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FORMULATION, *IN VITRO* BIOEQUIVALANECE AND STABILITY STUDIES OF METRONIDAZOLE SUSTAINED RELEASE TABLETS

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ABSTRACT

The aim of the study was to develop sustained release tablets of Metronidazole using HPMC K_4M, HPMC K100 and Eudragit S100 as polymers. Metronidazole is used for the treatment of amoebiasis and bacterial infections. The tablets were prepared by using direct compression method. The prepared tablets were evaluated in the terms of their precompression studies, hardness test, thickness test, weight variation test, friability test, *invitro* study and stability studies. The results of the study showed that formulation FMSR-7 is best compared with other formulations. The most satisfactory formulation was compared with marketed sample and also stable during stability studies conducted for 60 days as per ICH guidelines. The bioequivalence study result was showed FMSR-7 formulation is best. It showed no significant changes in the physicochemical parameters and *in vitro* release of drug.

KEYWORDS

Metronidazole, Different Polymers, Direct compression method, Bioequivalence studies and Stability Studies.

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INTRODUCTION

The oral drug administration is desirable but challenging owing to the nature of the gastrointestinal tract. The sustained release drug delivery system is most suitable for oral dosage forms. The oral sustained release dosage form by direct compression technique is a very simple approach in the pharmaceutical area for its ease, compliance, faster production, avoids hydrolytic or oxidative reactions occurred during processing of

dosage forms and also economics. Sustained or controlled drug delivery occurs while a drug embedded within a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and released drug at constant rate for desired time period[1].

Metronidazole is chemically 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole, had especially high activity *in vitro* and *in vivo* against the anaerobic protozoa *T.vaginalis* and *E.histolytica*. Metronidazole is clinically effective in trichomoniasis, amebiasis including amebic colitis and amebic liver abscess and giardiasis as well as in a variety of infections caused by obligate anaerobic bacteria[2]. The recommended dose is 500 to 750 mg metronidazole taken orally three times daily for 7 to 10 days. The daily dose for children is 35 to 50 mg/kg given in three divided doses for 7 to 10 days. While standard recommendations are for 7 to 10 days' duration of therapy, amebic liver abscess has been treated successfully by short courses (2.4 g daily as a single oral dose for 2 days) of metronidazole[3].

MATERIAL AND METHODS

Material

Metronidazole was obtained from JB Chemicals Ltd, India. HPMC K_4M, HPMC K100 and Eudragit S100 were gifted from Apex Pharmaceutical Pvt. Ltd, Chennai. Di basic calcium phosphate, Talc and Magnesium Stearate were purchased from Qualigens fine chemicals, Mumbai, India. All other chemicals and ingredients were used for study are of Analytical grade.

Method

Preparation of Metronidazole sustained release tablets

The composition of different formulations of metronidazole SR matrix tablets is shown in Table No.1. Different tablet formulations were prepared by direct compression technique. All the powders passed through 40/60 mesh sieve. The required quantity of pure drug, various polymers and other ingredients were mixed thoroughly. Talc and magnesium stearate were finally added as a glidant and lubricant respectively. The blend was directly compressed (10 mm diameter, round flat faced punches) using multiple punch tablet compression machine (Cad mach Machinery Ltd., Ahmedabad, India). Each tablet contained 400 mg of metronidazole[1].

EVALUATION PARAMETERS[1, 4-6]

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

The Fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using BOMEN MB SERIES FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR spectroscopy.

Pre-compression studies of tablet powder

Bulk density

3gm of powder were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated bulk density according to the formula

Formula

Bulk density = Mass / Volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of powder and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the powder in the cylinder and this minimum volume, the tapped density may be computed.

Formula

Tapped density = Weight of Powder/ Tapped volume of Powder

Angle of Repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method

used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal.

Formula

$$\theta = \mathbf{Tan^{-1}\ (h/r)}$$

Where,

θ = Angle of repose,

h = Height of the powder cone,

r = Radius of the powder cone.

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density.

The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where,

TD = Tapped density

BD = Bulk density.

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder.

Formula

Hausner's Ratio = Tapped density/Bulk density

Post compression studies of Metronidazole tablets

Hardness or Crushing strength Test

Hardness of the tablet was determined using the Monsanto hardness tester (The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets have a hardness of 3 kg and some sustained release tablets have a hardness of 10 -20 kg[6].

