Formulation and evaluation of oral biphasic drug delivery system of Metronidazole using HPMC polymer

Article · November 2016

7 authors, including:

Hani Naseef - shtaya
Birzeit University
12 PUBLICATIONS   **54** CITATIONS

SEE PROFILE

Aseel Samaro
Ghent University
1 PUBLICATION   **0** CITATIONS

SEE PROFILE

Mohammed I Enaia
Birzeit University
2 PUBLICATIONS   **20** CITATIONS

SEE PROFILE

Formulation and evaluation of oral biphasic drug delivery system of Metronidazole using HPMC polymer

Hani Naseef[1,2], Aseel Samaro[2], Moammal S. Qurt[2], Haneen Nakhleh[2], Noorhan Kadamani[2], Ramzi Moqadi[1], Mohammed Enaya[2]

[1]*Samih Darwazeh Institute of Industrial Pharmacy, Faculty of Pharmacy, Nursing and Health Professions, Birzeit University, Palestine*
[2]*Doctor of Pharmacy program,Faculty of Pharmacy, Nursing and Health Professions, Birzeit University, Palestine*

Abstract: *In the present study, a newly innovative drug delivery system of biphasic Metronidazole (MTZ) tablet has been studied. An attempt was made to improve the patient's adherence and the potential clinical outcomes by reducing the dosing frequency by formulating bilayer tablets containing Metrodinazole. Each bilayer tablet is composed of a sustained release (SR) layer and an immediate release (IR) layer for rapid drug release. Five different formulations of bilayer tablets were formulated using HPMC as hydrophilic polymer to retarded the drug release and the effect of Starch and MCC on the release profile were evaluated. Wet granulation method was used to prepare granules of the immediate and sustained release layers. The tablets were evaluated for their physical parameters and all valuesobtained found to be within the acceptable limits. The dissolution test has been carried out using the USP type II rotating paddle. Collected samples were analyzed using the high performance liquid chromatography. The mechanisms of Metrodinazole release from the sustained release layer were fitted into zero-order, first order, Higuchi, Hixon- Crowell model and Korsmeyer-Peppas release model. The results of the dissolution profiles showed that the drug release from the sustained release layer varied depending on the amount of HPMC and the presence of Starch or MCC. The kinetics of the release of MTZ from the different formulations showed good fitting with Higuchi model with correlation coefficients ($R2$) of 0.9965 - 0.9985. From values obtained for the diffusional exponent, n, Korsmeyer-Peppas equation observed that for all the formulations n value ranged from 0.4662 to 0.5370, and this demonstrates that the release mechanism followed non-Fickian type of release (anomalous transport).*

Keywords: *Biphasic tablets, HPMC immediate release, infectious diseases, Metronidazole, sustained release.*

I. Introduction

Oral drug delivery systems are the most utilized route of administration today; this is due to of the flexibility in modifying the release pattern of the drug. Tablets among all other orally administered dosage forms are highly preferred because of their stability, ease of manufacturing and ease of patients' administration. The biphasic delivery system is a new innovative drug delivery system utilized to provide immediate and sustained release doses within the same tablet, thus compliance problems associated with multiple dosing regimens can be overcome [1].

Diarrheal infections for example, were ranked at the top ten causes of death by the WHO[2]. Metronidazole (MTZ) is an antimicrobial, antiprotozoal medication that is used for multiple infectious diseases caused by different organisms, including protozoans, Helicobacter pylori, anaerobic bacteria, primarily Gram negative and Gram positive anaerobes. MTZ has a concentration dependent killing with rapid bactericidal property and good tissue penetration[3]. It is also well absorbed orally, with relatively short elimination half-life ranging from 6–8 hours; therefore the use of a sustained release system will be highly beneficial. The general dosing regimen of MTZ is from 2 to 4 times a-day for 7 to 14 days. It is available as 250, 500 mg immediate release tablets (IR) and 750 mg extended release tablets (ER) as well. A biphasic tablet of 1000 mg MTZ is a new novel that is developed to replace multi dosing regimen with once daily. This will improve patients' compliance, thus minimizing bacterial resistance as well as improving the clinical efficacy. Moreover, this biphasic tablet is designed to target specific conditions that use 1000 mg per day, such as: Pelvic inflammatory disease, bacterial vaginosis, trichomoniasis, *Helicobacter pylori* infection and others. Biphasic MTZ tablets are composed of two different layers; the first immediate release layer and the second extended release layer, in a quick\slow release pattern. This system provides an initial burst of drug (Loading dose) with rapid onset of action. A high Cmax will be achieved rapidly, which will support the mechanism of action of MTZ, followed by sustained release pattern to maintain plasma drug levels for extended period of time.

