Selecting Absorbance of Different Mediums

Table mediums	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Std	3	1.51500	.000000	.000000	1.51500	1.51500	1.515	1.515
gastric fluid	6	1.53183	.001472	.000601	1.53029	1.53338	1.530	1.534
Milk	6	1.74117	.001472	.000601	1.73962	1.74271	1.739	1.743
Oil	6	1.60533	.002160	.000882	1.60307	1.60760	1.602	1.608
Total	21	1.61024	.091416	.019949	1.56863	1.65185	1.515	1.743

One way Anova test between the groups and within the groups showing a significant difference i.e *p value* <0.05

Table 5: Results of one way Anova by selecting absorbances of different mediums

Variances	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.167	3	.056	21041.317	.000
Within Groups	.000	17	.000		
Total	.167	20			

One way Anova test between the groups and within the groups showing a significant difference i.e *p value* <0.05

Table 6: Results of post hoc tests by selecting absorbance of different mediums

Tests	Multiple comparison of standard	Medium	Sig.	95% Confidence Interval	
				Lower Bound	Upper Bound
Tukey HSD	std	gastric fluid	.000	-.02010	-.01356
		milk	.000	-.22944	-.22290
		oil	.000	-.09360	-.08706
LSD	std	gastric fluid	.000	-.01926	-.01441
		milk	.000	-.22859	-.22374
		oil	.000	-.09276	-.08791