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Venire caliper and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \text{ X } 100$$

Where,

I - Initial weight

F - Final weight

Weight variation test

Weights of 20 individual tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula,

$$\text{Percentage deviation} = [X\text{-}X^{*}/\ X] \times 100$$

X - Actual weight of the tablet

X^{*}- Average weight of the tablet.

Estimation of Drug Content

An accurately weighed amount of powdered Metronidazole (100 mg) was extracted with water and the solution was filtered through 0.45µ membrane filter paper. The absorbance was measured at 320 nm after suitable dilution.

Calculation

The amount of Metronidazole present in tablet can be calculated using the formula

$$A_t/As \text{ x } S_w/100 \text{ x } 100$$

Where,

A_t = Absorbance of sample preparation

A_s = Absorbance of Standard preparation

S_w = weight at Metronidazole working standard (mg).

***In vitro* drug release studies**

The dissolution was carried out using paddle type dissolution apparatus (USP dissolution testing

apparatus II); freshly prepared 0.1N Hcl (pH 1.2) (900 ml) was placed in dissolution flask and allowed to obtain temperature at 37±0.5°C and 100 rpm for first 2 h. Then replaced with 6.8 pH phosphate buffer and continued for 10 h. Aliquot volume of 10 ml was withdrawn at regular intervals and replaced with fresh buffer diluted. The samples were replaced with fresh dissolution medium. After filtration, the sample is measured the absorbance at 320 nm by using UV Spectrometer. The dissolution data obtained were plotted as percentage drug release versus time.

Bioequivalence studies

The bioequivalence study (FMSR-7 and METROGYL SR TAB) was carried out for 12 hours using USP paddle type dissolution apparatus in 0.1N Hcl (pH 1.2) (900 ml) was placed in dissolution flask and allowed to obtain temperature at 37±0.5°C and 100 rpm for first 2 h and phosphate buffer (pH 6.8) at 100 rpms maintaining temperature at 37 ± 0.5^0C for first 10 h. A 10ml samples were collected from each vessel at 0, 2, 4, 6, 8, 10 and 12 hours and analyzed by UV spectrophotometer at 320 nm. The withdrawn sample was immediately replaced by equal volume of fresh buffer. The dissolution data obtained were plotted as percentage drug release versus time.

Stability Studies

To assess the drug and formulation stability, the stability studies were carried out of the most satisfactory formulation (FMSR-7) as per ICH guidelines. The formulation is sealed in aluminum packaging and kept in humidity chamber maintained at 30 ± 2 °C /65 ± 5% RH and 40 ± 2 °C / 75 ± 5 % RH for 60 days. At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution, and other physicochemical parameters.

RESULTS AND DISSCUSION

Pre formulation studies

Compatability studies (Fourier Transform Infrared Spectroscopic studies)

The fourier transform infra-red analysis was conducted for the surface structure characterization. FTIR spectrum of the formulated tablets, pure drug and different polymers was recorded. The tablets were taken in a KBr pellet by using BOMEN MB SERIES FTIR instrument. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the different polymers and pure drug. Then all the functional groups are found in the IR spectrum of pure drug and different polymers.

Precompression studies of powders

Bulk density

The packing properties of the drugs and their formulations widely depend upon bulk density. It has been stated that bulk density values less than 1.2gm/cm^3 indicate good flow and values greater than 1.5 gm/cm^3 indicate poor flow. From the results it can be seen that the bulk density values are less than 1.2gm/cm^3. This indicates good flow characteristics of the powders. Values showed Table No.2.

Tapped density

From the results it can be seen that the Tapped density values indicate good flow characteristics of the powders. Values showed Table No.2.

Angle of Repose

Angle of repose is less than or equal to 40° indicates free flowing properties of the powders. However angle of repose is greater than 40° indicates poor flow of material. It can be observed that the angle of repose for various batches of the powders is found to be less than 40^0, it indicates good flow properties of the powders. Values showed Table No.2.

Compressibility Index or Carr's Index

Carr's Index is less than or equal to <10 indicates free flowing properties of the powders. However Carr's Index is greater than <10 indicates poor flow of material. It can be observed that the Carr's Index for various batches of the powders is found to be less than >10; it indicates good flow properties of the powders. Values showed Table No.2.

Hausner's Ratio

Hausner's Ratio is less than or equal to 1.024 indicates free flowing properties of the powders. However Hausner's Ratio is greater than 1.35 indicates poor flow of material. It can be observed that the Hausner's Ratio for various batches of the powders is found to be less than 1.35; it indicates

good flow properties of the powders. Values showed Table No.2.

