IJPSR (2023), Volume 14, Issue 12 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 September 2022; received in revised form, 08 August 2023; accepted 11 November 2023; published 01 December 2023

FORMULATION AND EVALUATION OF SUSTINED RELEASE MATRIX TABLET OF METRONIDAZOLE

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Keywords:

Antimicrobial resistance, Bacterial vaginosis, Metronidazole, Trichomoniasis, Vaginitis

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ABSTRACT: In this study matrix tablets of metronidazole were prepared by direct compression method which is now days considered a cost effective and simple method of manufacturing. It is considered as an appropriate method for hygroscopic and thermolabile substances. Six formulations of different polymer percentages were formulated (F1-F9). The mean hardness values were measured for all the formulation using Monsanto hardness tester. The hardness value ranges from 5.2±0.2 to 5.8±0.1kg/cm^2. Twenty tablets were randomly selected from each formulation and evaluated. The obtained data were almost uniform. The values of tablets average weight ranging from 549±5 to 558±7mg. All the tablets passed weight variation test as the % weight variation was within the USP Pharmacopoeia's limits of ±5% of the weight. The % drug content of all the formulated tablets were found within the limit. % Drug content value of drug was within 98.12±0.25% to 99.85±0.18%. The results within the range indicate uniform of mixing. When the regression coefficient values compared, it was observed that 'r^2' values of first order was maximum i.e., 0.937 hence indicating drug release from formulations was found to follow first order release kinetics.

INTRODUCTION: Matrix tablets precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development [1]. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(12).6029-37

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.14(12).6029-37

The preliminary study showed that Metronidazole is white and odourless powder. It is freely soluble in methanol soluble in ethanol and soluble in 0.1 N Hydrochloric acids, sparingly soluble 0.1 N NaOH, the melting point was in the range of 223- 226 °C which is compliance with the standard value of as per British Pharmacopoeia. Identification of Metronidazole was performed by UV/VIS Spectroscopy.

The 10 µg/ml solutions of Metronidazole was scanned in the range of 200-400nm to determine the λ_{max} for drug [2, 3]. The m_{ix} of Metronidazole was found to be 278nm. From the respective stock solution (1mg/ml) different concentration of 5, 10, 15, 20 and 25µg/ml Metronidazole was prepared and scanned in UV region. Their absorbances were noted at 278 nm and calibration curve was plotted as absorbance vs concentration and their linearity range was determined.

The melting point of Metronidazole was found 158-160ºC. The percentage of loss on drying of Metronidazole was found 0.487±0.02. From the FT-IR data of the physical mixture obviously functionalities of drug have stayed unaltered including forces of the peak. This proposes amid the procedure drug and excipient has not responded with the drug to offer ascent to reactant items.

So, there is no interaction between them which is in favour to proceed for formulation of vesicular drug delivery system. Preformulation studies reported that the formulation of floating of Metronidazole can be prepared with appropriate methods. This thesis deals with the investigations carried out on the preparation and characterization of matrix tablets containing Metronidazole with increase its oral bioavailability. Matrix tablets containing Metronidazole were prepared using direct compression method. Total nine formulations were prepared using varying amount of HPMC-K4 and ethyl cellulose. The prepared Tablets were further evaluated for Hardness, Friability, floating behaviour, and uniformity of drug content, and *In-vitro* Release Studies. The loose bulk density (LBD) and tapped bulk density (TBD) of the powders of different formulations were evaluated before the compression of powders in to tablets. The bulk density and the tapped density for all the formulations varied from 0.348 to 0.378gm/cm^3 and 0.472 to 0.485gm/cm^3 respectively [4, 5].

GRDF extend significantly the period of time over which the drugs may be released. Thus, they not only prolong dosing intervals but also increase patient complains beyond the level of existing controlled release dosage forms. This application is especially effective in delivery of sparingly soluble and insoluble drugs. It is known that as the solubility of drug decreases, the time available for drug dissolution become less adequate and thus the transits time becomes a significant factor affecting drug absorption [6, 7].

