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Formulation and Bioequivalence Evaluation of Extended Release Solid Drug Delivery System for Metronidazole Using Eudragit NM30D and Methocel Premium K4M as Retardant Material

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ABSTRACT

A conventional dosage form of Metronidazole produce a drug blood level time profile which does not maintain within the therapeutic range for extended period of time. In the present study, an attempt was made to develop an extended release Metronidazole composition that will be capable of delivering acceptable bioavailability for up to 24 hours. Extended release formulations of Metronidazole were prepared using various proportions of Eudragit NM30D and Methocel Premium K4M, separately through wet granulation. Eudragit NM30D and Methocel Premium K4M were used as retardant material. Three formulations (U-1 to U-3) were developed using Eudragit NM30D and while another five (M-1 to M-5) using Methocel Premium K4M. The granules for tabletting were evaluated for moisture content, compressibility index and angle of repose etc. Tablets were subjected to thickness, hardness, friability and *in vitro* release studies. Dissolution study of the formulated tablet matrices were carried out in 0.1 N Hydrochloric acidfor 24 hours period. Dissolution profiles were then compared with innovator's drug Flagyl ER in term of difference factor (f_1) and similarity factor (f_2). It was observed that, formulation U-1, U-2, M-2, M-3, M-4 meet the specification of bioequibalance with Flagyl ER. Among them, M-3 showed the highest similarity and lowest difference factor. It is evident from the study that, formulation M-3 posses all the required characteristics to provide an extended release Metronidazole composition that will be stable enough and capable of delivering acceptable bioavailability for up to 24 hours.

Keywords: Retardant material, Eudragit NM30D, Methocel Premium K4M, Metronidazole.

INTRODUCTION

Metronidazole (2-methyl-5-nitroimi-dazole-1-ethanol) is an oral synthetic nitroimidazole antibiotic medication used for the treatment of infections caused by anaerobic bacteria and protozoa[1]. It is an antibiotic, amebicide, and antiprotozoal[2]. In the past several matrix-type and polymeric-coated Metronidazole formulations has been widely investigated[3] because it has a short plasma elimination half life ranging from 6 to 7 hours. A wide range of controlled release matrices have been developed based on hydrophilic polymers such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), sodium alginate, chitosan and xanthan gum[4-7]. In the present study, an attempt was made to develop an extended release Metronidazole composition that will be capable of delivering acceptable bioavailability for up to 24 hours. For this purposeEudragit NM30D and Methocel Premium K4M were used as retardant material. Using various proportions of Eudragit NM30D and Methocel Premium K4M, extended release formulations of Metronidazole were prepared separately through wet granulation. The technology of polymeric drug delivery has been studied in details over the past 30 years and numerous excellent reviews are available[8-10].The three key advantages that polymeric drug delivery products can offer are localized, extended delivery and stabilization of the drug. Several reviews have been presented on the mechanisms and the mathematical aspects of release of drugs from polymer matrices[11-13]. For a given drug, the release kinetics from the polymer matrix is governed predominantly by three factors the polymer type, polymer morphology and the excipients present in the system. The mechanisms of drug release from various polymeric matrix systems have been extensively discussed[14,15]. The diffusion of drug molecules to & from the matrix across the hydrodynamic diffusion layer may be treated as one-dimensional diffusion to a plane surface[16]. Eudragit NM30D gives time controlled release and p^H independent dissolution, makes it suitable for extended release Metronidazole tablet. On the other hand, Methocel Premium K4M showed better release retardant effect for controlled release of tablet[17]. The objective of this study was to prepare an extended release Metronidazole tablet which will sustain bioavailability of the drug for up to 24 hours.

MATERIALS AND METHODS

Materials used for Metronidazole Extended Release tablet

Metronidazole was used as the active material for preparing Metronidazole extended release tablet. The active ingredient, rate -retarding polymer and other excipients are shown in the Table 1.

Preparation of extended release Metro-nidazole tablet using Eudragit NM30D as matrix forming agent

Formula U-1, U-2 and U-3 were proposed for preparation of Metronidazole extended release formulation uses Eudragit NM30D as release retardant and matrix forming agent (Table 2).

Granulation

First portion of the Lactose Monohydrate BP and Metronidazole BP were loaded in a poly bag and then passed through a 500 micron sieve. Granules were dry mixed for one minute. Purified Talc (after sieving

through 500 micron screen) was added with Eudragit NM30D and Dimethicone in a beaker. Purified water was added in the beaker and stirrer for about 15 minutes to prepare slurry. This slurry was then mixed with already mixed Metronidazole BP and Lactose Monohydrate BP. These materials were mixed until getting satisfactory mass. Then the materials were loaded into tray dryer and dried at 70°C to get moisture content bellow 2-3%. 4/5 portion of the granules were passed 25 mesh (710 micron) screen and rest of the material were passed through 18 mesh (1 mm) screen and loaded into a poly bag. Second portion of the Lactose Monohydrate BP and Metronidazole BP and Colloidal Anhydrous Silica (Aerosil-200) were sieved through 500 micron screen, added in the poly bag and blended for 1 minute. Finally Magnesium Stearate BP was added with the granules and again blended for 1 minute.