Postcompression studies

Hardness Test

The hardness of the tablet various batches were determined. The various batches of the tablets of hardness values are found within limits and it indicates good strength of the tablets. Values showed Table No.3.

Thickness Test

The thicknesses of tablets were almost uniform in the all formulations and were found to be in the range of 0.54mm. Values showed Table No.3.

Friability Test

The tablets friability values are found to be less than 1% in all cases and considered to be satisfactory. Values showed Table No.3.

Weight variation test

All this tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weight of the all tablets was found to be uniform with low standard deviation values. Values showed Table No.3.

Estimation of Drug Content

Drug content of all the batches are within the acceptable range which shows the proper mixing of the drug and excipients. Values showed Table No.3.

***In vitro* drug release studies**

Among all the batches FMSR-7 formulation showed the better *invitro* release of drug (Table No.4 and Figure No.1 (a and b)).

Bioequivalence studies

The bioequivalence study was done with best formulation (FMSR-7) and marketed sample (METROGYL) Table No.5.

Stability Studies

Stability studies were carried out of the most satisfactory formulation FMSR-7 at 30 ± 2°C / 65 ± 5 % RH and 40 ± 2°C / 75 ± 5 % RH for two months as per ICH guidelines. At various time intervals of 30 days and 60 days end, samples were evaluated. There was no major change in the various physicochemical parameters evaluated Table No.6.

Table No.1: Formulation of different batches of Metronidazole sustained release tablets

S.No	Ingredients	FMSR-1	FMSR-2	FMSR-3	FMSR-4	FMSR-5	FMSR-6	FMSR-7
1	Metronidazole	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
2	HPMC K_4M	180 mg	-	-	90 mg	-	90 mg	60 mg
3	HPMC K100M	-	180 mg	-	90 mg	90 mg	-	60 mg
4	Eudragit S100	-	-	180 mg	-	90 mg	90 mg	60 mg
5	Di basic calcium phosphate	140 mg	140 mg	140 mg	140 mg	140 mg	140 mg	140 mg
6	Talc	15mg	15mg	15mg	15mg	15mg	15mg	15mg
7	Magnesium stearate	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg

Total weight of the tablet – 750mg/Tab

Table No.2: Precompression studies of powders

S.No	Formulations	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Angle of Repose (θ)	Carr's Index (%)	Hausner's Ratio
1	FMSR-1	0.709	0.728	31.05	2.60	1.026
2	FMSR-2	0.700	0.717	31.07	2.37	1.024
3	FMSR-3	0.694	0.711	30.09	2.39	1.024
4	FMSR-4	0.707	0.728	32.12	2.88	1.029
5	FMSR-5	0.697	0.721	32.54	3.32	1.034
6	FMSR-6	0.691	0.715	31.68	3.35	1.034
7	FMSR-7	0.684	0.714	30.24	4.20	1.043

Table No.3: Postcompression studies of Metronidazole sustained release tablets

S.No	Formulations	Hardness Test (kg/cm)	Thickness Test (cm)	Friability Test (%)	% of Weight variation test	Estimation of Drug Content
1	FMSR-1	12.5	0.54	0.533	99.5	98.2
2	FMSR-2	12.3	0.54	0.533	99.4	98.2
3	FMSR-3	12.3	0.54	0.533	99.4	98.2
4	FMSR-4	12.5	0.54	0.466	99.2	98.8
5	FMSR-5	12.4	0.54	0.466	99.2	98.7
6	FMSR-6	12.3	0.54	0.466	99.2	98.8
7	FMSR-7	12.3	0.54	0.4	99.7	99.5

Table No.4: Comparative dissolution study of Metronidazole sustained release tablets

S.No	Time (hrs)	% of drug release (FMSR-1)	% of drug release (FMSR-2)	% of drug release (FMSR-3)	% of drug release (FMSR-4)	% of drug release (FMSR-5)	% of drug release (FMSR-6)	% of drug release (FMSR-7)
1	0	00.00	00.00	00.00	00.00	00.00	00.00	00.00
2	2	12.08	12.23	12.54	15.62	14.92	14.58	16.37
3	4	25.12	25.56	25.82	29.24	28.72	28.25	34.06
4	6	38.35	38.76	39.74	43.82	42.16	41.58	48.25
5	8	52.74	53.18	53.75	59.58	58.65	58.24	67.12
6	10	65.53	65.86	67.06	74.12	73.35	73.02	81.53
7	12	78.65	79.25	80.84	83.72	83.24	82.83	96.45