To address this, oral administration of sparingly soluble drugs is carried out frequently after several time per day. As a mechanism to override this problem, erodible gastroprotective dosage forms have been developed that provide continuous controlled administration of this drug at the absorption site. In addition, these dosage forms are useful for delivering drugs incorporated in to vesicles such as liposomes, nanoparticles proteinoid microspheres and pharma cosomes, etc. compare with other applications, the frequency of dosing may be the some, but the gastroprotective dosage forms will alter beneficially the absorption profile of the active agent thus enhancing its bioavailability.

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhance bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastro intestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is release to contact time which the small intestinal mucosa[1]. Davis, 1968 firstly described the concept of floating drug delivery system (FDDS) after experiencing gagging or chocking by some persons, while swallowing medicinal pills. The researchers suggested that such difficulty could be overcome by providing pills having a density of less than 1.0 g/ml, so that pill will float on water surface.

Since, then, several approaches have been proposed for ideal floating drug delivery system. These buoyant delivery systems include hollow microspheres (micro balloons)' powders, granules, tablets (pills), capsules are unreliable due to their all or nothing emptying process and irreproducible residence time in stomach. In turn, multiple unit dosage forms represent a batter option as they reduce the intrasubject variability in absorption and the chances of dose dumping summarize the development of floating drug delivery system [8, 9, 10].

MATERIALS AND METHODS:

Preformulation Study: Preformulation study is the initial phase in the rational development of dosage type of a medication substance. It can be characterized as an examination of physical and chemical properties a medication substance alone

and when joined with excipients. The general target of preformulation testing is to create data helpful to the formulator in developing stable and bioavailable dosage frames which can be mass delivered. Clearly, the sorts of data required rely upon the dosage frame to be produced. Preformulation thinks about incorporate investigations of:

1. The physiochemical properties of drug, and an assessment of their relevance to the final formulation.
2. The chemical and physical stability of drug.
3. Chemical /physical compatibility of the active with potential excipients. These investigations give hints as to how to achieve the desired performance of the completed items.

Indeed, even after developing a formulation and technique for manufacture on these principles, it is as yet necessary to affirm stability and bioavailability, however there is a smaller probability that the formulation will fail.

In the event that a few formulations are created in parallel, there is much greater probability that one will be significantly limit the dangers of failure and increase the probability of delivering a high quality [1, 4, 11].

Characterization of Metronidazole:

Physical Evaluation: It refers to the evaluation by sensory characters- color, odor, texture of the drug, etc.

Solubility: Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5 ml of the solvent (water, ethanol, methanol, 0.1N HCl, 0.1 N NaOH, chloroform and phosphate buffer pH 7.4) Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature) [35]. Identification of Metronidazole was done by FTIR Spectroscopy with respect to marker compound. Metronidazole was obtained as white to pale yellow powder. It was identified from the result of IR spectrum as per specification [12].

Sample of Pure Metronidazole: The IR spectrum of sample drug shows the peak values which are characteristics of the drug and the graph were shown in figure no. 7.1:

Loss on Drying: The moisture in a solid can be expressed on a wet weight or dry weight basis. On a wet weight basis, the water content of a material is calculated as a percentage of the weight of the wet solid. The term loss on drying is an expression of moisture content on a wet weight basis [4, 12].

Determination of λ max of Metronidazole: The λmax of Metronidazole was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer. Accurately weighed 10 mg of drug was dissolved in 10 ml of 0.1 N HCl solutions in 10 ml of volumetric flask. The resulted solution (1000µg/ml) was used to prepare the concentration 10µg/ml. The spectrum of this solution was recorded in 200-400 nm range using U.V. spectrophotometer (Labindia-3000+). After the complete scan λmax of Metronidazole was found 278 nm [13].

Preparation of Calibration Curve: From stock solutions of Metronidazole, 1 ml was taken and diluted up to 10 ml. from this solution 0.5, 1.0, 1.5, 2.0- and 2.5-ml solutions were transferred to 10ml volumetric flasks and make up the volume up to 10 ml with 0.1 N HCl, gives standard drug solution of 5, 10, 15, 20, 25µg/ ml concentration [14].

Preparation of Matrix Tablet of Metronidazole: The matrix tablets were prepared by direct compression method which is now days considered a cost effective and simple method of manufacturing [36]. It is considered as an appropriate method for hygroscopic and thermolabile substances. Six formulations of different polymer percentages were formulated (F1-F9).

