Investigation of different pharmacokinetic parameters along with in-vitro dissolution study of Metronidazole immediate release tablets of various market preparations available in Bangladesh.

A PROJECT REPORT SUBMITTED TO THE DEPARTMENT OF PHARMACY, EAST WEST UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF BACHELOR OF PHARMACY (HONS.)

SUBMITTED BY:
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ID: 2007-3-70-016

1st June, 2011

DEPARTMENT OF PHARMACY
EAST WEST UNIVERSITY

DEDICATED TO MY PARENTS

CERTIFICATE

This is certify that, "**In-Vitro dissolution study of Metronidazole immediate release tablets of various market preparations and investigation of other pharmacokinetic parameters",** presented to the Department of Pharmacy, East West University is outcome of the investigations performed by me under the supervision of Muhammad Shahidul Islam, Senior Lecturer, Department of Pharmacy, East West University. This is also certify that no part of this project report has been or is being submitted elsewhere for the award of any degree.

26.06.2014

Dr. Sufia Islam, Ph.D

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Department of Pharmacy

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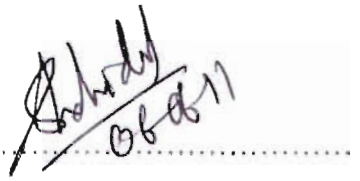

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Acknowledgement

First of all, I am grateful to Allah who gives me the opportunity of completing my research work. Then I am delighted to offer my heartiest and deep gratitude to my supervisor and my respected teacher Muhammad Shahidul Islam, Senior Lecturer, Department of Pharmacy, East West University, Dhaka, for his expert supervision, constant inspiration, invaluable counseling, constructive instructions and concrete suggestions throughout the research work.

I also wish to express my humble regards to all of my respected teachers of the Faculty of Pharmacy, East West University, for their continuous support, affection and sincere advice to complete my investigation.

I am also thankful to laboratory assistants and employees of the Faculty of Pharmacy for their cooperation in doing my research work.

I am also thankful to Kazi Rashidul Azam, Assistant Professor, Department of Pharmacy, Northern University Bangladesh, for his kind help for the UV Visible spectrophotometer.

Finally I would be glad to extend my gratitude to the members of my family and to my friends for their prayerful concerns and supports.

CONTENTS

CHAPTER 1: INTRODUCTION

CHAPTER 2: MATERIALS & METHOD

Title: **Page No.**

CHAPTER 3: RESULTS & DISCUSSION

CHAPTER 4: CONCLUSION

CHAPTER 5: REFERENCE

LIST OF TABLES

LIST OF FIGURES

Abstract

This experiment describes in vitro evaluation of Metronidazole immediate release tablet. Drug release study was evaluated for 75 minutes using United State Pharmacopeia (USP), paddle type (type-2) dissolution apparatus using 0.1 N HCl as the dissolution medium. The release mechanisms were explored and explained with zero order, first order, Hihuchi equations, and Korsmeyer equation. The content of active ingredient was a vital factor in controlling drug release pattern. It was found that after 75 minutes better market preparation Metronidazole maximum released. In this experiment various types of Metronidazole market preparations were used. Their other physical parameters were also studied. Generally, dissolution test is applied to evaluate various formulations for the selection of an optimum one. For this purpose, dissolution parameters are varied to investigate a method that can predict oral rate of absorption of metronidazole.

Key words: metronidazole; dissolution; Immediate release; pharmacokinetics.

Purpose of Study

At present, the popularity of immediate release dosage forms is rapidly increasing. This is due to some advantages shown over conventional dosage forms. Fabrication of immediate release dosage form is not very simple, because the several physicochemical factors of the active ingredients and the excipients have a great effect on this task. Among the systems that bring about immediate action, matrix system has been attracting much attention due to the technological simplicity in comparison with other release systems developed to achieve oral release.

Simpler immediate release tablet designs, seceded when used with high solubility drugs, failed when applied to low solubility drugs.

Microencapsulation is an increasingly adopted technique used for multipurpose study especially in the development of modified-release dosage form. Metronidazole, a biopharmaceutical classification system (BCS) class I drug, is an antibiotic. It is a readily water soluble compound with good permeability. For such drugs, dissolution is a rate limiting step in their in vivo absorption. Mathematical modeling for such drugs is possible, if the release kinetics is modified. In present study, metronidazole was microencapsulated into ethylcellulose to develop its modified release dosage form. Currently no mathematical simulation study of microencapsulated metronidazole is found in literature. We need to developed a model in this regard that can predict metronidazole oral absorption from its encapsulated form in human.

CHAPTER 1

INTRODUCTION

1.1 General introduction:

The overall effect of any drug occurs in a sequence of three distinct yet interdependent stages as listed in the following;

Phases of drug action

1. **Pharmaceutical Phase:** Releases from a dosage form
2. **Pharmacokinetic Phase:** Includes absorption, distribution, and elimination
3. **Pharmacodynamic Phases:** Includes drug interactions with receptors

Ideally, a thorough understanding of each of these stages for a given drug is essential for achieving its most effective therapeutic efficacy in patients. The pharmaceutical phase describes the process of a drug's conversion from a chemical form into a dosage form. This phase includes the characterization of physicochemical drug profiles, design and production of dosage forms and biopharmaceutical evaluation of drug products. The pharmaceutical phase can initially influence the pharmacokinetic phase, which is measured by blood-level-versus-time profiles. The pharmacokinetic phase then directly affects the Pharmacodynamic or efficacy phase.

At present drugs are administered in pure chemical form. Rather, these drugs are prepared in a vehicle which is called a drug delivery system. The drug delivery system provides a therapeutic amount of drug to the proper site in the body to achieve the desired drug concentration. That is, the drug-delivery system can deliver the drug at a rate dictated by the body needs over the period of treatment. This idealized objective points to the two aspects most important to drug delivery, namely, spatial placement and temporal delivery of a drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the newer approaches under investigation may allow spatial placement as well.[1]

1.2 Immediate Release:

For immediate release tablets, the drug is intended to be released rapidly after administration, or the tablet is dissolved and administered as a solution. This is the

most common type of tablet and includes disintegrating, chewable, effervescent, sublingual and buccal tablets.[3]

1.2.1 THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows:

Class 1: High Solubility – High Permeability

Class 2: Low Solubility – High Permeability

Class 3: High Solubility – Low Permeability

Class 4: Low Solubility – Low Permeability

In addition, IR solid oral dosage forms are categorized as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool to help sponsors justify requests for biowaivers.