Compression

Previously prepared granules were compressed for desired tablet with specific weight (1000mg ± 3%), shape (caplet) and hardness (above 5Kp). For this purpose ERWEKA TR-16 compression machine was set with 19 X 9.208 mm caplet shaped punch and die set.

Preparation of extended release Metronidazole Tablet using Methocel Premium K4M as matrix forming agent

Formula M-1, M-2, M-3, M-4 and M-5 were proposed for preparation of Metronidazole extended release formulation uses Methocel Premium K4M as release retardant and matrix forming agent (Table 3).

Granulation

Lactose Monohydrate BP, Methocel Premium K4M and Metronidazole BP were taken in a poly bag and then passed through a 500 micron sieve and loaded in RMG. Granuleswere dry mixed for one minute. Purified water was added and mixed until getting satisfactory mass. Then the materials were loaded into FBD and dried at 70°C to get moisture content bellow 1.5-2%. One third portion (1/3) of the granules were passed 12 mesh (1.7 mm) screen and rest of the material were passed through 18 mesh (1 mm) screen and loaded into a poly bag. Colloidal Anhydrous Silica (Aerosil-200) was sieved through 500 micron screen, added in the poly bag and blended for 1 minute. Finally Magnesium Stearate BP was added with the granules and again blended for 1 minute.

Compression

Previously prepared granules were compressed for desired tablet with specific weight (1100mg ± 3%), shape (caplet) and hardness (above 5Kp).For this purpose, ERWEKA TR-16 compression machine was set with 19 X 9.208 mm caplet shaped punch and die set.

Evaluation of granules

The granuleswere evaluatedin accordance with USP Pharmacopoeia (USP30-NF25) for moisture content, compressibility index and angle of repose.

Moisture content

Moisture content (MC) of the granule was determined using Halogen moisture analyzer. For that purpose 1 g of the granules was put into the drying chamber of the moisture analyzer and dried at constant temperature until constant weight is observed. The MC was deduced as difference between the initial (W_o) and final weight (W_f) of the granules, expressed as a percentage and calculated as $MC= \{(W_o-W_f) / W_o\} X 100$.

Compressibility index

A quantity of 5 g of powder from each formula, previously lightly shaken to break

any agglomerates formed, was introduced into a Pharmatest Densitometer (Germany) with 50 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2 cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. Using the following equation LBD and TBD was calculated as LBD = weight of the powder / volume of the packing and TBD = weight of the powder / tapped volume of the packing. The compressibility index of the granules was determined by Carr's compressibility index as Carr's Index (%) = {(TBD – LBD) x 100} / TBD.

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and the angle of repose was calculated as Angle of Repose, $\theta = \tan^{-1} h/r$, where, h = height of the powder cone and r = radius of the powder cone.

Evaluation of tablets

All parameters for evaluating tablets have been donein accordance with USP Pharmacopoeia (USP30-NF25).

Hardness

Five tablets of each of the formulations were taken and hardness was measured by hardness tester (Sotax HT10, Switzerland). The average value was calculated and the testing unit was Kilopond (Kp).

Thickness

Six tablets of each of the formulations were taken and thickness was measured by thickness tester (Sotax HT10, Switzerland). The values were reported in millimeter (mm).

Friability

Ten tablets of each of the formulations were weighed out and taken into the rotating disk of a friability tester (Pharmatest, Germany). It was allowed to rotate at 25 rpm for 4 minutes (100 revolutions). At the end of the rotation, tablets were collected, dedusted and reweighed. The friability was calculated as the percent of weight loss. Friability = (Weight Loss/ Initial Weight) X 100.

Drug content assay

Tablets (20) were weighed and powdered. A quantity of powder containing 0.2 gm of Metronidazole was transferred to a sintered glass crucible and extract with six 10 ml quantities of hot acetone. Cool, add to the combined extracts 50 ml of acetic anhydride and 0.1 ml of a 1% w/v solution of brilliant green in anhydrous acetic acid and titrate with 0.1 M perchloric acid VS to a yellowish-green end point. Operation was repeated without powdered tablets. The difference between the titrations represents the amount of perchloric acid required. Each ml of 0.1 m perchloric acid VS is equivalent to 17.12 mg of Metronidazole. Calculation = {(Titrate volume X Factor X Eq. Wt. X Average Wt.) / Sample wt in mg} mg.