Accurately weighed quantity of all the excipients and drug such as Metronidazole, HPMC K15, Ethyl cellulose, PVP K30 were mixed and passed from 16 no sieve. Then blend was feed in hopper and tablets were prepared by direct compression using multi station automatic rotatory punching machine [13].

The tablets were prepared using the punch of 8 mm diameter using the rotary tablet processing machine. The composition of formulation was given in **Table 1.**

TABLE 1: VARIOUS FORMULATIONS OF METRONIDAZOLE MATRIX TABLETS

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metronidazole	400	400	400	400	400	400	400	400	400
HPMC K-15	80	100	120	-	-	-	40	50	60
Ethyl cellulose	-	-	-	80	100	120	40	50	60
PVP K30	15	15	15	15	15	15	15	15	15
Talc	10	10	10	10	10	10	10	10	10
Lactose	45	25	5	45	25	5	45	25	5
Total Weight	550	550	550	550	550	550	550	550	550

Evaluation of Precompression Parameter:

Bulk Density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed number of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas [37].

LBD (Loose Bulk Density) = Mass of powder / Volume of packing

TBD (Tapped Bulk Density) = Mass of powder / Tapped volume of packing

Carr's Compressibility Index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:

$$\text{Carr's index \%} = \text{TBD} - \text{LBD} / \text{TBD} \times 100$$

Hauser's Ratio: It is determined by comparing tapped density to the bulk density by using following equation: -

$$\text{Hauser's ratio} = \text{Tapped density/Bulk density}$$

Hauser's ratio value <1.25 shows better flow properties

Evaluation of Tablets: All the tablets were evaluated for following various parameters which includes.

General Appearance: Five tablets from various batches were randomly selected and organoleptic properties such as colour, odour, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and Diameter: Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated[38].

Drug Content: Twenty tablets were taken and amount of drug present in each tablet was determined [39]. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ max of 278nm using of 0.1 N HCl as blank.

Hardness: For each formulation, the hardness of five tablets was resolved utilizing the Monsanto hardness tester [40].

Friability: The friability of a sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of Weight: Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Dissolution Rate Studies: *In-vitro* drug release of the sample was done using USP-type II dissolution apparatus (Paddle type) [41-42]. The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask maintaining the temperature of 37±0.5°C and rpm of 75. One Metronidazole tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 12 hours. Sample measuring 5ml were pulled back after time intervals up to 12 hours using 5ml pipette. The new disintegration medium (37°C) was supplanted each time with a similar amount of the sample and takes the absorbance at 278 nm using spectroscopy.

Mathematical Treatment of *In-vitro* Release Data: The quantitative analysis of the qualities got in dissolution/release tests is simpler when mathematical formulas that express the dissolution comes about as an element of a portion of the measurement frames attributes are utilized.

Zero-order Kinetics: The pharmaceutical dosage frames following this profile release a similar measure of medication by unit of time and it is the ideal method of medication release keeping in mind the end goal to accomplish a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$Qt = Qo + Ko\ t$$

Where Qt is the amount of drug dissolved in time t, Qo is the initial amount of drug in the solution (most times, Qo=0) and Ko is the zero-order release constant.

First-order Kinetics: The following relation expresses this model:

$$\log Q_t = \log Q_o + K_{1t}/\ 2.303$$

Where Qt is the amount of drug dissolved in time t, Qo is the initial amount of drug in the solution and K1 is the zero-order release constant.

Along these lines a graphic of the decimal logarithm of the released measure of drug versus time will be linear. The pharmaceutical dosage shapes following this dissolution profile, for example, those containing water-solvent drugs in permeable frameworks, discharge drug in a way that is corresponding to the measure of drug staying in its inside, in such way, that the measure of drug released by unit of time reduce [15, 16].

RESULTS AND DISCUSSION:

Physical Evaluation: It refers to the evaluation by sensory characters-taste, appearance, odour, feel of the drug, *etc* **Table 2.**

TABLE 2: LIST OF SENSORY CHARACTERS

1.	Colour	White to pale yellow crystalline powder
2.	Odour	Odourless
3.	Appearance	Crystalline powder

Results of Solubility: Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5 ml of the solvent (water, ethanol, methanol, 0.1N HCl, and 7.4 pH phosphate buffer) Shake vigorously and kept for some time **Table 3**. Note the solubility of the drug in various solvents (at room temperature).