Observed in vivo differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to differences in drug dissolution in vivo. However, when the in vivo dissolution of an IR solid oral dosage form is rapid in relation to gastric emptying and the drug has high permeability, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal transit time. Under such circumstances, demonstration of in vivo bioavailability or bioequivalence may not be necessary for drug products containing Class 1 drug substances, as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients. The BCS approach outlined in this guidance can be used to justify biowaivers for highly soluble and highly permeable drug substances (i.e., Class 1) in IR solid oral dosage forms that exhibit rapid in vitro dissolution using the recommended test methods. The recommended methods for determining solubility, permeability, and in vitro dissolution are discussed below.[3]

A. Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a biowaiver request. A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.[3]

B. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic bioavailability) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., in vitro epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.[3]

C. Dissolution

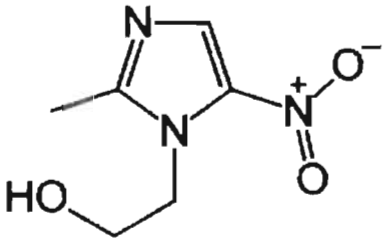
In this guidance, an IR drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using U.S. Pharmacopeia (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.[3]

1.3 Metronidazole

Metronidazole (INN) is a nitroimidazole antibiotic medication used particularly for anaerobic bacteria and protozoa. Metronidazole is an antibiotic, amebicide, and antiprotozoal. It is the drug of choice for first episodes of mild-to-moderate *Clostridium difficile* infection. Metronidazole was developed in 1960. Metronidazole is used also as a gel preparation in the treatment of the dermatological conditions and fungating tumours.[2] [4]

1.4 Chemical structure [2]

1.4.1 Structural formula:



1.4.2 Molecular formula: $C_6H_9O_3N_3$

1.4.3 Molecular weight: 171.16

1.4.4 Chemical names:

- 2-(2-Methyl-5-nitroimidazol-1-yl)ethanol
- 2-methyl-5-nitroimidazole-1-ethanol
- 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole

1.5 Physical properties

1.5.1 Properties of the substance

1.Colour: Pale yellow; darkens on exposure to light.

2. State/Form: Crystalline powder

3. Description

- ✓ Slightly soluble in water, in alcohol, in acetone or in methylene chloride; very slightly soluble in ether.
- ✓ pH of a saturated aqueous solution at 20°C is about 6.5.
- ✓ Melting point 160°C

1.6 Mechanism of Action:

Metronidazole, taken up by diffusion, is selectively absorbed by anaerobic bacteria and sensitive protozoa. Once taken up by anaerobes, it is non-enzymatically reduced by reacting with reduced ferredoxin, which is generated by pyruvate oxido-reductase. This reduction causes the production of toxic products to anaerobic cells, and allows for selective accumulation in anaerobes.

The metronidazole metabolites are taken up into bacterial DNA, and form unstable molecules. This function only occurs when metronidazole is partially reduced, and because this reduction usually happens only in anaerobic cells, it has relatively little effect upon human cells or aerobic bacteria[6][4]

1.7 Pharmacokinetics:

1.7.1.Bioavailability:

For both oral and intravenous administration, the area under the plasma clearance curve is equivalent.[2]

1.7.2.Absorption :

Maximum plasma concentrations occur at the conclusion of the infusion after intravenous administration. Traces are detected after 24 hours. The biological half-life of a single intravenously administered dose of metronidazole has been determined as 7.3 hours 1.0 hours.[2]

1.7.3. Distribution:

Metronidazole is widely distributed in body tissues and fluids. It diffuses across the blood-brain barrier, crosses the placenta and appears in the saliva and breast milk of nursing mothers in concentrations equivalent to those found in the plasma. It attains therapeutic concentrations in the bile and the CSF.[2]

1.7.4. Metabolism :

An oral or intravenous dose of metronidazole is partially metabolised in the liver by hydroxylation, acid side-chain oxidation and glucuronide conjugation. The major metabolite, 2-hydroxymethyl metronidazole, has some antiprotozoal activity in vitro.[6]

1.7.5. Excretion :

Approximately three-fourths of a single 750mg oral dose is excreted as nitro-containing compounds (unchanged drug and its metabolites) in the urine within 5 days. Most of the remainder is excreted in the faeces. Urine may be dark or reddish brown in colour following oral and IV administration of the drug due to the presence of water-soluble pigments, which result from its metabolism. [6]

1.7.6. Elimination by route of exposure:

Main route of elimination is by kidney but it is also secreted in bile and breast milk. 77% is recovered from urine and 14% from stool.Urine of some patients may become reddish-brown due to some unidentified pigment derived from this drug.[10] [13]

1.7.7. Biological half-life by route of exposure:

Elimination half-life after an intravenous infusion of 1.5 g is between 6.6 to 10.3 hours, with a mean of 8.4 hours. The half-life of hydroxy metabolites is between 13.3 and 19.1 Hours. Repeated doses every 6 to 8 hours may result in some accumulation.In cases of impaired liver function, elimination is slower. In renal failure half-life of metronidazole is unchanged but that of metabolites is increased.[10] [11]

1.8 Indications:

Metronidazole is indicated:

1. For treatment of anaerobic infections in patients for whom oral administration is not possible.

2. When immediate anti-anaerobic therapy is required.

3. Where prophylactic cover is required at lower abdominal surgical sites presumed contaminated or potentially contaminated by anaerobic micro-organisms. Procedures of this type include appendicectomy, colonic surgery, vaginal hysterectomy, abdominal surgery in the presence of anaerobes in the peritoneal cavity and surgery performed in the presence of anaerobic septicaemia.[14]

1.9 Contraindication: [14]

Metronidazole is contraindicated:

1. In patients with evidence of or a history of blood dyscrasias. (Occasionally a mild leukopenia has been observed during administration; however no persistent haematological abnormalities have been observed in animals or clinical studies.)