In vitro dissolution study of Metronidazole extended release tablets

Dissolution test

The rotating paddle method consists of a paddle held by a motor shaft. The sinker is used to hold the sample immersed into the dissolution medium. The entire flask is immersed in a constant temperature bath set

at 37°C. The temperature range is maintained at 37°C ± 0.5°C. The rotating speed and the position of the basket must meet specific requirements set forth in the USP30-NF25.

Dissolution medium

All dissolution studies were carried out for extended release Metronidazole formulations according to USP II. Hydrochloric acid (0.1N HCl) was used as dissolution medium. The amount of drug dissolved in the medium was determined by UV spectrophotometer at 278 nm.

Standard solution preparation

Metronidazole WS (44.50 mg) was weighed accurately in a volumetric flask. 50-60 ml of 0.1N HClwas added and sonicated it in ultrasonic bath for 10 minutes to dissolve and make volume with the same and mixed. 2 ml of this solution was diluted to 50 ml with the 0.1N HCl and mixed.

Sample solution preparation

Dissolution medium (900 ml) was taken into 6 vessels each and maintained temperature 37±0.5°C. One tablet was placed in 6 individual vessels. To exclude air bubbles from the surface of the tablet care was taken, immediately operate the apparatus at 100 rpm. 5 ml from each vessel was pipetted at 1st 2nd, 4th, 6th, 8th 10th and 12th hours from starting time and each time solution were replaced with fresh medium.

Data analysis

To analyze the data model independent method i.e., similarity factor (f_2) and difference factor (f_1) were used to compare the release profile of proposed formulations with the patent drug Flagyl ER (750 mg) tablet.

RESULTS AND DISCUSSION

The present study was designed to develop extended release tablets of Metronidazole by using Eudragit NM30D and Methocel Premium K4M as rate retarding factor separately by wet granulation method. Eudragit NM30D was used in the proposed formulations (U-1 to U-3) and Methocel Premium K4M in (M-1 to M-5) in order to evaluate the amount of polymer required to provide desired release rate for 24 hours period. The granules of proposed formulations were evaluated for moisture content, angle of repose; compressibility index and drug content (Table 4).

Evaluation of granules

Moisture content

Moisture content of the granules for formulation U-1 to U-3 ranged from 2.32 to 2.87 and for formulation M-1 to M-5 ranged from 1.63% to 1.85%.

Angles of repose

The results of angles of repose of proposed formulations ranged from 19.64±0.02 (°) to 23.15 ± 0.03 (°) (Table 4).

Compressibility index (%)

The results of compressibility index (%) of proposed formulations ranged from 14.55±0.02 to 20.34 ± 0.04 (Table 4).

Drug content

The drug content in a weighed amount of all formulations ranged from 99.14% to 100.21%. All these results indicate that the granules possess satisfactory flow properties, compressibility and drug content (Table 4).

Evaluation of tablet

The tablets of the proposed formulations (U-1 to U-3 and M-1 to M-5) were subjected to various evaluation tests such as thickness, hardness, weight variation test and friability test and drug content (Table 5).

Thickness

The thickness of the tablets for formulation U-1 to U-3 ranged from 6.50 ± 0.05 to 6.66 ± 0.07 and for formulation M-1 to M-5 ranged from 6.83±0.03 to 6.95±0.02 (Table 5).

Hardness

Hardness of the tablet of proposed formulations was ranged from 6.1±0.15 to 13.9 ± 0.15 (Table 5).

Friability

Friability of the tablet of proposed formulations was ranged from 0.20 ± 0.01% to 0.53 ± 0.02% (Table 5).

Weight variation

Weight variation of tablet in each formula were within pharmacopoeial limit and for formulation U-1 to U-3 were ranged from 1.08 ± 0.05% to 1.30 ± 0.02 % and for formulation M-1 to M-5 were 1.15 ± 0.07% to 2.10 ± 0.03 % (Table 5).

Drug content

The drug content in a weighed amount of all formulations ranged from 99.09 ± 0.01 % to 100.77±0.10% (Table 5). Drug content among tablets from all formulations meets the Pharmacopoeial specification (USP30-NF25). Good uniformity in drug content among different batches of the tablets was found and the percentage of drug content was more than 99%. In this study, the percentage friability for all the formulations was below 1%, indicating that the friability was within the limits (USP30-NF25).