Table No.5: Comparative dissolution study of Metronidazole sustained release tablet (FMSR-7) and Marketed Sample (METROGYL)

S.No	Time (hrs)	% of drug release (FMSR-7)	Marketed Sample (METROGYL)
1	0	00.00	00.00
2	2	16.37	15.62
3	4	34.06	32.87
4	6	48.25	46.92
5	8	67.12	66.05
6	10	81.53	80.24
7	12	96.45	95.12

Table No.6: Stability studies of Metronidazole sustained release tablets (FMSR-7)

S.No	Time (hrs)	After 30 days		After 60 days	
		30±2°C /65±5% RH	40±2°C /75±5% RH	30±2°C /65±5% RH	40±2°C /75±5% RH
1	0	00.00	00.00	00.00	00.00
2	2	16.37	16.37	16.15	16.10
3	4	34.06	34.06	33.87	33.75
4	6	48.25	48.25	48.02	47.91
5	8	67.12	67.12	66.94	66.82
6	10	81.53	81.53	81.24	81.03
7	12	96.45	96.45	96.30	96.12

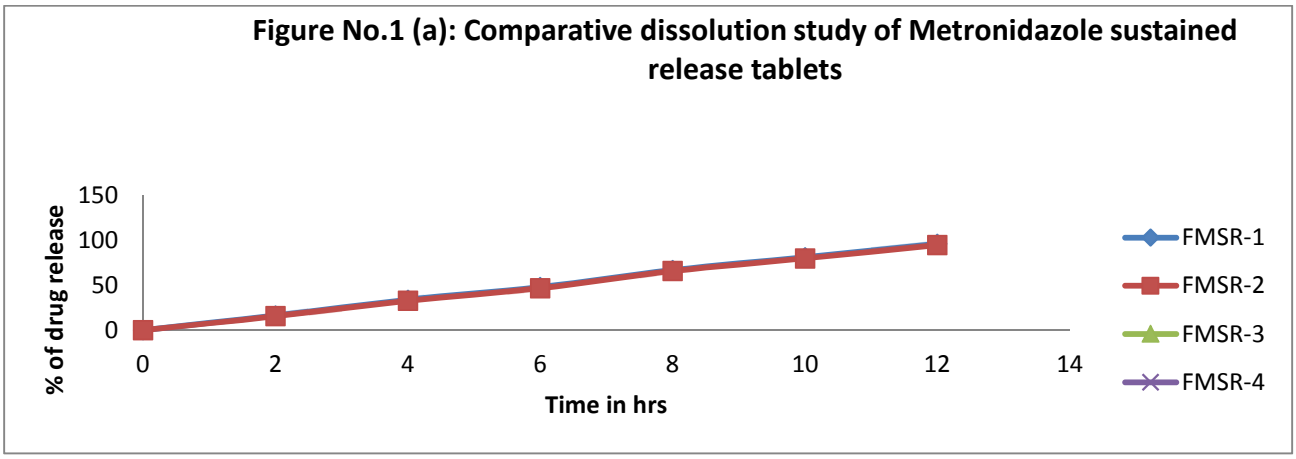

Figure No.1 (a): Comparative dissolution study of Metronidazole sustained release tablets