2. In the presence of active organic disease of the central nervous system.

3.Iin patients who are hypersensitive to metronidazole or other nitroimidazoles

1.10 Interactions With Other Drugs:

Coumarin Anticoagulants: Oral or IV metronidazole potentiates the effects of oral anticoagulants resulting in prolongation of prothrombin time; concurrent administration should be avoided if possible. If metronidazole is used in patients receiving an oral anticoagulant, prothrombin times should be monitored and the dosage of the anticoagulant adjusted accordingly.[9]

Alcohol: Metronidazole appears to inhibit alcohol dehydrogenase and other alcohol oxidising enzymes. Mild disulfiram-like reactions including flushing, headache, nausea, vomiting, abdominal cramps and sweating have occurred in patients ingesting alcohol while being treated with metronidazole.

Patients should be advised not to take alcohol during therapy or for at least one day afterwards because of the possibility of a disulfiram-like reaction.[7]

Disulfiram: Administration of disulfiram with metronidazole has been associated with acute psychoses and confusion in some patients; therefore the two drugs should not be administered. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks.[8] [9]

Cyclosporin: There is a risk of cyclosporin serum levels increasing when it is used in combination with metronidazole. Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.

5-flourouracil: Metronidazole used in combination with 5-fluorouracil may lead to reduced clearance of 5-flourouracil, resulting in increased toxicity.

Phenobarbital and Phenytoin: The simultaneous administration of drugs which induce microsomal liver enzyme activity, such as phenobarbital, pentobarbital and phenytoin may accelerate the elimination of metronidazole, resulting in reduced plasma concentrations and increased concentrations of its 2-hydroxymethyl metabolite; impaired clearance of phenytoin has also been reported.[14]

Lithium: Inhibition of short-term metronidazole therapy in patients stabilised on relatively high dosage of lithium has been reported to increase serum lithium concentrations, resulting in signs of lithium toxicity in several patients. Serum lithium and serum creatinine levels should be obtained several days after commencing metronidazole therapy to detect any increase that may precede clinical symptoms of lithium intoxication.[10]

Cimetidine: Simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease the plasma clearance of metronidazole. It is not clear if ranitidine exerts a similar effect.[12]

CHAPTER 2

MATERIALS & METHOD

2. Materials and Methods:

2.1 Sample Collection:

For sample Metronidazole collection, I went to nearest various pharmacy stores. and collected six different types of Metronidazole market preparations.

2.2.Materials:

TABLE 2.2.1: List of Instruments and Equipments used in the Experiment.

Serial No.	Name	Model
1.	UV-Visible Spectrometer	HACH-Spectrometer. Model-DR/4000U
2.	Tablet Dissolution Tester	VANGUARD PHARMACEUTICAL MACHINERY INC. Model- RC- 6
3.	Electronic Balance	Electronic Balance, Type: AY220, No: D432812964, Capacity: 220 g, Readability: 0.1 mg
4.	pH Meter	Phep®, Original from HANNA INSTRUMENT (Italy)
5.	Friability Machine	VEEGO, Ser No: 43/03 05, Type: VPT-2D, Volts: 230 Volts, 50 Hz

TABLE 2.2.2: List of Apparatus/Glasswares used throughout this Project.

Serial No.	Name	Serial No.	Name
1.	Several Plastic Containers	8.	Measuring Cylinder (1000 mL & 2000 mL)
2.	Mortar and Pastels	9.	Measuring Flask (1000 mL)
3.	Test Tubes	10.	Beakers
4.	Volumetric Flasks (10mL and 100 mL)	11.	Laboratory Mixer
5.	Micro Pipette	12.	Spatula
6.	Pipette	13.	Glass rod
7.	Volumetric Pipette	14.	Disposable Syringes

2.3 Methods:

2.3.1 Thickness test of tablets:

2.3.1.1 Procedure:

1. One tablet was placed horizontally between two jaws.
2. The screw of the caliper was run to hold the tablet.
3. Reading in cm was taken from the scale.

2.3.1.2 Calculation:

Thickness of the Tablet is:

Reading of cm scale + Reading of Vernier scale + Vernier Error

2.3.2 Diameter Test of Tablets:

2.3.2.1 Procedure:

1. One tablet was placed vertically between two jaws.
2. The screw of the caliper was run to hold the tablet.
3. Reading in cm was taken from the scale.

2.3.2.2 Calculation:

Diameter of the Tablet is:

Reading of cm scale + Reading of Vernier scale + Vernier Error

2.3.3 Hardness Test of Tablets:

2.3.3.1 Procedure:

1. The sliding scale of the hardness tester was made zero.
2. One tablet was placed vertically between two jaws.
3. Force was applied with a screw thread and spring until the tablet fractured.
4. Reading in Kg was taken from the sliding scale.

2.3.3.2 Measurement Units:

Most materials testing is performed using the International System of Units. The Newton is the preferred unit of force as is recognized by the SI system. However the kilogram can also be used.

Kilogram (kg) – The kilogram is recognized by the SI system as the primary unit of mass.

Newton (N) – The Newton is the SI unit of force and is the unit that should be used for tablet hardness testing. 9.807 Newtons = 1 kilogram.

Pound (lb) – Technically a unit of mass but can also be used for force and should be written as pound force or lbf in this case. Sometimes used for tablet strength testing in North America, but it is not an SI unit. 1 kilogram = 2.204 pounds

2.3.4 Friability Test of Tablets:

2.3.4.1 Procedure:

1. 5 tablets were weighed. It was considered as an initial reading.
2. The tablets were placed in the section 1 of the drum of the friability tester and rotated 100 times.
3. The tablets were re-weighed. It was considered as a final reading.
4. The percent loss was calculated.
5. According to USP, the tablets should not lose more than 1% of their total weight.