TABLE 3: SOLUBILITY OF METRONIDAZOLE

S. no.	Solvent used	Results of Solubility
1.	Water	Soluble
2.	0.1 N HCl	Soluble
3.	Ethanol	Soluble
4.	Methanol	Freely soluble
5.	Chloroform	Freely soluble
6.	Phosphate buffer pH 7.4	Soluble
7.	0.1 N NaOH	Slightly Soluble

Results of Melting Point: The melting point of Metronidazole was found 158-160ºC.

Loss on Drying: The percentage of loss on drying of Metronidazole was found 0.487±0.02.

Calibration Curve of Metronidazole at 278nm Table 4:

TABLE 4: CALIBRATION CURVE OF METRONIDAZOLE IN 0.1 N HCL

S. no.	Concentration (µg/ml)	Mean Absorbance
1.	5	0.312±0.001
2.	10	0.625±0.002
3.	15	0.912±0.001
4.	20	1.231±0.001
5.	25	1.512±0.002

(n=3; mean±SD)

S. no.	Parameter	Remark
1.	Linearity Range	5-25 µg/ml
2.	Regression Equation	Y = 0.060x + 0.007
3.	Correlation Coefficient	0.999

Result of Pre-compression Properties of Metronidazole Matrix Tablets: The loose bulk density (LBD) and Tapped bulk density (TBD) of the powders of different formulations were evaluated before the compression of powders in to tablets. The bulk density and the tapped density for all the formulations varied from 0.348 to 0.378gm/cm^3 and 0.472 to 0.485gm/cm^3 respectively. The values obtained lies within the acceptable range. The difference exists between the bulk density and tapped density found to be very few. This result helps in calculating the % compressibility of the powder. The result of Hauser's ratio of all formulations ranges from

1.262 to 1.390. Results of Hauser's ratio indicates that the flow ability of all the formulation. The results of the Compressibility index of all the formulations ranges from 20.763% to 28.081%. Results of Compressibility index clearly showed that the flow ability of all the formulations was good and also the powder had good compressibility **Table 5**, **Fig. 1.**

TABLE 5: RESULT OF PRE-COMPRESSION PROPERTIES OF METRONIDAZOLE MATRIX TABLETS

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hauser ratio
F1	0.358	0.485	26.186	1.355
F2	0.369	0.482	23.444	1.306
F3	0.378	0.478	20.921	1.265
F4	0.356	0.495	28.081	1.390
F5	0.365	0.473	22.833	1.296
F6	0.374	0.472	20.763	1.262
F7	0.348	0.476	26.891	1.368
F8	0.369	0.475	22.316	1.287
F9	0.374	0.482	22.407	1.289