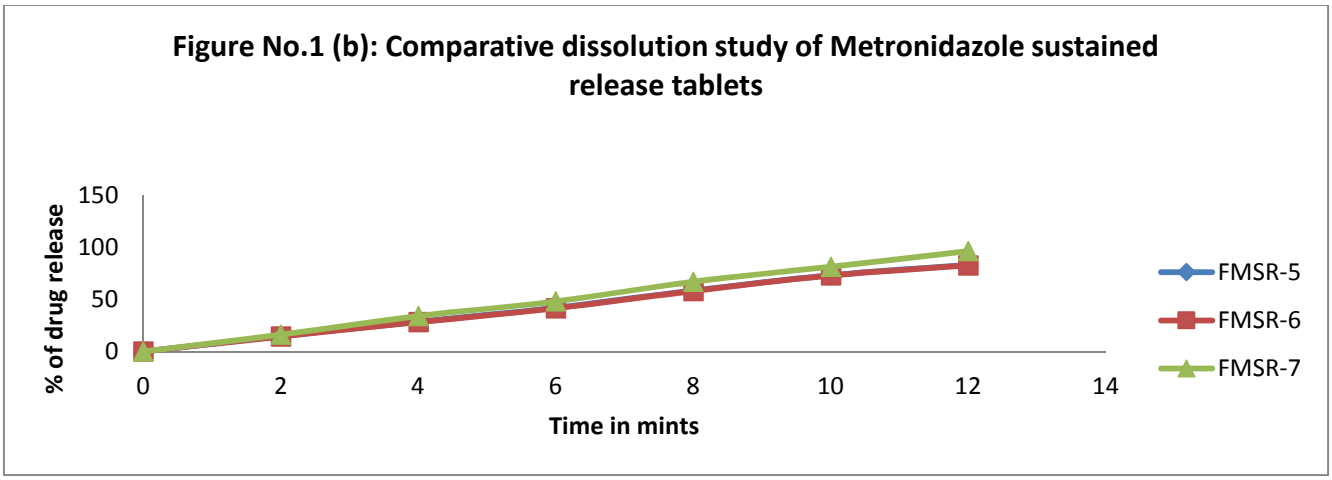

Figure No.1 (b): Comparative dissolution study of Metronidazole sustained release tablets

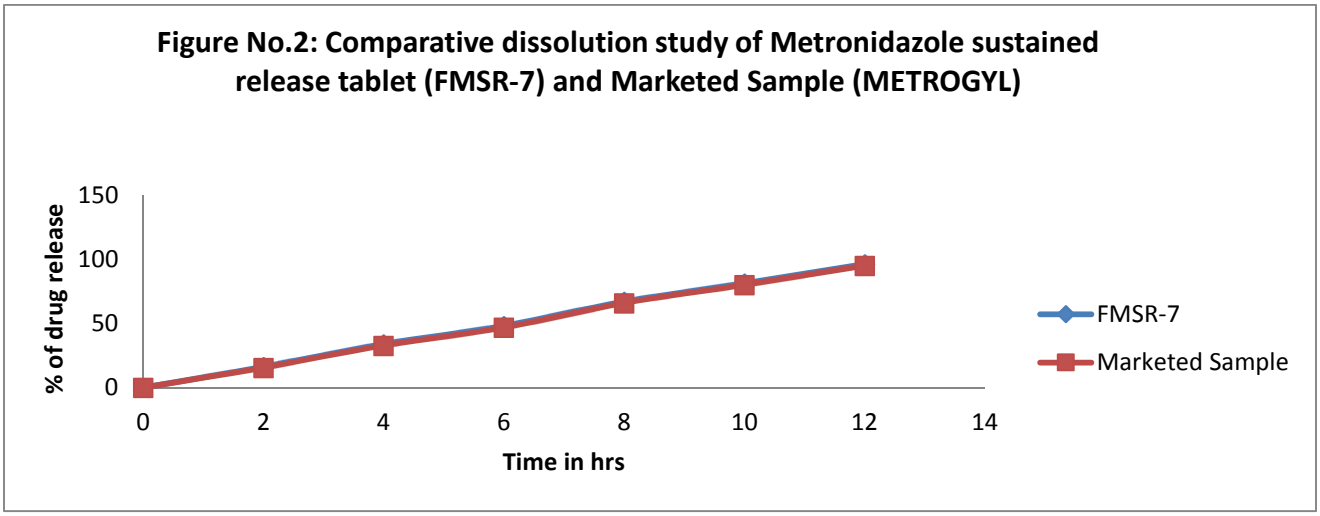

Figure No.2: Comparative dissolution study of Metronidazole sustained release tablet (FMSR-7) and Marketed Sample (METROGYL)

CONCLUSION

The present study was developed in the sustained release tablets of Metronidazole. The tablets possessed the required physicochemical parameters such as hardness, thickness, friability, weight variation, estimation of drug content. The *in vitro* drug release showed best formulation is FMSR-7 compared all. The most satisfactory formulation (FMSR-7) has compared with marketed sample. From that the result showed the formulation FMSR-7 is best when compared to marketed sample. The stability studies were done for best formulation. The results showed no significant change in physicochemical properties, drug content, *in vitro* dissolution pattern after storage at 30 ± 2 °C / 65 ± 5 % RH and at 40 ± 2 °C /75 ± 5 % RH during stability studies for two months. Therefore, it was concluded that the most satisfactory formulation (FMSR-7).

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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