2.3.4.2 Calculation:

$$\% \text{ Loss} = \frac{\text{(Initial weight – Final weight)}}{\text{Initial weight}} \times 100$$

2.3.5 Weight Variation Test of Tablets:

2.3.5.1 Procedure:

1. 5 tablets were taken and weighed all the tablets.
2. The average was taken and it was considered as the standard weight of an individual tablet.
3. All the tablets were weighed individually and observed whether the individual tablets are within the range or not.

N.B.: The variation from the average weight in the weights not more than two tablets must not differ more than the percentage listed below:

Average weight	**Percentage difference**
130 mg or less	± 10
More than 130 to 324 mg	± 7.5
Mare than 324 mg	± 5

2.3.5.2 Calculation:

$$\text{Highest weight variation} = \frac{\text{Highest weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

$$\text{Lowest weight variation} = \frac{\text{Lowest weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

2.3.6 Dissolution Test of Tablets:

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus: USP dissolution apparatus II (Paddle apparatus)

Speed: 50 rpm

pH of the media: 1.4

Temperature: 37.5^0 C

Time: 75 Min

λ_{max}: 368 nm

2.3.6.1 Preparation of Dissolution media (0.1 N HCl):

10 mL concentrated hydrochloric acid was taken in a 1000 mL volumetric flask containing small amount of distilled water. Now required amount of water was added to make it volume. Thus, 1000 mL 0.1 N HCl was prepared.

2.3.6.2 Procedure:

1. The disintegration tester was assembled.
2. 900 ml distilled water in each 1000 ml beaker was placed.
3. The temperature of the liquid was maintained at 35-39°C.
4. Two tablets were placed in two tubes.
5. Operate the apparatus for the prescribed period.
6. During operation 10 mL solutions from two vessels were transferred to two test tubes with an interval of 15 min.
7. All the tablets or capsules must disintegrate within the prescribed time.
8. After completion of the operation the absorbance of each interval was taken by using UV-spectroscopy and the reading was noted.

Table 2.3.7: Data for the standard Curve of Metronidazole at 368 nm

Sample No.	Concentration (µg/mL)	Absorbance
1	0.0	0.000
2	1.0	0.116
3	2.0	0.209
4	3.0	0.294
5	4.0	0.380
6	5.0	0.461
7	6.0	0.550
8	7.0	0.642
9	8.0	0.753
10	9.0	0.841
11	10.0	0.984