HPMC polymer has been used in many studies successfully to sustain the release of different formulations [4][5][6] Moreover, sustained release matrix tablets of MTZ were successfully prepared using

HPMC polymer to retard the release of the drug[7]. HPMC retardation of drug release occurs by swelling of the matrices upon the exposure to the gastric fluids. By time the matrix willerode and \ or dissolve and release the drug slowly [8][9]. Starchand Microcrystalline cellulose (Avicel® PH 101) were used to increase the drug release[10]. Magnesium stearate was used a lubricant andPolyvinylpyrrolidone (PVP) was used as a binder.

The aim of this study was to prepare biphasic MTZ tablets using HPMC polymer. This dosage form is composed of 250 mg MTZ in the IR layer and 750 mg in the ER layer which will provide an initial loading dose with rapid onset of action followed by sustained release pattern to maintain a plasma drug levels over a long period of time.

II. Materials And Methods

1. Materials:
MTZ was obtained as a gift from Jerusalem Pharmaceutical Company. HPMC (10000SH) was gifted from Pharmacare Phamaceutical Company. Microcrystalline cellulose (Avicel®PH 101), corn starch 1500, magnesium stearate and polyvinylpyrrolidone (PVP) were gifted from SamihDarwazeh Institute of Industrial Pharmacy. All reagents used in these experiments were of analytical grades.

2. Preparation of immediate and sustained release layers
The wet granulation method was used to prepare granules of the immediate and sustained release. The composition of the different formulations is shown in TABLEI. The excipients and the active ingredient wereblended and granulated with 70% ethanol using granulate stand mixer apparatus. The wet mass was passed through sieve #18 and the granules were dried at temperature of 40° C for 2 hours. The dried granules were then blended with magnesium stearate.

3. Compression of bilayer tablets
The immediate release granules were placed in the die cavity and precompressed . Then the sustained release granules were placed in the die cavity and allowed for punching with optimum hardness to form bilayer tablets. Compression was done using 19x8 mm diameter caplet die in a single rotary punch MINIPRESS MII machine.

4. Granules evaluation
4.1 Angle of repose
Angle of repose test was carried out to characterize the flow properties for the IR and the SR granules. The funnel method was used to determined the angle of repose of granules. A measured quantity of each type of granules was placed in a funnel. The funnel was fixed in place, 5 cm above the bench surface. The granules were then allowed to flow through the funnel orifice. The height (h) and the radius (r) of the heap formed were measured[11]. The test was repeated three times and the angle of repose (Q) was calculated through the following equation:

Q = tan-1 (h/r)   equation.1

4.2 Bulk and Tap Densities
Bulk density (BD) and tap density (TB) were determined using method I outlined in the USP[12].A measured quantity of each type of granules was added to a graduated cylinder of tapped density apparatus (COPLEY). After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface. The tapping was continued until no further change in volume was noted. BD and TB were calculated using the following formulas.

BD = Weight of the powder/Volume of the powder (V_{bulk})   equation.2
TD = Weight of the powder/Minimum volume of the powder (V_{tap}).   equation.3

4.3 Percentage Compressibility (Carr's index) and Hausner's Ratio
The percentage compressibility (CI) was calculated from the difference between the TD and BD divided by the TD and the ratio expressed as a percentage. The Hausner's ratio (HR) is the ratio between the TD and BD[11].

CI = [(TD-BD)/TD] ×100   equation.4
HR = TD/BD   equation.5

5. Tablets evaluation
The prepared tablets were subjected to various evaluation tests such as weight variation, hardness, friability, and dissolution test.

5.1 Weight Variation Test

Weight variation test was done by weighing 20 tablets individually and collectively, calculating the average weight from the collective weight and comparing the individual tablet weight to the average weight [13].

5.2 Hardness

Hardness was determined using Hardness Tester (Pharmatest PTB 311E). Ten tablets were randomly selected; the mean and standard deviation were calculated.

5.3 Friability

Ten pre-weighed tablets were taken randomly and placed into the Three Drum Automated Friability Testing (Pharmatest PTF 3DR).The machineset to rotate 100 times. Tablets were reweighed after the removal of fines and the percentage of weight loss was calculated. Friability results below 1% was considered acceptable based on US [14].

F= (W initial – W final)/ W initial *100%.equation.6

5.4 In Vitro Release study

Six tablets of each formulation of MTZ were taken and tested for dissolution. The USP type II rotating paddle (SOTAX dissolution tester CLI119) was used to study the drug release from the bilayer tablets. The dissolution medium consisted of 750 ml 0.1 M HCL for the first two hours, then 250 ml buffer was added to achieve 1000 ml phosphate buffer pH 6.8 for the next 22 hours according to method A in USP[15]. The dissolution test was performed at $37 \pm 0.5^{o}C$, with a rotation speed of 50 rpm. A sample of 5 ml from the dissolution medium was withdrawn using SOTAX autosamplar at the interval of 30 min up to 120 min. After that samples were withdrawn at 3rd hour followed by 2 hr intervals up to 24 hrs. The sample volume was replaced by an equal volume of dissolution medium after each withdrawal. Collected samples were analyzed using the high performance liquid chromatography device (HPLC). MTZ release were determined using a validated HPLC method. The HPLC analysis was performed using shimadzue HPLC consisting of a pump, autosampler, column oven, UV detector and LC solution. C_8 column was used at a UV detection wavelength of 278 nm. Methanol/water (20:80, v/v), as the mobile phase. Column temperature was maintained at 30°C. Flow rate and injection volume were 1.0 ml/minand 10 um, respectively.