p value <0.05

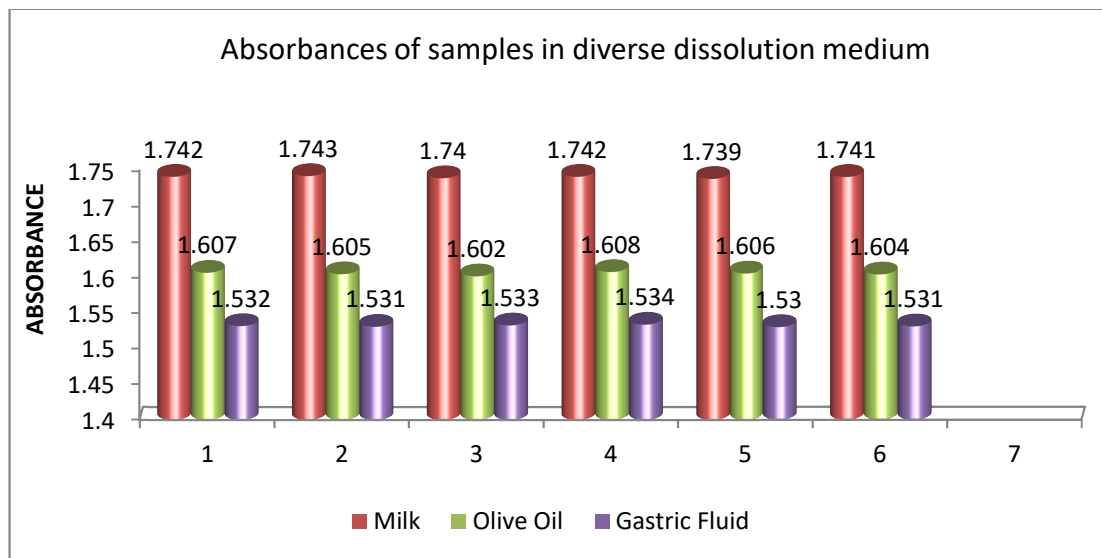


Figure 2: Absorbance of samples in diverse dissolution medium

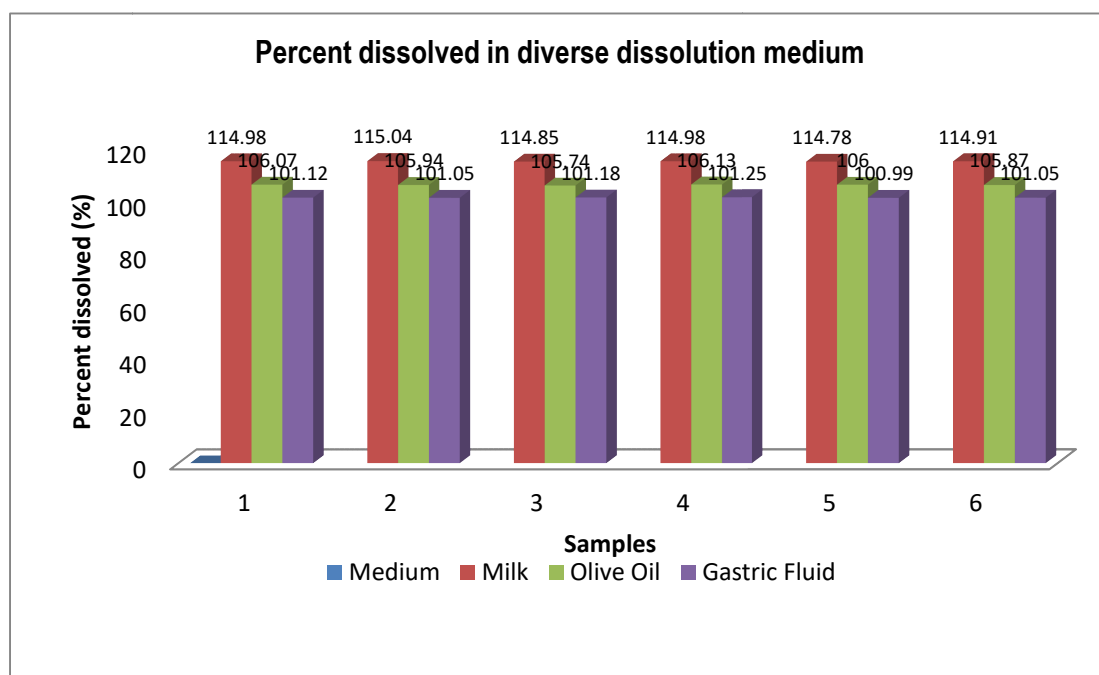


Figure 3: Percent dissolved in diverse dissolution medium

DISCUSSION:

In this research activity we identified dissolution profile of metronidazole 400mg tablet in different dissolution medium (milk, oil, GI p H 1.2) and also comparative study has been conducted which became very productive for the better therapeutic action of metronidazole. For such practical work firstly standard solution have been prepared and then Simulated GI conditions have been created using milk and oil, using dissolution apparatus dissolution phenomenon has been identified and the results are observed with the help of UV spectrophotometer indicating clear difference of dissolution rate among different mediums used.

Amber N *et al* in 2015 revealed that the release rate found relatively faster in gastric medium containing black tea and after 60 minutes the Metronidazole release as compare to the

green tea. Results are clearly presenting the point that black tea is the better medium to be used with metronidazole tablet for the purpose of achieving its prompt and maximum effect³. When compared the results of gastric medium with fatty mediums the results presenting the point that milk is the best medium to be used with metronidazole tablet for the purpose of achieving its prompt and maximum effect. *The results of one way ANOVA test between the groups and within the groups showing significant difference i.e p value < 0.05 as expressed in table 5.* Multiple comparisons performed by Tukey HSD and LSD test of standards with different dissolution mediums like gastric fluid, milk and oil showing a significant difference between the medium i.e. *p value < 0.05 . The results are expressed in table 6.*

Conclusion

It has been concluded that the investigation related to this study will clearly act as an innovative step for medical practitioner and other persons in health establishment. A different approach can be made that comparison in fatty foods like milk and oil metronidazole tablets 400 mg gave distinct results and gave better results in oily food as compare to the milk. However through these observations we concluded that oily food with metronidazole 400 mg table increases therapeutic effectiveness and patient compliance. Through this study it is suggested to the mankind administer metronidazole either with oil and milk as both shows a encouraging results and outcomes, but if decision has to be made among these two fatty food with metronidazole, oil will be a good vehicle with metronidazole. In the end it was concluded through our research study that metronidazole showed not contraindicated with milk, oil with gastric fluid.

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