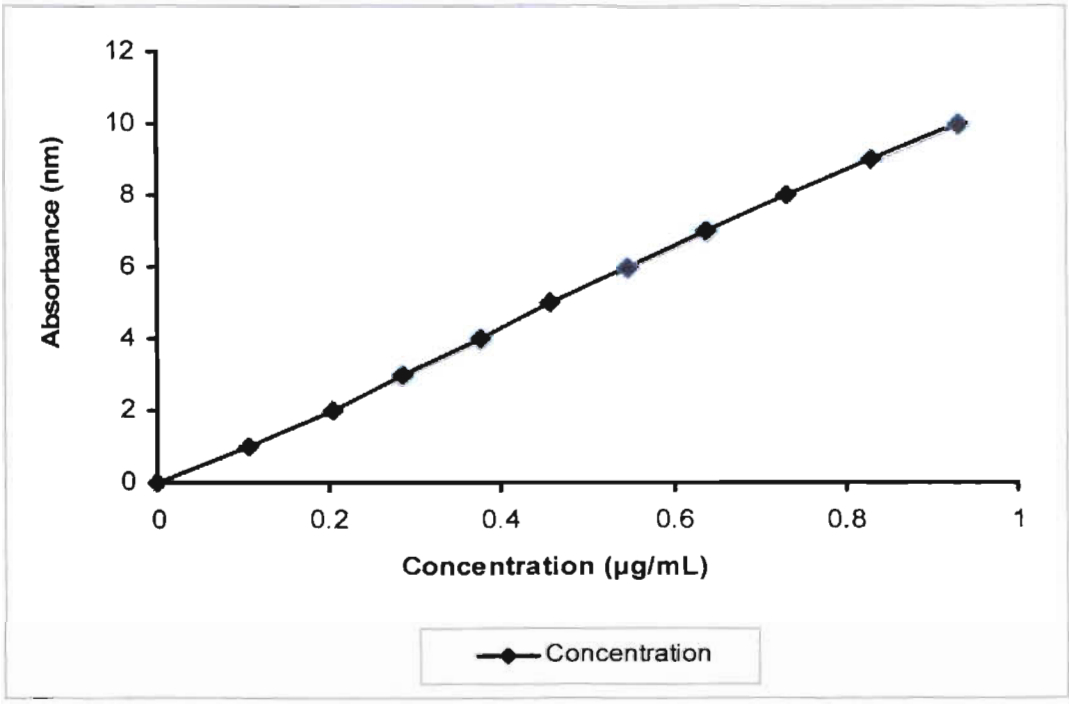


Figure 2.3.7: Standard curve of Metronidazole

2.3.8 Instrument Figure

Figure: Electronic Balance

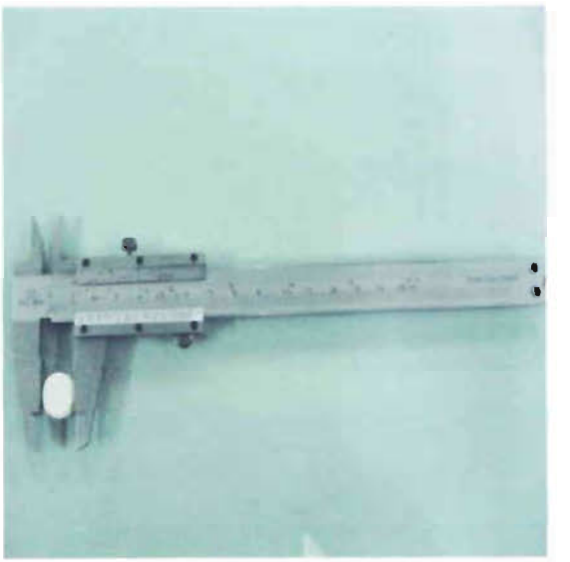


Figure: Slide Caliperse

Figure: Tablet Friability Tester

Figure: Distilled Water maker

Figure: Tablet Dissolution Tester

Figure: UV-Spectrophotometer

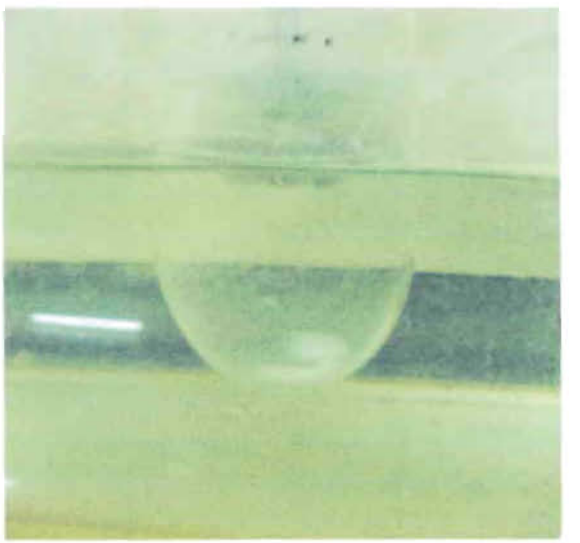


Figure: After 60 minutes

CHAPETR 3

RESULTS & DISCUSSION

Table 3.1: Physical properties of Metronidazole marketed preparations

No. of formulation	Average Hardness (kg)	Friability (%)	Average Diameter(mm)	Average Thickness (mm)	Average Tablet Weight (g)	Weight variation (%)
BC-1	2.7	0.381	17.15	4.75	0.822	2.66
BC-2	2.6	0.299	17.16	4.68	0.891	2.69
BC-3	2.4	0.278	17.16	4..73	0.844	2.76
BC-4	2.4	0.351	17.15	4.75	0.841	2.67
BC-5	2.7	0.271	17.15	4.75	0.992	2.69
BC-6	2.6	0.377	17.16	3.69	0.899	2.68

3.2 Kinetic Modeling of Drug Release:

The dissolution profile of all the batches was fitted to zero order (Mockel and Lippold 1993), first-order, Higuchi (Higuchi, 1963) and Korsmeyer (Korsmeyer, 1983) to ascertain the kinetic modeling of drug release. After linear transformation of dissolution curves, the results were tested with the following mathematical models:

The Zero order equation assumes that drug release is constant:

$$M = M_o - K_o t \quad \text{——————————} \quad (I)$$

In this equation M is the amount of drug remaining undissolved at time t, M_o is the amount of drug undissolved at t=0 and K_o is the corresponding release rate constant. Zero order plot of drug release is obtained by plotting percent release of drug versus time in hour. The percentage of drug release of six marketed preparations of Metronidazoole IR at different time intervals are shown at table 3.2

A form of the Higuchi Square Root Law is given by equation:

$$Q = K_H \sqrt{t} \quad \text{——————————} \quad (II)$$

Where Q (Q = 100 - M) is the amount of drug dissolved at time t and K_H is the corresponding rate constant. The average release pattern is given in the figure 3.3, represents the Higuchi plot of this impact that is obtained by plotting percent release of drug versus square root of time. The percentage of drug release of six marketed preparations of Metronidazole IR at different time intervals are shown at table 3.3

Release behavior generally follows the following first order release equation:

$$\ln M = \ln M_o - K_1 t \quad \text{(III)}$$

Where M is the amount of drug undissolved at time t, M_o is the amount of drug undissolved at t=0 and K_1 is the corresponding release rate constant. Log % remaining is

plotted as a function of time to demonstrate the first order release profile of Metronidazole Log % remaining of drug release of six marketed preparations of Metronidazole IR at different time intervals are shown at table 3.4

The Korsmyer's equation is:

$$M_t / M_\alpha = K_k t^n \quad \text{(IV)}$$

Where K_k is the Korsmeyer release rate constant and n is the diffusion exponent. Log fraction release as a function of log of time (hour) gives the Korsmeyer release pattern from various formulations of gastro retentive matrix tablets. Log fraction releases of drug release of six marketed preparations of Metronidazole IR at different time intervals are shown at table 3.5.

When n is bellow 0.45, the Fickian diffusion phenomenon dominates, and n between 0.45 and 0.89 is an anomalous transport, often termed as first-order release. After the n value reaches 0.89 and above, the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the release is characterized by zero-order release.

In this work, Equations I-IV was used for the modeling of release kinetics from the various tablets of Metronidazole.

3.3 Successive Fractional Dissolution Time:

To characterize the drug release rate in different experimental conditions, $T_{25\%}$, $T_{50\%}$ (mean dissolution time) and $T_{80\%}$ were calculated from dissolution data according to the following equations:

$$T_{25\%} = (0.25/k)^{1/n}$$

$$T_{50\%} = (0.5/k)^{1/n}$$

$$T_{80\%} = (0.8/k)^{1/n}$$

Mean Dissolution Time can also be calculated by the following equation (Mockel and Lippold, 1993).

$$MDT = (n/n+1).\ K^{-1/n}$$

Mean dissolution time (MDT) value is used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer. A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa. The MDT value was also found to be a function of polymer loading, polymer nature and physico-chemical properties of the drug molecule.