6. Kinetic Data Analysis

6.1 Mechanism of Drug Release

To explain the mechanisms of MTZ release from sustained release layer of different formulations , the obtained data of drug release were fitted into zero-order, first order, Higuchi, Hixon- Crowell model and Korsmeyer-Peppas release model [16-21].

6.2 Zero – order question

To analyze release kinetics, the in vitro release data were plotted as cumulative amount of drug released versus time. Zero order describes the kinetics where the drug release rate from the tablet is independent from the concentration of dissolved drug. The release rate data are fitted into the following equation.

$Q_t=Q_0+K_0 t$ equation.7

Where,

Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and

K_0 is the zero order release constant expressed in units of concentration/time.

6.3 First order equation

To study the First order release kinetics the release rate data are fitted to the following equation. The data are expressed as log cumulative percentage of drug remaining versus time. According to First equation order the drug release rate depends on its concentration.

$logC=logC_0- K_t/2.303$ equation.8

where,

C = The amount of drug un-dissolved at t time,

C_0 = Drug concentration at t = 0,

K_t = First order release rate constant.

6.4 Higuchi equation

Higuchi equations assumes that the drug released from the tablet by diffusion mechanism. The data are expressed as   cumulative percentage of drug release versus square root of time which fitted to the following equation:

$Q=k\sqrt{t}$equation.9

Where,

Q_t is the amount of drug dissolved in time t,

K_0 is Higuchi release constant.

6.5 Hixon- Crowell model

Hixson-Crowell cube root model represents the drug release pattern depending on the change in surface area and diameter of the particles / tablets. This model is applied for the systems which erode over time. The following equation where used

$$Q_0^{(1/3)} - Q_t^{(1/3)} = k\,t \qquad\qquad\qquad equation.10$$

Where,

Q_t is the amount of drug release in time t,

Q_0 is the initial amount of drug in the tablet

K_0 is the rate constant for Higuchi, Hixon- Crowell cube root model

The data are expressed as Cube root of cumulative percentage of drug remaining versus time.

6.6 Korsmeyer-Peppas release model

To elucidate the mechanism of drug release the data were further analyzed using equation proposed by Korsmeyer and Peppas. The following equation where used

$$Q/Q_0 = k\,t^n \qquad equation.11$$

where

Q/Q_0 = the fraction of drug release at time t

k is the kinetic constant, and n is the diffusion or release exponent which depends on the release mechanism. When n = 0.45 indicate Fickian diffusion release, when $0.45 < n < 0.89$ indicate anomalous release kinetics (coupled diffusion/relaxation), and when $0.89 < n < 1$ indicate a zero-order release.

III. Result And Discussion

The granules for both Layers of the different formulations were evaluated for Bulk Density, Tab Density, Compressibility index, Hausner ratio and Angle of Repose (Table II). The values of precompression parameters showed that the granules for all formulations have sufficient compressibility and flow properties.

1. Physical Evaluation of tablets

The result of physical evaluation of bi-layer tablets like weight variation, hardness and friability were represented in Table III. Weight variation of the prepared tablets was found within the limits of pharmacopoeia [13].One of the main reasons for weight uniformity test is to guarantee appropriate flowability of powders. Friability test results range between [0.2-0.71 %], which met the acceptable limits of less than 1% according to USP [14], which indicate good mechanical resistance. Hardness ranged between [10-12] newton, which reflects good mechanical strength.