Bioequivalence study

The release rate of formulations were compared with the innovator's drug Flagyl ER tablet in terms of difference factor (f_1) and similarity factor (f_2) (Figure 1 and 2)[18]. For this purpose Flagyl ER worldwide brand product of Pfizer, was collected from market and dissolution of this was studied for 24 hours. Here the release of Flagyl ER treated as reference standard. Difference factor (f_1) and similarity factor (f_2) are summarized in Table 6. Here, to compare the release kinetics of proposed Metronidazole ER tablets with Flagyl ER tablet approaches were used including model independent method of the difference factor (f_1) and similarity factor (f_2).Among all the proposed formulation U-2 and M-3 showed better dissolution rate (Figure 1 and 2), from which M-3 was suitable candidate for stability study as U-2 has poor hardness for blister packing. Moreover, in bioequivalence study M-3 showed more identical release pattern in term of difference factor (f_1) and similarity factor (f_2) than U-2.

Effect of Eudragit NM30D on release pattern of Metronidazole BP from matrix tablet

Different Eudragit NM30D matrix tablet containing Metronidazole BP as active ingredient having Eudragit NM30D polymer 9 mg, 12 mg and 15 mg per tablet in the matrix tablet with the formulation code U-1, U-2 and U-3 were prepared to evaluate the effect of this polymer. After preparation according to formulation shown in the Table 2, their dissolution studies were carried out in paddle method (USP-II). Six tablets from each formulation were used in dissolution study. The release profile of Metronidazole was monitored up to 24 hours. Korsmeyer release pattern has been obtained by plotting log cumulative percent drug release vs log time (Figure 3 and Table 7). The total % of Metronidazole release from the formulation U-1, U-2 and U-3 was 98.63% 94.12% and 77.56% respectively. It has been observed that the release rate has been extended with the increase of polymer % and with the decrease of lactose %. The highest percent of drug release within 24 hours is obtained from U-1 where polymer content is 9 mg tablet. But in U-3, the polymer content is 15 mg per

tablet andthe release of drug is controlled with 77.56% within 24 hours.

Effect of Methocel Premium K4M on release pattern of Metronidazole from matrix tablet

For this experiment, formulation M-1, M-2, M-3, M-4 and M-5were prepared containing Metronidazole as active ingredient having Methocel Premium K4M polymer 30 mg, 35 mg, 38.5 mg, 40 mg and 45 mg per tablet in the matrix. After preparation according to formulation shown in the Table 3, their dissolution studies were carried out in paddle method (USP-II). Korsmeyer release pattern has been obtained by plotting log cumulative percent drug release log of time (Figure 4 and Table 8). The total % of Metronidazole release from the formulation M-1, M-2, M-3, M-4 and M-5 were 98.96%, 99.00%, 98.63%, 94.11% and 60.98% respectively. It has been observed that the release rate has been extended with the increase of polymer % and with the decrease of lactose %. The highest percent of drug release within 24 hours is obtained from M-1 where polymer content is 30mg per tablet. But in M-5, the polymer content is 45 mg per tablet and the release of drug is controlled with 60.98% within 24 hours.

CONCLUSION

Extended release matrix tablets of Metronidazole were prepared successfully using Eudragit NM30D and Methocel Premium K4M as polymer which retard the release and achieve required dissolution profile. The types and amounts of pharmaceutical excipients in tablets were found to crucially control Metronidazole release characteristics. Release profiles of tablets change significantly with change of polymer content and polymer type. From the study it is evident that release of Metronidazole from Methocel Premium K4M matrices is more controlled than from Eudragit NM30D matrices. Results were also in favor of the formulations containing Methocel Premium K4M matrices in terms of hardness of the tablets which was too much poor for tablets containing Eudragit NM30D matrices for blister packing. *In vitro* bioequivalence studies revealed that dissolution profile is much more identical in case of Methocel Premium K4M matrices especially in case of proposed formulation M-3 in terms of difference factor (f_1) and similarity factor (f_2). So, from all concerns, from the study it is evident that proposed formulation M-3 posses all the required characteristics to provide an extended release Metronidazole composition that will be stable enough and capable of delivering acceptable bioavailability for up to 24 hours.

REFERENCES

1. Mourya DK, Malviya R, Bansal M, Sharma PK. Formulation and release characteristics of novel monolithic hydroxyl propyl methyl cellulose matrix tablets containing Metronidazole. *International J of pharma and bio sciences* 2010; 1 (3):3-4.
2. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC *et al.* Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infection Control and Hospital Epidemiology 2010; 31 (5): 431–55. doi: 10.1086/651706.
3. Robinson JR, Lee VHL. Controlled Drug Delivery Fundamentals and applications. 2nd ed. Lippincott Williams's publisher; 1994.
4. Dhopeshwarkar V, Zata J. Evaluation of xanthan gum in the preparation of sustained releasematrix tablets. *Drug*