Table 3.2 Zero order release profile of Metronidazole

Time (Min)	BC-1	BC-2	BC-3	BC-4	BC-5	BC-6
0	0.000	0.000	0.000	0.000	0.000	0.000
15	26.312	23.436	21.699	19.851	17.612	15.751
30	43.400	41.876	40.000	38.100	36.900	35.121
45	68.987	64.001	61.900	59.300	57.626	55.023
60	87.324	84.900	83.101	79.900	76.091	73.200
75	99.090	97.001	95.345	92.011	88.000	84.500

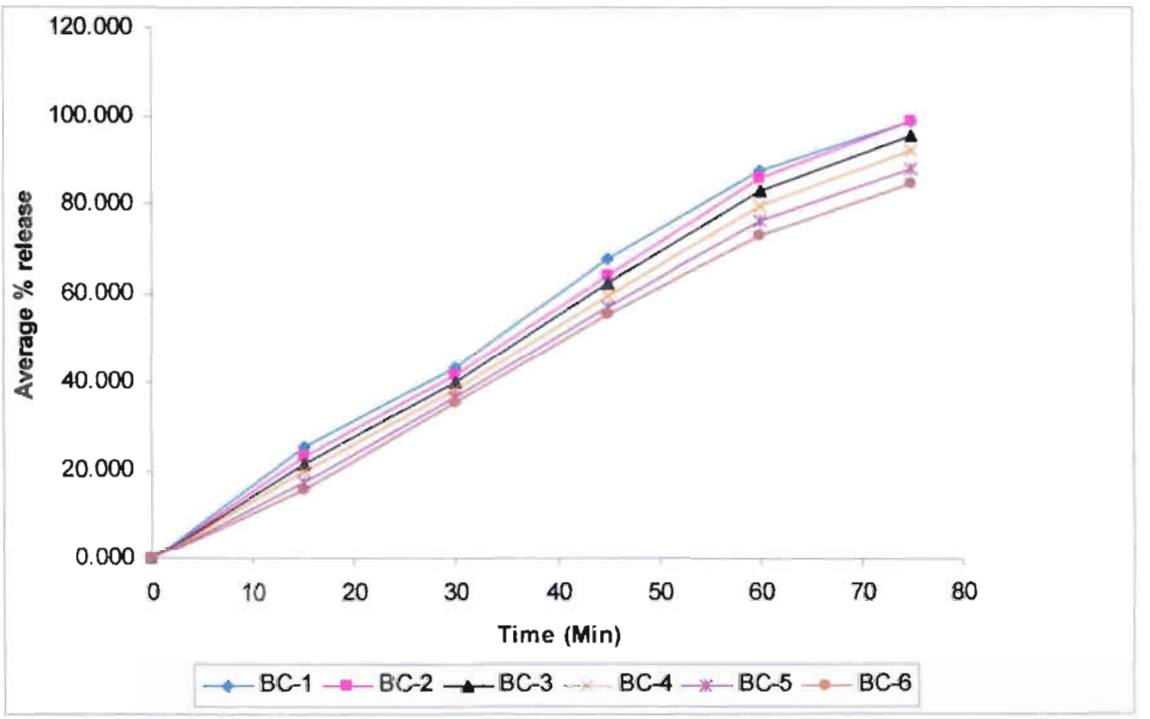


Figure 3.2: Zero order plot of release kinetics of Metronidazole

3.2.1 Zero order release profile of Metronidazole Immediate release tablets of different market preparations:

After collection of the market preparations their dissolution studies were performed with a rotation of 50 rpm at $37^0 \pm 0.5^0$ C using USP apparatus-II (Paddle method), placed in 900 mL dissolution media. Three tablets are used in each dissolution study and the release pattern of Metronidazole was monitored up to 75 minutes. The percentage of drug release of these six samples at different time intervals is shown at Table 3.2.

From the figure 3.2, release profile of these IR tablets was obtained. After 75 minutes the total percent release of Metronidazole from BC-1, BC-2, BC-3, BC-4, BC-5 and BC-6 was respectively. So, it was observed that drug release rate has been increased with the increase in time.

The highest percent of drug release within 75 minutes is from BC-1 whereas lowest percent of drug release within 75 minutes is from BC-6. The remaining samples shows intermediate release rate. From the zero order graph it has been shown that the rate of drug release is proportional to time elapsed. From these data, it seems that BC-1, BC-2, and BC-3 are the best market preparations.

Table 3.3 Higuchi release profile of Metronidazole

SQRT of Time (Min)	BC-1	BC-2	BC-3	BC-4	BC-5	BC-6
0.000	0.000	0.000	0.000	0.000	0.000	0.000
3.852	26.312	23.436	21.699	19.851	17.612	15.751
5.488	43.400	41.876	40.000	38.100	36.900	35.121
6.818	68.987	64.001	61.900	59.300	57.626	55.023
7.099	87.324	84.900	83.101	79.900	76.091	73.200
8.781	99.090	99.001	95.345	92.011	88.000	84.500