2. In vitro dissolution

The dissolution profile of different formulations of sustained release MTZ layer and from biphasic MTZ tablets are shown in Fig.1 and Fig.2 respectively. The dissolution data were analyzed and plotted as the cumulative percent drug release vs time. Formulations F1, F3, F5, F7 and F9 showed release for 24 hr up to 84.17%, 87.5%, 91.33%, 96.13% and 99.51% respectively(Fig.1). The drug release from the sustained release layer varied depending on the amount of HPMC and the presence of Starch or MCC. Formulation F1 showed release less than F3 and F5 due to combination of the hydrophilic polymer(HPMC) in the formulations F3 and F5 with Starch or MCC respectively. From Fig.1 it was seen that the drug release was higher for Starch and highest for MCC than the formulations without filler. This release behavior can be attributed to the solubility of MCC in water which forms pores in the gel layer resulting in more penetration of dissolution medium to the core of the tablets. On the other hand the use of starch in the tablets retarded the drug release and this behaviorcausedby two reasons. The first is due to the interaction between Starch and HPMC.This interaction can affect the properties of the gel layer around the tablets causing to slower penetration of dissolution medium to the core of the matrix. The second is due to the property of starch to hydrate and form a gel layer barrier due to intramolecular hydrogen bonds in the highly branched amylopectinwhich affect the gel layer and retard the drug release[22-23]. Formulations F3 and F5 showed less release than F7 and F9 due to less concentration of hydrophilic polymer(HPMC) in the formulations F7 and F9. Formulations F2, F4, F6, F8 and F10 showed release for 24 hr up to 84.51%, 88.11%, 91.2%, 94.1% and 99.5% respectively(Fig.2). For all formulations more than 40% of MTZ was released within 2 hours of dissolution test. This burst release of MTZ can be due to the immediate release layer of the formulation. Further release of MTZ was from the sustained release layer for 24 hours.

3. Kinetics and mechanism of drug release

To explain and evaluate the pattern and mechanism of drug release kinetics the in vitro data obtained from MTZ dissolution of sustained release layer were fitted to kinetic models, Zero order, first order , Higuchi , Hixson-Crowell equations and Korsmeyer-Peppas. The suitability of the model has been judged on the basis of best fit to the model using the correlation coefficient value (R^2). The data obtained from analysis of drug release kinetics are listed as shown in TABLE (IV). Figure (3) show the results of data analysis according to Zero order (Fig.3-a), first order (Fig.3-b), Higuchi (Fig.3-c), Hixson-Crowell equations (Fig.3-d) for formulation F1.

From the results shown in TABLE (IV), it can be observed that the release kinetics of MTZ from the different formulations showed good fitting with first order, zero order and Hixson-Crowell with R^2 values 0.8453 - 0.9891, 0.9162 - 0.9526 and 0.9728-0.9907 respectively. On the other hand the model with the highest correlation coefficients (R^2) were given by Higuchi with R^2 values 0.9965 - 0.9985. Although the results indicate that the drug is   released due to erosion of the gel layer formed around the tablet and simultaneous diffusion of the drug from this layer. The drug released by diffusion appears to be the main mechanism. These results can be confirmed by the apparent swelling behavior of the tablets. It was observed during the dissolution experiments a continuous increase in the thickness of the gel layer formed around the tablets. In addition, the release profile of MTZ from all formulations displayed good fitting with Hixson-Crowell cube root model of drug release, implying that erosion might have resulted in the release of MTZ from the tablets . It can be concluded that the kinetics of this drug release from the tablets can be attributed to erosion and diffusion mechanism with the diffusion mechanisms maybe the predominant.

To explain the mechanism of MTZ release, the dissolution data were also fitted to exponential Korsmeyer–Peppas equation and value of release exponent (n) explains the release mechanism of the drug from the tablets.

The calculated n values are shown in TABLE (IV). From values obtained for the diffusional exponent, n, it can be observed that for all the formulations n value ranged from 0.4662 to 0.5370, and this demonstrates that the release mechanism followed non-Fickian type of release (anomalous transport). For all formulations the n values were less than 0.89 indicating a close to Highuchi release mechanism. Such release pattern could be attributed to the physical structure of the polymer network and to the strong entanglements HPMC chains which resisted the gel layer erosion by the dissolution medium [24].

It can also be observed from the results shown in TABLE (IV) that the presence of filler (Starch 13% or MCC 16.6 %) has no significant influence on the kinetics of drug release. The values of n for tablets without fillers (F1) and for tablets with fillers (F3 and F5) were 0.5370, 0.5031 and 0.4763 indicating an anomalous behavior corresponding to diffusion, erosion and swelling mechanisms. A linear trend of decreasing n values can be observed from tablets without filler to Starch and to MCC respectively. Tablets containing MCC exhibited a drug release closer to a diffusion-controlled process compared to Starch and to tablets without filler. Other research groups have reported similar results that the drug release mechanism was affected by the presence of filler. They found that the matrices containing lactose exhibited a drug release closer to a diffusion-controlled process compared to MCC and Starch 1500 [25].

IV.   Conclusion

The present study was carried out to design oral bilayer tablet of Metrodinazole containing   250 mg MTZ in the IR layer and 750 mg MTZ in the ER layer using HPMC 100000SH. The granules of different formulations have good flow properties and the prepared tablets have good physical characteristics. The Bilayer tablets showed an initial burst effect to provide the loading dose of the drug, followed by sustained release for 24 h, indicating a promising potential of the Metrodinazole bilayer tablet as an alternative to the immediate release dosage form.The drug release from the sustained release layer varied depending on the amount of HPMC and the presence of Starch or MCC. The analysis of the release kinetic data for the different formulations in this study shows that Higuchi's model can best describe the kinetics of MTZ conforming to the diffusion assisted mechanism. Furthermore analysis of release kinetics data using Korsmeyer–Peppas equation shows that the release mechanism followed non-Fickian type of release (anomalous transport). It can beconcluded that the present study indicates that the bilayer tablets of MTZ provides a better option fordevelopment of a once daily formulation of the drug.