Dev. and Ind. Pharm. 1993;19(9): 999-017. doi:10.3109/03639049309062997
5. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv Drug Deliv Rev*. 2001; 48(2-3): 139–57. PMID: 11369079
6. Davaran S, Rashidi MR, Khani A. Synthesis of chemically cross-linked hydroxypropyl methyl cellulose hydrogels and their application in controlled release of 5-amino salicylic acid. *Drug DevInd Pharm*. 2007; 33(8): 881–87.PMID: 17729106
7. Paul W, Sharma, CP. Chitosan, A drug carrier for the 21st century: a review. STP Pharma Sci. 2000; 10(1):5–22. INIST-CNRS, Cote *INIST*: 20449 A, 35400008626773.0010
8. Gombotz J, Nellore RV and Pettie K. Identification of critical formulation and processing variables for metoprolol tartarate extended release tablets. *J. Control Release*.1995; 59:327- 42. PMID: 10332064.
9. Sinha, VR and Khosla, L. Bioabsorbable polymers for implantable therapeutic systems. *Drug DevInd Pharm*. 1998; 24(12):1129-138. PMID:9876570.
10. Langer, R, Cima, LG, Tamada, JA and Wintermantel, E. Future directions in biomaterials.Biomaterials.1990;11(9): 738-45. PMID: 2090313.
11. Batycky, RP, Hanes, J, Langer, R, Edwardrs, DA.A theoretical model of erosion and macromolecular drug release from biodegrading microspheres. *J Pharm Sci.* 1997; 89(12): 1464-77.PMID: 9423163.
12. Brazel JG, Peck, GH and Peppas YT. Pharmaceutical granulation and tablet formulation using neural network in sustained release formulations. *J Control Release*.2000; 26(2): 211-15.
13. Comets, MF and Sannet, HJ. Implications of pharmaceutical science. *Drug Devind Pharm*. 2000; 21 (1): 119-155.
14. Higuchi, T. Mechanism of sustained action medication,theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci*.1963;52 (12): 1145-49. PMID: 14088963.
15. Roseman, TJ, Cardinelli N.F. Controlled release technologies. *J. Pharm Sci*. 1980; 59: 353.
16. Perkins, W.G. and Beageal, T.F. Biopharmaceutics of orally administered drugs. NewYork: *Ellis Horwood*; 1971; pp 72-73.
17. Islam MS, Haque T, Jahangir R, Fatema K, Vhuiyan MI, Biva IJ. *In vitro* Release Kinetic Study of Ciprofloxacin HCl from Methocel K15M CR, Methocel K4M CR and Methocel K4M Premium Matrix Tablets. *Stamford Journal of Pharmaceutical Science*.2009; 2(1):37-43.
18. Laila S, Haque T, Talukder MMU, Ahmed I, Islam MR, Rahman MH. Development of GlycerylMonostearate Based Ciprofloxacin Hydrochloride Sustained Release Matrix Tablet: an *In vitro* Study. *Dhaka University Journal of Pharmaceutical Science*.2009; 8(1): 81-88.

Table 1. List of polymers and other excipients used in preparation of matrix tablets

Name	Category	Source	Country of Origin
Metronidazole BP	Active	Alt Laboratory Limited	China
METHOCEL Premium K4M	Matrix forming agent	Colorcon Asia Pvt. Ltd	USA
Eudragit NM30D	Matrix forming agent	Evonik Rohm GmbH	Germany
Dimethicone	Antifoaming agent	Shenyang Jin Yi Lai Chemical Co. Ltd	China
Lactose Monohydrate BP	Filler	Foremost Farms	USA
Purified Talc BP	Lubricant	Merek	Germany
Colloidal Anhydrous Silica BP (Aerosil-200)	Glidant	Evonik Industries	Belgium
Magnesium stearate BP	Antiadherent	Peter Greven	Netherland

Table 2. Formulation for Metronidazole extended release tablet having Eudragit NM30D matrices

Name of materials	Quantity per tablet (mg/tablet)		
	U-1	U-2	U-3
Metronidazole BP	600	600	600
Lactose monohydrate BP	61.65	58.65	55.65
Eudragit NM30D	0.03ml (9mg)	0.04ml (12mg)	0.05ml (15mg)
Dimethicone	0.3	0.3	0.3
Purified Talc	6	6	6
Metronidazole BP	150	150	150
Lactose monohydrate BP	170	170	170
Magnesium Stearate BP	2.05	2.05	2.05
Colloidal Anhydrous silica BP	1	1	1

Eudragit NM30D contain 30% solid as w/v.