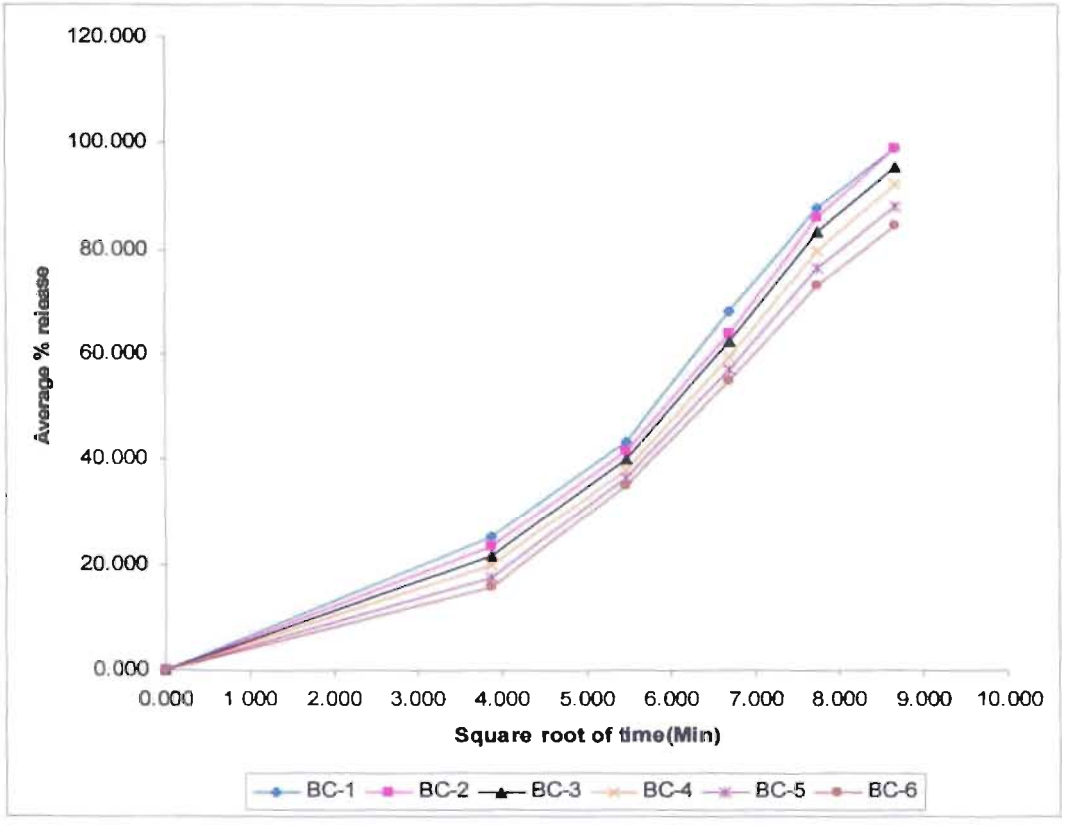


Figure 3.3: Higuchi plot of release kinetics of Metronidazole

3.3.1: Higuchi release profile of Metronidazole Immediate release tablets of different market preparations:

After collection of the market preparations their dissolution studies were performed with a rotation of 50 rpm at $37^0 \pm 0.5^0$ C using USP apparatus-II (Paddle method), placed in 900 mL dissolution media. Three tablets are used in each dissolution study and the release pattern of Metronidazole was monitored up to 75 minutes. The percentage of drug release of these six samples at different time intervals is shown at table 3.3.

From the figure 3.3, release profile of these IR tablets was obtained. After 75 minutes the total percent release of Metronidazole from BC-1, BC-2, BC-3, BC-4, BC-5 and BC-6 was respectively. So, it was observed that drug release rate has been increased with the increase in time.

The highest percent of drug release within 75 minutes is from BC-1 whereas lowest percent of drug release within 75 minutes is from BC-6. The remaining samples shows intermediate release rate. From the Higuchi graph it has been shown that the rate of drug release is proportional to time elapsed. From these data, it seems that BC-1, BC-2, and BC-3 are the best market preparations.

Table 3.4: First order release profile of Metronidazole

Time (Min)	BC-1	BC-2	BC-3	BC-4	BC-5	BC-6
0	2.000	2.000	2.000	2.000	2.000	2.000
15	1.673	1.888	1.887	1.903	1.916	1.927
30	1.769	1.767	1.775	1.792	1.803	1.812
45	1.509	1.551	1.577	1.608	1.633	1.654
60	1.078	1.151	1.223	1.308	1.377	1.431
75	0.000	0.000	0.672	0.902	1.079	1.191

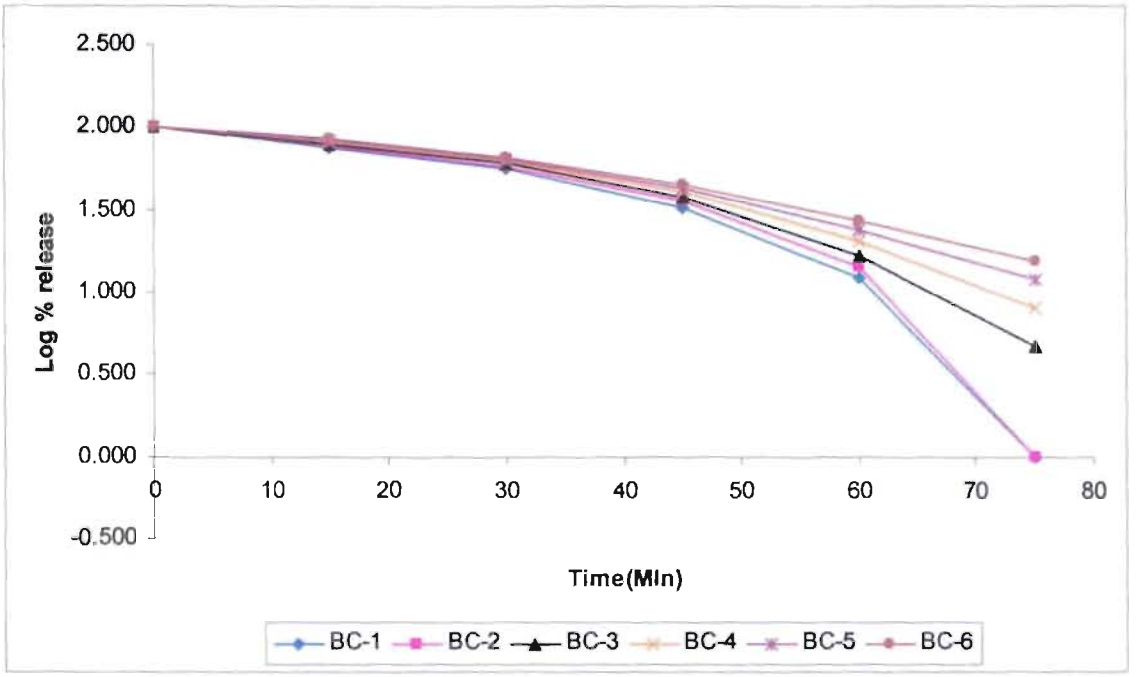


Figure 3.4: First order plot of release kinetics of Metronidazole

3.4.1: First order release profile of Metronidazole Immediate release tablets of different market preparations:

After collection of the market preparations their dissolution studies were performed with a rotation of 50 rpm at $37^0 \pm 0.5^0$ C using USP apparatus-II (Paddle method), placed in 900 mL dissolution media. Three tablets are used in each dissolution study and the release pattern of Metronidazole was monitored up to 75 minutes. The percentage of drug release of these six samples at different time intervals is shown at table 3.4.