Table I: Composition of biphasic Metronidazole tablets

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Sustained Release Layer										
API	750	750	750	750	750	750	750	750	750	750
HPMC	80	80	80	80	80	80	60	60	60	60
Mg Stearate	9	9	9	9	9	9	9	9	9	9
STARCH	-	-	126	126	-	-	126	126	-	-
MCC	-	-	-		168	168	-	-	167.8	167.8
Immediate Release Layer										
API	-	250	-	250		250	-	250	-	250
PVP	-	10	-	10		10	-	10	-	10
Mg Stearate	-	2	-	2		2	-	2	-	2
AVECIL	-	50	-	50		50	-	50	-	50

Table II: Pre-compression evaluation tests on the prepared granules

Test	F1		F2	F3	F4		F5	F6		F7	F8		F9	F10	
	SR	IR	SR	SR	IR	SR	SR	IR	SR	SR	IR	SR	SR	IR	SR
Bulk Density	0.421	0.5	0.421	0.466	0.488	0.466	0.47	0.498	0.47	0.452	0.501	0.452	0.312	0.499	0.312
Tab Density	0.46	0.55	0.46	0.532	0.46	0.532	0.52	0.28	0.52	0.37	0.38	0.37	0.371	0.556	0.371
Carr's Index	8.4	9	8.4	12.4	13	12.4	9.6	14.2	9.6	16.2	7.1	16.2	16	10.2	16
Angle of Repose (δ)	29	26	29	32	28	32	25	32	25	34	27	34	33	26.5	33
H	1.09	1.1	1.09	1.14	1.15	1.14	1.1	1.16	1.1	1.19	1.07	1.19	1.18	1.14	1.18

Table III: Post-compression evaluation tests on the prepared biphasic MTZ tablets

Formulations	Hardness N ±SD (n 10)	Friability (%) (n 6)	Weight (mg) ±SD (n 10)	Release in 24 hours (%)
F1	10	0.47	820 ± 0.07	84.16%
F2	10.5	0.32	1140 ± 0.08	84.51%
F3	12	0.55	960 ± 0.02	87.5%
F4	10.8	0.65	1260 ± 0.07	91.3%
F5	11.6	0.71	900 ± 0.09	88.1%
F6	12	0.70	1280 ± 0.09	91.2%
F7	10.7	0.20	950 ± 0.01	96.1%
F8	12.2	0.25	1260 ± 0.02	94.1%
F9	10.4	0.30	990 ± 0.06	99.51%
F10	11.9	0.38	1300 ± 0.09	99.5%

Table IV: Kinetics data of Metrodinazole release from plots of formulation F-1 , F3, F5, F7, and F9