Table 3. Formulation for Metronidazole extended release tablet having Methocel Premium K4M matrices

Name of materials	Quantity per tablet (mg/tablet)				
	M-1	M-2	M-3	M-4	M-5
Metronidazole BP	750	750	750	750	750
Lactose monohydrate BP	314.85	309.85	306.35	304.85	299.85
Methocel Premium K4M	30	35	38.5	40	45
Colloidal Anhydrous silica BP	2.75	2.75	2.75	2.75	2.75
Magnesium Stearate BP	2.4	2.4	2.4	2.4	2.4

Table 4. Properties of granules of Metronidazole containing Eudragit NM30D and Methocel Premium K4M as release retardant

Formulations	Angle of Repose	Compressibility Index (%)	Drug Content (average) (%)
U-1	23.15±0.03	15.25 ±0.01	99.14
U-2	23.05±0.01	14.55±0.02	99.67
U-3	19.64±0.02	17.64±0.02	99.94
M-1	21.25±0.04	20.34 ±0.04	99.54
M-2	21.44±0.02	17.54 ±0.02	100.13
M-3	22.53±0.01	19.67 ±0.03	99.98
M-4	21.13±0.04	17.74 ±0.02	99.23
M-5	22.43±0.03	17.39 ±0.04	100.21

Table 5. Properties of granules of Metronidazole containing Eudragit NM30D and Methocel Premium K4M as release retardant

Formulations	Thickness (mm)	Weight Variation (%)	Drug Content (%)	Hardness (Kp)	Friability (%)
U-1	6.50 ± 0.05	1.12 ± 0.02	100.77±0.10	6.1 ± 0.15	0.50 ± 0.01
U-2	6.66 ± 0.07	1.08 ± 0.05	99.93 ± 0.05	7.2 ± 0.13	0.53 ± 0.02
U-3	6.53 ± 0.03	1.30 ± 0.02	99.09 ± 0.05	6.4 ± 0.17	0.33 ± 0.01
M-1	6.95 ± 0.02	2.10 ± 0.03	100.67±0.05	12.2 ± 0.11	0.35 ± 0.03
M-2	6.90 ± 0.01	1.25 ± 0.01	99.93 ± 0.03	11.8 ± 0.16	0.26 ± 0.02
M-3	6.83 ± 0.03	1.23 ± 0.04	99.09 ± 0.01	13.9 ± 0.15	0.33 ± 0.01
M-4	6.87 ± 0.06	1.17 ± 0.03	100.09±0.04	12.3 ± 0.14	0.20 ± 0.01
M-5	6.93 ± 0.05	1.15 ± 0.07	99.09 ± 0.01	13.1 ± 0.14	0.48 ± 0.01

Table 6. Summary of bioequivalence analysis

Formulation	Difference factor (f_1)	Specification (f_1)	Similarity factor (f_2)	Specification (f_2)
U-1	10.03	*Not more than 15*	56.21	*Not less than 50*
U-2	4.48		70.21	
U-3	23.93		37.96	
M-1	16.38		46.03	
M-2	9.92		56.49	
M-3	4.34		72.39	
M-4	7.08		61.85	
M-5	34.78		29.32	

Table 7. Summary of bioequivalence analysis

Log of Time	U-1	U-2	U-3
0.0000	1.3043	1.2167	1.0831
0.3010	1.6637	1.5812	1.4755
0.6021	1.8346	1.7870	1.6204
0.7782	1.9634	1.8704	1.7758
0.9031	1.9939	1.9097	1.8273
1.0000	1.9950	1.9488	1.8640
1.0792	1.9940	1.9737	1.8896

Table 8. Korsmeyer release profile Methocel Premium K4M based Metronidazole Matrix Tablets

Log of Time	M-1	M-2	M-3	M-4	M-5
0.0000	1.4200	1.2584	1.1691	1.0896	1.0748
0.3010	1.7202	1.6642	1.6113	1.5496	1.4347
0.6021	1.9090	1.8481	1.8124	1.7288	1.6345
0.7782	1.9837	1.9601	1.9219	1.8579	1.7176
0.9031	1.9948	1.9917	1.9643	1.9225	1.7497
1.0000	1.9947	1.9954	1.9907	1.9548	1.7647
1.0792	1.9955	1.9956	1.9940	1.9736	1.7852