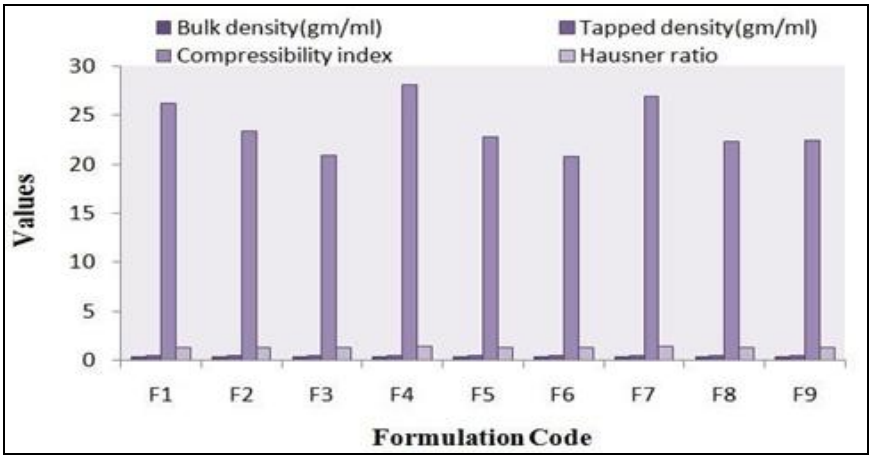

FIG. 1: GRAPH OF PRE-COMPRESSION PROPERTIES

Results of Post Compression Properties of Metronidazole Matrix Tablets: The formulated tablets were subjected for post- compressional evaluation such as friability, hardness, weight variation, thickness, uniformity of drug content, and In vitro dissolution study. The thickness of the tablets was reported in the micrometre (mm). The thickness of tablet indicates that, die fill was uniform. The thickness depends on the size of the punches (8 mm) and the weight of one tablet (550mg). The value of thickness ranges between 3.14±0.12 to 3.26±0.11mm [17, 18]. Friability determines the strength of the tablets. The friability for all the formulations was below 1% indicating that the friability was within the prescribed limits. The results of friability test indicate that the tablet possesses good mechanical strength. The friability value ranges from 0.698±0.014 to 0.882±0.012. The mean hardness values were measured for all the formulation using Monsanto hardness tester. The results were tabulated in **Table 6.** The hardness value ranges from 5.2±0.2 to 5.8±0.1kg/cm^2 **Table 6** & **Fig. 2.** Twenty tablets were randomly selected from each formulation and evaluated. The obtained data were almost uniform [19, 20]. The values of tablets average weight ranging from 549±5 to 558±7mg. All the tablets passed weight variation test as the % weight variation was within the USP Pharmacopoeia's limits of ±5% of the weight **Table 7** & **Fig. 3.** The % drug content of all the formulated tablets were found within the limit. % Drug content value of drug was within 98.12±0.25% to 99.85±0.18%. The results within the range indicate uniform of mixing **Table 8.**

TABLE 6: RESULTS OF POST COMPRESSION PROPERTIES OF METRONIDAZOLE MATRIX TABLETS

Formulateon code	Thickness(mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability(%) n=3	Drug content (%) n=3
F1	3.25±0.12	5.2±0.2	555±4	0.785±0.025	98.12±0.25
F2	3.21±0.15	5.4±0.3	545±3	0.852±0.023	98.85±0.12

F3	3.15±0.16	5.6±0.2	549±5	0.698±0.014	98.65±0.32
F4	3.22±0.14	5.5±0.1	553±6	0.754±0.032	98.78±0.25
F5	3.14±0.12	5.4±0.1	550±5	0.762±0.014	99.05±0.26
F6	3.18±0.14	5.3±0.3	557±4	0.745±0.018	98.74±0.21
F7	3.17±0.12	5.4±0.2	558±7	0.882±0.012	98.85±0.24
F8	3.21±0.14	5.7±0.1	552±8	0.658±0.014	99.85±0.18
F9	3.26±0.11	5.4±0.2	549±5	0.745±0.013	98.69±0.15

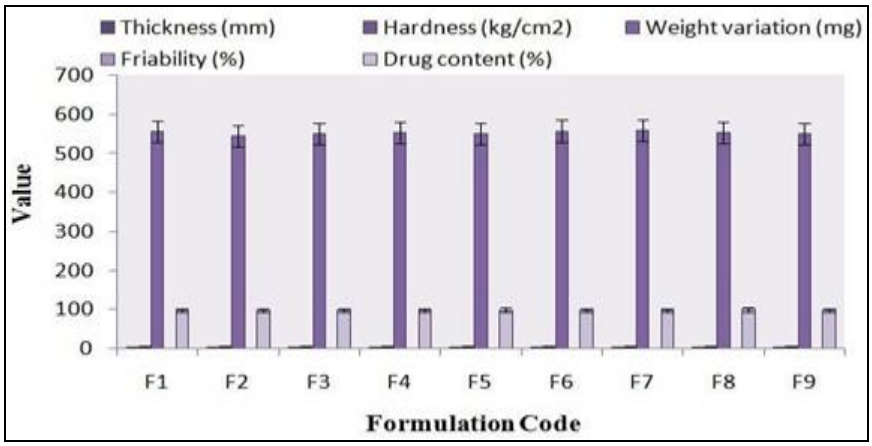

FIG. 2: GRAPH OF POST-COMPRESSION PROPERTIES

TABLE 7: *IN-VITRO* DRUG RELEASE STUDY OF METRONIDAZOLE MATRIX TABLETS

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	35.65	32.25	33.36	36.65	32.25	30.45	30.25	26.65	19.98
1	45.65	43.32	39.98	43.32	45.56	39.98	43.32	39.95	26.54
1.5	65.85	59.98	55.65	63.32	59.98	45.58	56.65	48.78	33.74
2	78.85	69.98	69.98	63.32	64.47	56.69	69.98	65.58	46.57
3	98.87	83.32	78.89	75.65	73.32	67.78	75.56	72.23	65.74
4	-	98.97	89.98	86.65	88.85	78.85	88.85	81.47	73.32
6	-	-	98.78	98.85	95.58	86.65	92.23	89.94	82.45
8	-	-	-	-	99.83	98.78	99.78	94.47	86.45
12	-	-	-	-	-	-	-	99.86	90.65