| Formula Code	Zero-order		First-order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas	
	Y equation	r^2	Y equation	r^2	Y equation	r^2	Y equation	r^2	n	r^2
F1	y=3.228x+14.44	0.9526	y=-0.029x+1.967	0.9891	y=17.241x-1.8465	0.9981	y=-0.081x+4.4694	0.9907	0.537	0.9990
F3	y=3.296x+16.70	0.9376	y=-0.032x+1.961	0.9846	y=17.744x-0.3022	0.9985	y=-0.0864x+4.4369	0.987	0.5031	0.9985
F5	y=3.366x+19.04	0.9338	y=-0.037x+1.962	0.9733	y=18.156x+1.593	0.9979	y=-0.0943x+4.4132	0.9858	0.4763	0.9981
F7	y=3.589x+20.64	0.9264	y=-0.048x+1.985	0.9496	y=19.431x+1.845	0.9976	y=-0.1115x+4.4226	0.9851	0.4711	0.9982
F9	y=3.772x+22.01	0.9162	y=-0.069x+2.061	0.8453	y=20.521x+1.997	0.9965	y=-0.135x+4.4666	0.9728	0.4662	0.9977
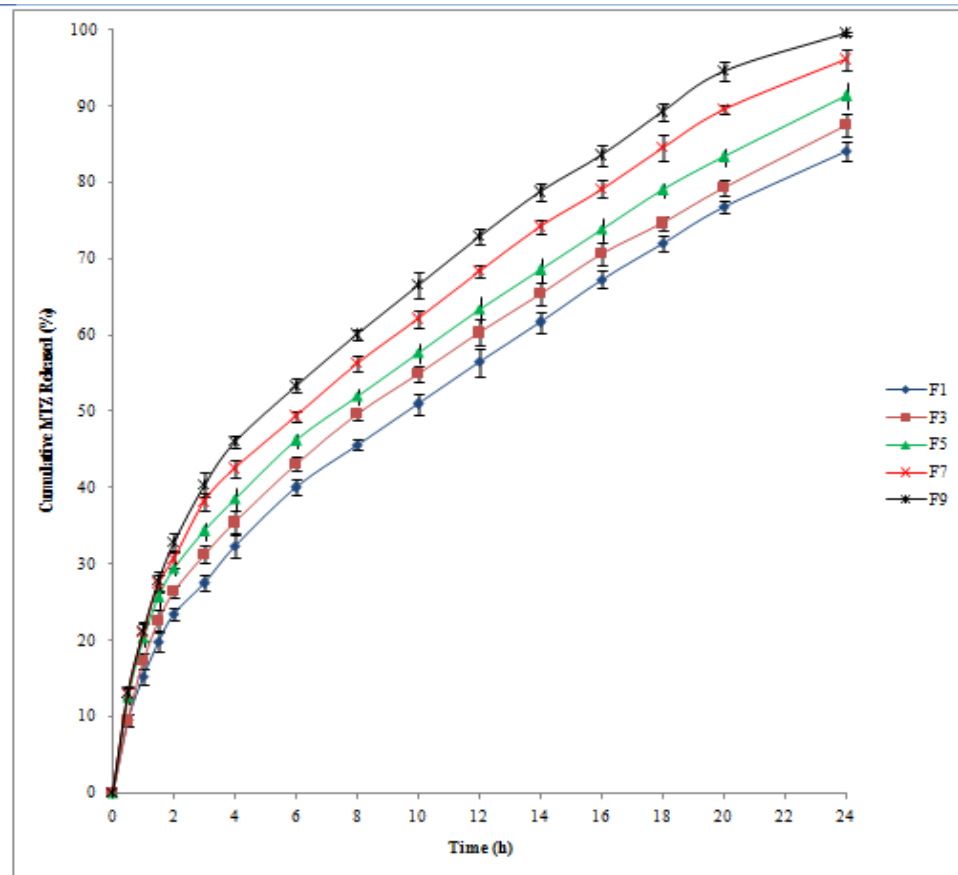
Figure 1: Cumulative MZT released *vs.* time from different formulations (mean ± *SD*, *n* = 6)
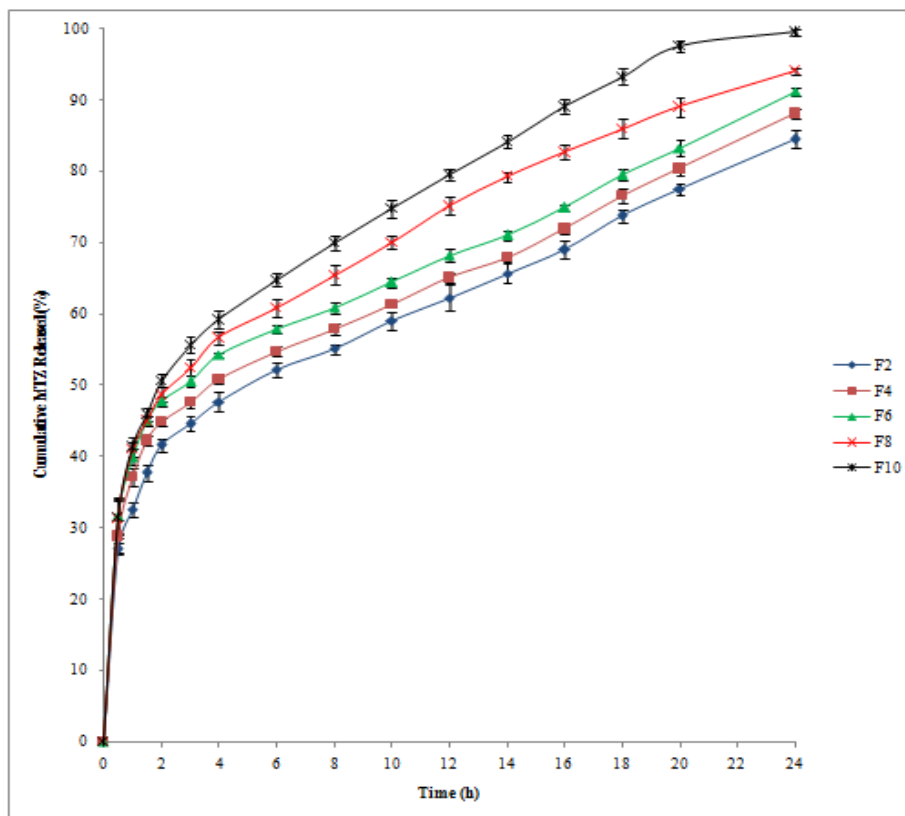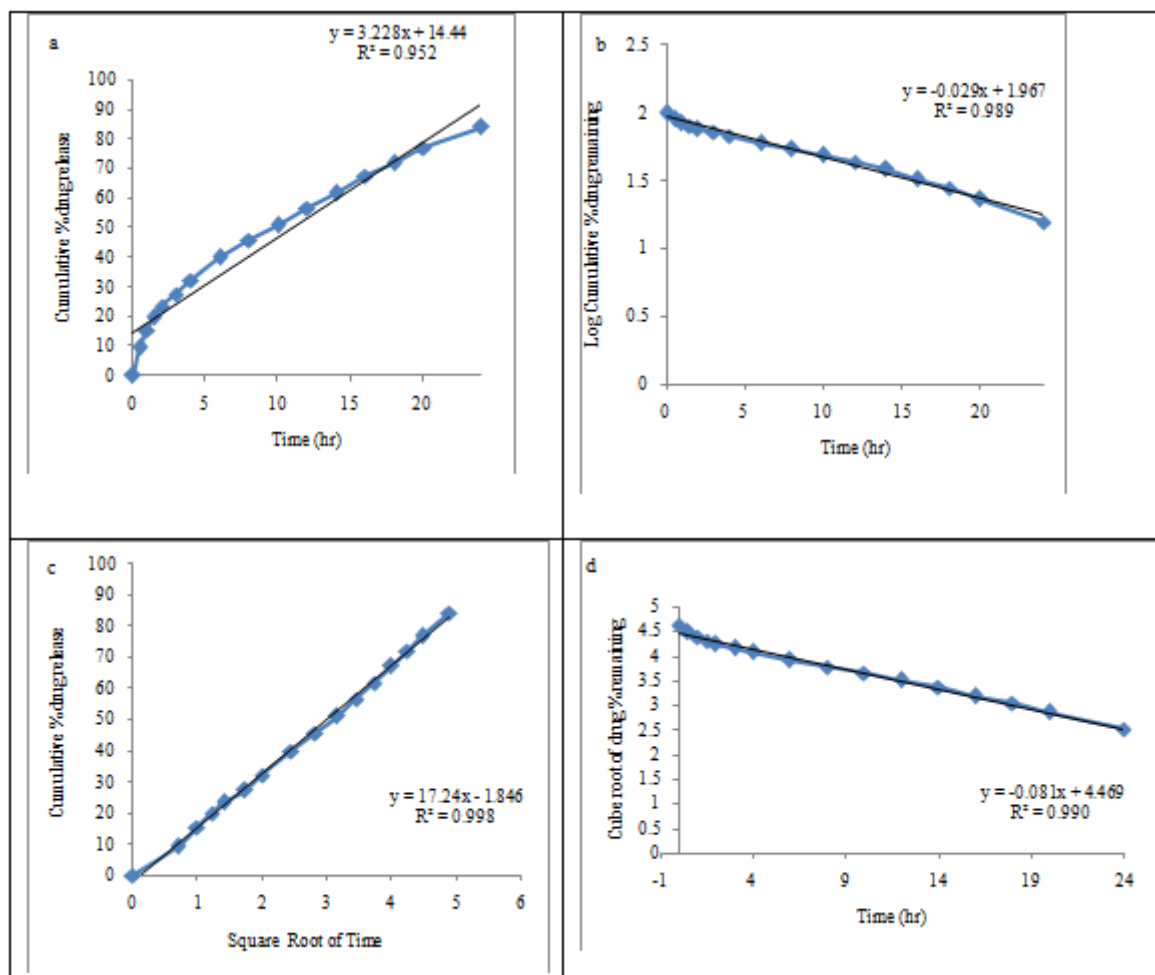