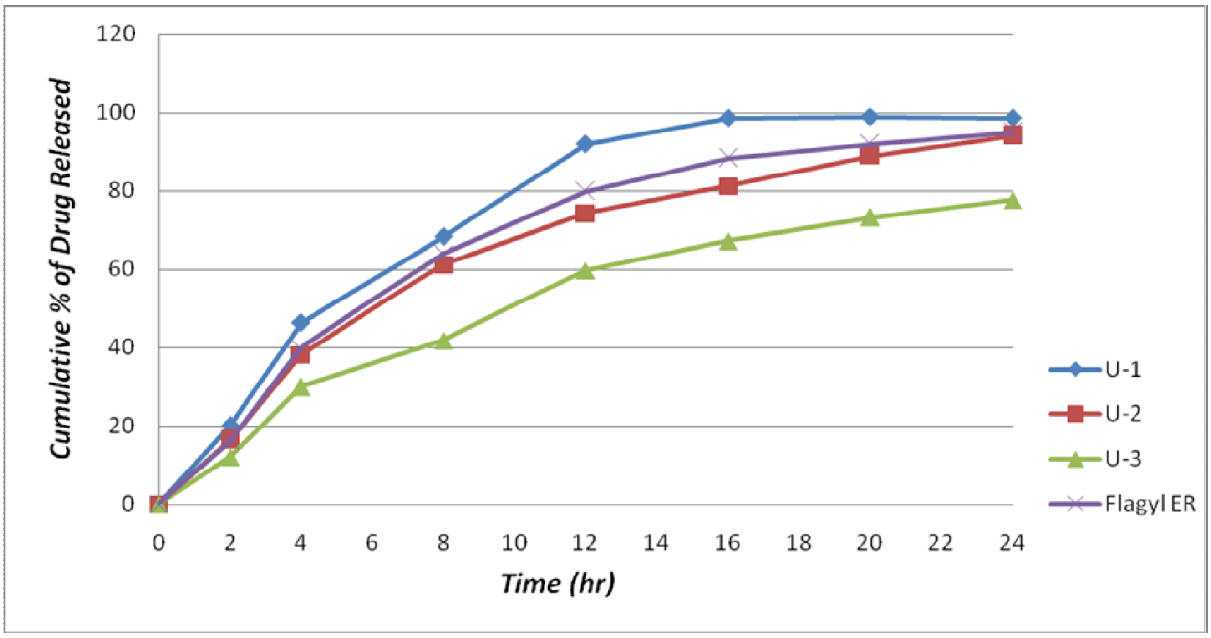

Figure 1. Comparative *In vitro* Metronidazole release profile for f_1 and f_2 test where reference is Flagyl ER tablet and test is prepared U-1, U-2 and U-3

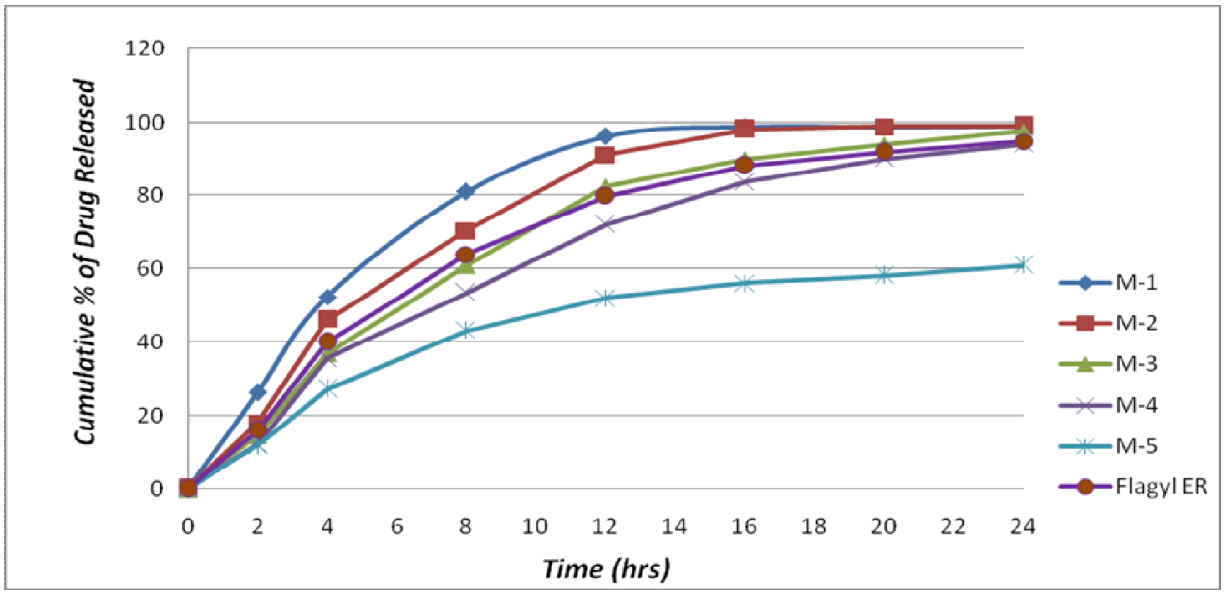

Figure 2. Comparative *In vitro* Metronidazole release profile for f_1 and f_2 test where reference is Flagyl ER tablet and test is prepared U-1, U-2 and U-3