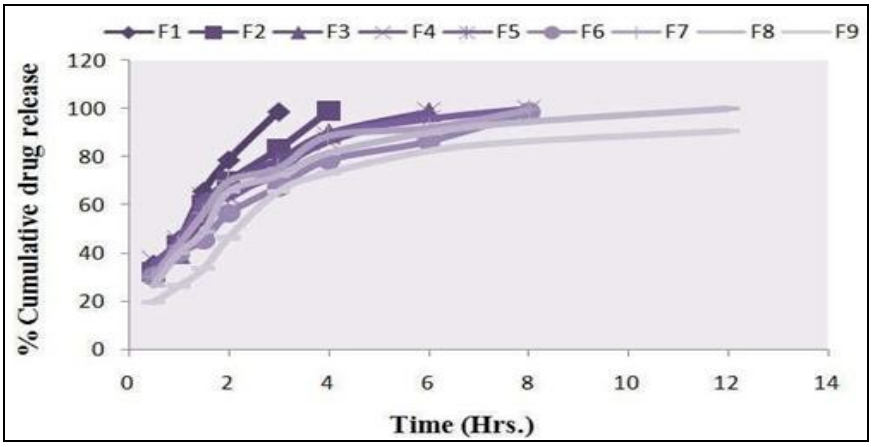

FIG. 3: *IN-VITRO* DRUG RELEASE STUDY OF MATRIX TABLETS 7.3.2 RELEASE KINETICS OF METRONIDAZOLE MATRIX TABLETS

TABLE 8: *IN-VITRO* DRUG RELEASE DATA FOR OPTIMIZED FORMULATION F8

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative* % Drug Release	Log Cumulativee % Drug Release	Cumulativee % Drug Remaining	Log Cumulative e % Drug Remaining
0.5	0.707	-0.301	26.65	1.426	73.35	1.865
1	1.000	0.000	39.95	1.602	60.05	1.779

1.5	1.225	0.176	48.78	1.688	51.22	1.709
2	1.414	0.301	65.58	1.817	34.42	1.537
3	1.732	0.477	72.23	1.859	27.77	1.444
4	2.000	0.602	81.47	1.911	18.53	1.268
6	2.449	0.778	89.94	1.954	10.06	1.003
8	2.828	0.903	94.47	1.975	5.53	0.743
12	3.464	1.079	99.86	1.999	0.14	-0.854

Batch	Zero Order	First Order	Higuchi	Korsmeyer Peppas
	R^2	R^2	R^2	R^2
F8	0.758	0.937	0.897	0.937

When the regression coefficient values of were compared, it was observed that 'r^2' values of first order was maximum i.e., 0.937 hence indicating drug release from formulations was found to follow first order release kinetics.

CONCLUSION: The matrix tablets of Metronidazole were successfully prepared by direct compression method using gaur gum as natural polymer and confirmed that it is a best method for preparing Metronidazole tablets.

The formulation F-8 of matrix tablets showed better release rate compare to other formulations. The *in-vitro* dissolution studies showed that Metronidazole tablets formulation F8 showed better sustained effect over a period of 12 hours than matrix formulations.

ACKNOWLEDGEMENT: We would like to acknowledge and express our obligations to Sagar Institute of Pharmacy and Technology for providing research facility to carry out this work.

Ethics Approval and Consent to Participate: Not applicable

Consent for Publication: Not applicable

Funding: None

CONFLICT OF INTEREST: The authors declare no conflict of interest, financial or otherwise.

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How to cite this article:
Shah RK and Patel G: Formulation and evaluation of Sustined release matrix tablet of Metronidazole. Int J Pharm Sci & Res 2023; 14(12): 6029-37. doi: 10.13040/IJPSR.0975-8232.14(12).6029-37.