From the figure 3.4, release profile of these IR tablets was obtained. After 75 minutes the total percent release of Metronidazole from BC-1, BC-2, BC-3, BC-4, BC-5 and BC-6 was respectively. So, it was observed that drug release rate has been increased with the increase in time.

The highest percent of drug release within 75 minutes is from BC-1 whereas lowest percent of drug release within 75 minutes is from BC-6. The remaining samples shows intermediate release rate. From the first order graph it has been shown that the rate of drug release is proportional to time elapsed. From these data, it seems that BC-1, BC-2, and BC-3 are the best market preparations.

Table 3.5 Korsmeyer release profile of Metronidazole

Log(Time)	BC-1	BC-2	BC-3	BC-4	BC-5	BC-6
0.000	0.000	0.000	0.000	0.000	0.000	0.000
1.177	-0.597	-0.632	-0.665	-0.699	-0.769	-0.804
1.577	-0.364	-0.380	-0.387	-0.419	-0.441	-0.461
1.753	-0.168	-0.185	-0.219	-0.226	-0.250	-0.260
1.768	-0.057	-0.078	-0.081	-0.099	-0.119	-0.136
1.874	-0.004	-0.005	-0.021	-0.037	-0.058	-0.077

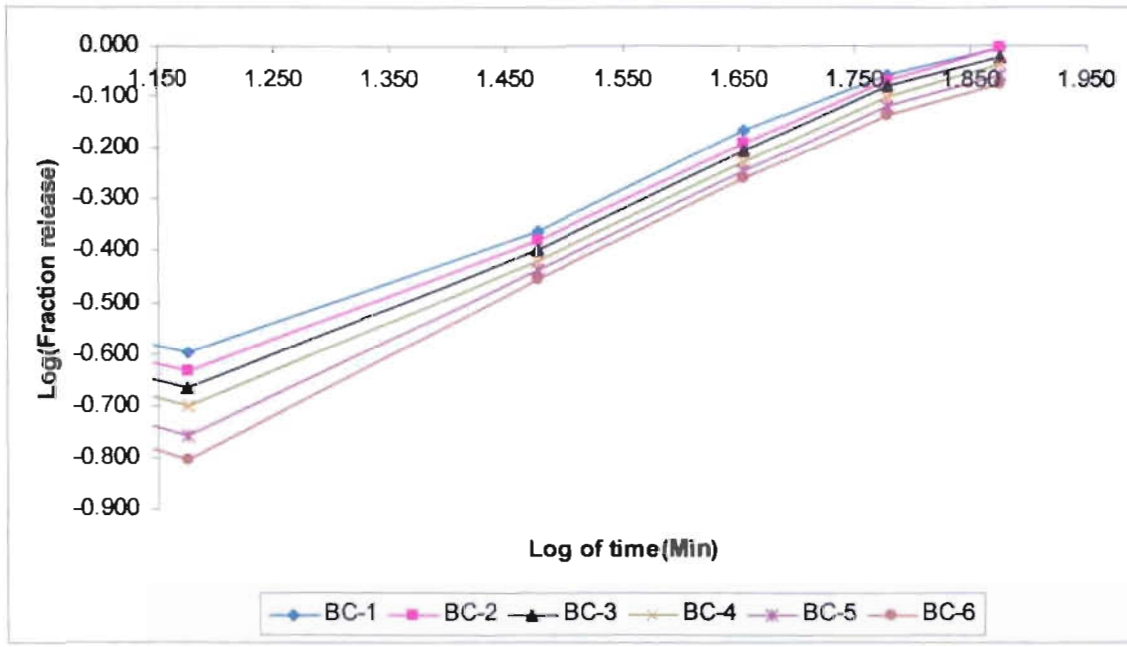


Figure 3.5: Korsmeyer plot of release kinetics of Metronidazole

3.5.1:Korsmeyer release profile of Metronidazole Immediate release tablets of different market preparations:

After collection of the market preparations their dissolution studies were performed with a rotation of 50 rpm at $37^0 \pm 0.5^0$ C using USP apparatus-II (Paddle method), placed in 900 mL dissolution media. Three tablets are used in each dissolution study and the release pattern of Metronidazole was monitored up to 75 minutes. The percentage of drug release of these six samples at different time intervals is shown at table 3.5.

From the figure 3.5, release profile of these IR tablets was obtained. After 75 minutes the total percent release of Metronidazole from BC-1, BC-2, BC-3, BC-4, BC-5 and BC-6 was respectively. So, it was observed that drug release rate has been increased with the increase in time.

The highest percent of drug release within 75 minutes is from BC-1 whereas lowest percent of drug release within 75 minutes is from BC-6. The remaining samples shows intermediate release rate. From the Korsmeyer graph it has been shown that the rate of drug release is proportional to time elapsed. From these data, it seems that BC-1, BC-2, and BC-3 are the best market preparations.

CHAPTER 4

CONCLUSION

4.1 Conclusion:

Metronidazole is bactericidal in vitro against many anaerobic gram-negative bacilli including Bacteroides fragilis and other Bacteroides species; also other species including Fusobacterium. The drug is effective against many anaerobic gram-positive cocci including Clostridium species, Eubacterium, and anaerobic Streptococcus. Metronidazole is also active against a wide range of pathogenic protozoa including Trichomonas vaginalis and other trichomonads, Entamoeba histolytica, Giardia lamblia, Balantidium coli and the causative organisms of acute ulcerative gingivitis. Each tablet contains 400 mg of Metronidazole. The physical properties of various marketed preparations described in table: 3.1 were found to be optimal for the manufacturing process. After performing dissolution study, Metronidazole release profiles were analyzed on the basis of various mathematical models such as zero order kinetic model, first order kinetic model, Higuchi release pattern, and Korsmeyer release pattern.

CHAPTER 5

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