Figure 2: Cumulative MZT released *vs.* time from different formulations (mean ± *SD*, *n* = 6)

Figure 3: kinetic evaluation of formulation (F1): a) Zero Order plot, b) First Order plot, c) Higuchi plot, d) Hixson-Crowell plot.

References

[1].   P.Preetha, A.Srinivasa and P.Pushpalatha, Biphasicdrug delivery in controlled release formulations – A REVIEW, *International Journal Of Pharmacy &Technology, 6(4),* 2015,3046-3060.

[2].   Baylor College of Medicine, Introduction to Infectious Diseases. 2016,//www.bcm.edu/departments/molecular-virology-and-microbiology/emerging-infections-and-biodefense/introduction-to-infectious-diseases

[3].   Freeman CD, Klutman NE, Lamp KC, Metronidazole. A therapeutic review and update, *International Journal of Pharma and Bio Sciences, 54(5),* 1997, 679-708.

[4].   U. Shah B. Patel BP, Formulation and evaluation of controlled release matrix tablet of Diltiazem HCl by using HPMC and Guar gum as polymeric matrix material, *Ars Pharmaceutica, 53(4)*, 2012, 16-20.

[5].   B.Prajapati, R.Patel, D.Patel, P.Shah, Metformin hydrochloride sustained release tablet using different matrixing tablet, *e-Journal of Science & Technology,8(4),*2013,61-72.