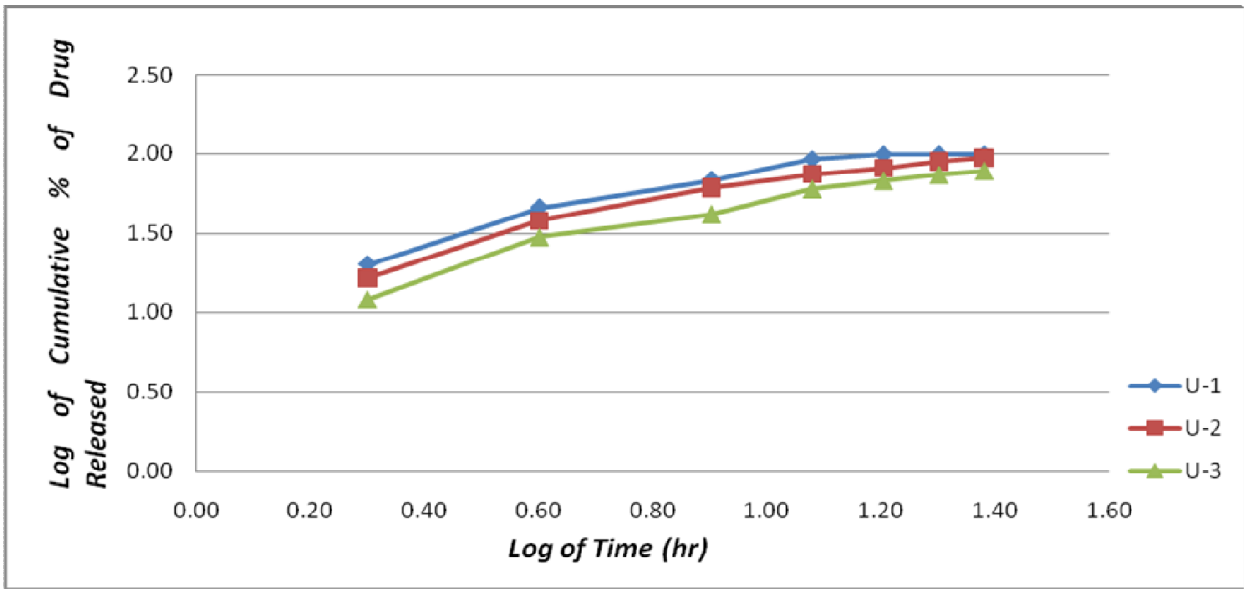

Figure 3. Korsmeyer plot of release kinetics of Metronidazole from Eudragit NM30D Matrices

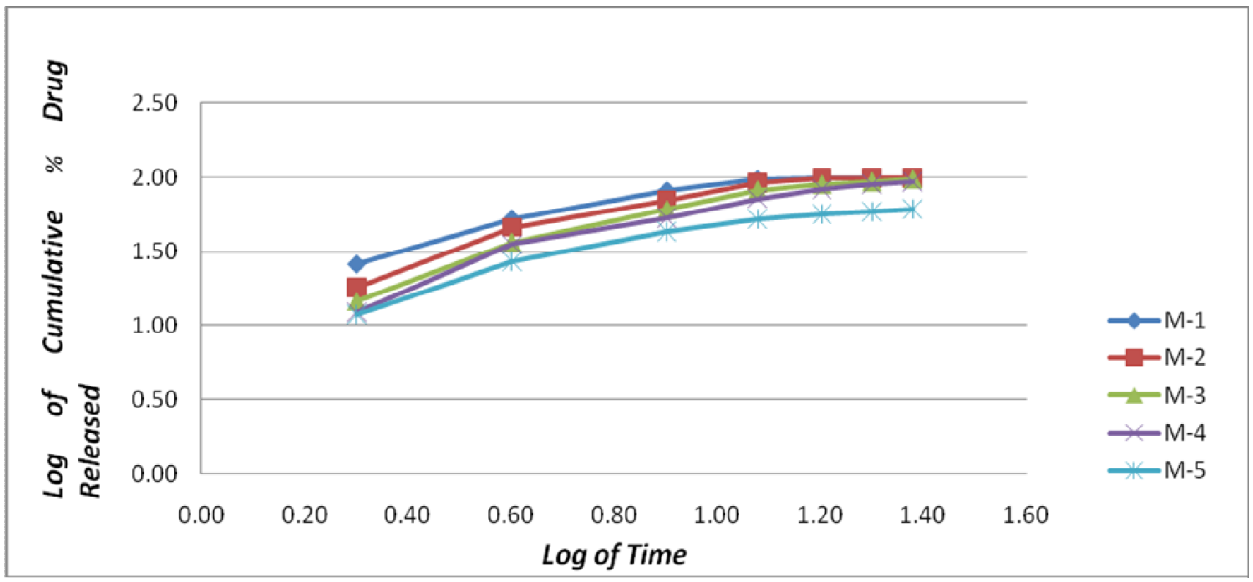

Figure 4. Korsmeyer plot of release kinetics of Metronidazole from Eudragit Methocel Premium K4M Matrices