[6].   U. Khatavkar, K. Kumar, S. Shimipi, Novelapproachesfordevelopment of oral controlled release compositions of Galantamine Hydrobromine and Paroxetine Hydrochloride Hemihydrate: A REVIEW, *Int J App Pharm, 8(3)*, 2016, 1-6

[7].   D. Mourya, R. Malviya, M. Bansal, P. Sharma, Formulation and release characteristics of Novel Monolithic Hydroxyl Propyl Methyl Cellulose Matrix Tablets containing Metronidazole , *International Journal of Pharma and Bio Sciences, 1(3)*, 2010, 1-7.

[8].   R.C. Rowe, P. sheskey, M.E.Quinn, handbook-of-pharmaceutical-excipients(Lambeth High Street, London,Pharmaceutical Press and American Pharmacists Association, 2009)

[9].   A. Nokhodchi, S. Raja, P.Patel, K.Asare-Addo, The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems, *BioImpacts BI, 2(4),* 2012,175–87.

[10].   Harish Gopinath, Sangeetha Shanmugasundrama,Pragati Kumara, A Brief Review On Disintegrants, *Journal of Chemical and Pharmaceutical sciences, 5 (3)*, 2012, 105-122.

[11].   Carr, R.L., Evaluating Flow Properties of Solids. *Chem. Eng*., 1965,72, 163 – 168

[12].   United States Pharmacopeia and National Formulary USP 30-NF 25.Rockville, MD. USA: United States Pharmacopoeial ConventionInc; 2015, Vol 2. Rockville, MD: United, General Chapters: <616> BulkDensity and Tapped Density of Powder.

[13].   Banker GS, Anderson NR. Tablets. In: Lachman L, Lieberman HA, Kanig JL, editors. *The Theory and Practice of Industrial Pharmacy*. 3rd ed. Mumbai : Varghese Publishing House; 1987. pp. 297–29

[14].   United States Pharmacopeia and National Formulary USP 30-NF 25.Rockville, MD. USA: United States Pharmacopoeial ConventionInc; 2015, Vol 2. Rockville, MD: United, General Chapters: General Chapters: <1216> Tablet Friability

[15].   United States Pharmacopeia and National Formulary USP 30-NF 25.Rockville, MD. USA: United States Pharmacopoeial ConventionInc; 2015, Vol 2. Rockville, MD: United, General Chapters: General Chapters: <1216>Dissolution

[16].   T. Higuchi, Rate of release of medicaments from ointment bases containing drugs in suspension, *J Pharm Sci*, *50*, 1961,874–875.

[17].   T. Higuchi, Mechanism of sustained-action medication, Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, *J Pharm Sci,52*, 1963,1145-1149.

[18].   RW. Korsmeyer, R. Gurny, EM. Doelker, P. Buri, NA. Peppas, Mechanism of solute release from porous hydrophilic polymers, *Int J Pharm, 15*, 1983, 25–35.

[19].   P.L. Ritger, N.A. Peppas, A Simple Equation for Description of Solute Release. II. Fickian and Anomalous Release from Swellable Devices, *J ContRel, 5*,1987, 23-36.

[20].   N.A. Peppas, Analysis of Fickian and non-Fickian drug release from polymers. *Pharm ActaHelv*, *60*, 1985,110–111.

[21].   M. Efentakis, H. Naseef and M. Vlachou, Two- and three-layer tablet drug delivery systems for oral sustained release of soluble and poorly soluble drugs, *Drug Development and Industrial Pharmacy, 36(8),* 2010, 903–916.

[22].   P.Gawali, A. Gupta, S. Kachare, S. Kshirsagar, Formulation and Evaluation of Matrix-based Sustained Release Tablets of Quetiapine fumarate and the Influence of Excipients on Drug Release, *Journal of Chemical and Pharmaceutical Research, 4(6),* 2012, 3073-3081.

[23].   V. Michailova, S. Titeva, R. Kotsilkova, E. Krusteva, E. Minkov et al, Influence of hydrogel structure on the processes of water penetration and drug release from mixed hydroxypropylmethyl cellulose/thermally pregelatinized waxy maize starch hydrophilic matrices.*Int. J. Pharm, 222*(1), 2001, 7-17.

[24].   M. Li, S. Qui, Y. Lu, K. Wang, X. Lai, M. Rehan, Investigation of the effect of hydroxypropylmethylcellulose on the phase transformation and release profile od carbamazepine – nicotinamide cocrystal, *Pharmaceutical Research, 31(9),* 2014, 2312-25.

[25].   M. Levina, A. Rajabi-Siahboomi, The Influence of Excipients on Drug Release from Hydroxypropyl Methylcellulose Matrices. *JOURNAL OF PHARMACEUTICAL SCIENCES, 93(11)*, 2004,2746-54.