2003

TRAZODONE HYDROCHLORIDE CONTROLLED RELEASEMATRIX AND MATRIX-MINI TABLETS

Kiran Penumatcha
University of Rhode Island

TRAZODONE HYDROCHLORIDE CONTROLLED RELEASE MATRIX AND MATRIX-MINI TABLETS

BY

KIRAN PENUMATCHA

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT

FOR THE DEGREE OF MASTER OF SCIENCE

IN

APPLIED PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND
2003

MASTER OF SCIENCES THESIS

OF

KIRAN PENUMATCHA

APPROVED:

Thesis committee

Major Professor Hossein Zia

R. Choudary Hanumala

Harold D Bibb

DEAN OF THE GRADUATE SCHOOL

UNIVERSITY OF RHODE ISLAND

2003

Abstract

The aim of present study was to prepare controlled release trazodone hydrochloride matrix tablets. The dissolution profiles at three pHs were carried out for 24 hrs to monitor release of drug from tablets. The effect of three variables, drug, HPMC, and Avicel contents, on the release of drug from the matrix was evaluated using a full 2^3 factorial design. T_{50} and T_{90} (time to release 50% and 90% drug respectively) were used as response parameters to study the effect of three variables mentioned above. The effect of tablet size was also studied by comparing the release from matrix-mini tablets and matrix tablet, which were made from the same formulation contents. The effect of three variables on the release of drug from the matrix was more evident on T_{90} rather than T_{50}. The percentage of drug release was slower at higher level of drug and HPMC and lower level of Avicel. Among the three variables, the amount of drug has significant effect on drug release. Even though drug release from the matrix tablets was closer to zero-order, 100% of the drug was not released completely. Matrix tablets have longer T_{50} and T_{90} compared to matrix-mini tablets. The experimental design was shown to be very useful in determining the direction for further optimization in order to achieve zero-order release.

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to my major advisor Dr. Hossein Zia for his continuous encouragement and incessant help throughout my master's degree.

I am grateful to Dr. Thomas Needham for his valuable suggestions. I would also like to thank Dr. R. C. Hanumara for being a committee member and for his great help in statistical analysis.

My special thanks to Dr. Phenil Patel, Mr. Subuddhi and to my friends for their help throughout this study. It is my pleasure to express my indebtedness to my parents and siblings for their tremendous support.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

1.1 Trazodone hydrochloride

Trazodone hydrochloride (1.2,4–Triazolo [4,3–a] pyridin-3(2H)-one, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl]- monohydrate) is an antidepressant agent structurally not related to the tricyclics, tetracyclic or monoamine oxidase inhibitors. It is a relatively specific but weak serotonin reuptake inhibitor, with minimal effects on dopamine and norepinephrine reuptake (Calkin et al. 1998). Therapeutic oral doses of trazodone in adult patients have ranged from 50 to 600 mg/day. Most patients respond to 100 to 300 mg/day in single or divided doses (Rawls 1982). Trazodone is used primarily in the treatment of mental depression or depression/anxiety disorders. The drug has also shown some efficacy in the treatment of benzodiazepine or alcohol dependence, diabetic neuropathy, and panic disorders. Trazodone has proven to be both safe and effective in elderly patients, having less adverse influence on cognitive and performance skills than amitryptiline (Bayer et al. 1989).

Trazodone has consistently been found to significantly improve insomnia, with little tolerance developing to its hypnotic effect. Trazodone improves sleep not only in major depressive disorder and dysthmic disorder but also in chronic primary insomnia associated with other anti- depressant medications (Calkin et al. 1998).

Trazodone has 89% to 95% plasma protein bonding and is rapidly and completely absorbed from the gastrointestinal tract. The drug is metabolized in the liver and excreted primarily in urine. The mean half-life is 4 to 7.5 hours. Therapeutic response may be seen within 3 to 7 days although optimal effects are seen after 2 to 6 weeks. Trazodone possesses a low incidence of of anticholinergic effects and produces minimal cardiovascular effects. However, ventricular arrythmias, hypotension, and heart block have occurred. Other adverse effects include drowsiness, weight gain, blurred vision, dizziness, and priapism.

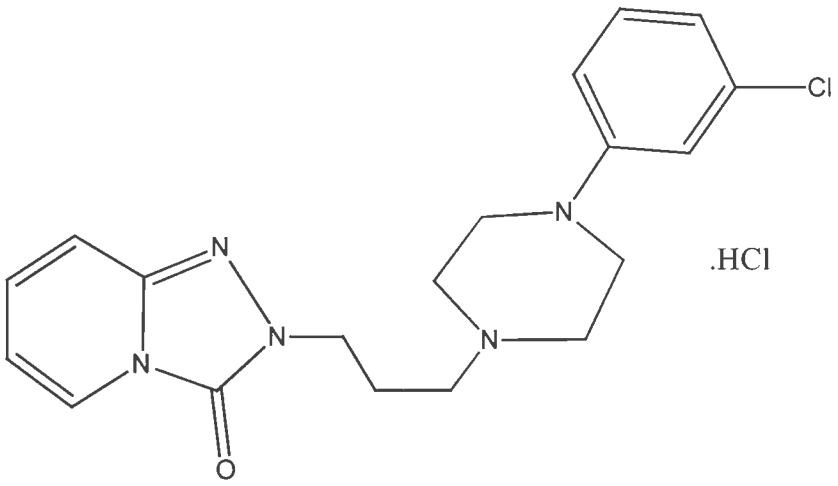


Figure 1: Chemical structure of trazodone hydrochloride

1.2 Controlled release dosage form

During the past two decades, significant advances have been made in the area of controlled release as evidenced by an increasing number of patents, publications, as

well as commercial controlled release products for the delivery of a variety of pharmaceutical compounds. This proliferation of interest is a reflection of the growing awareness that by achieving predictable and reproducible release rates of bioactive agents, particularly pharmaceuticals, to the target environment for a desired duration, optimum biological responses, compliance by patients, prolonged efficacy, decreased toxicity as well as reduction of required dose level as compared to the conventional mode of delivery can be effectively achieved (Lee et al. 1987).

Controlled release drug delivery system is capable of achieving, (1) maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuation; (2) predictable and reproducible release rates for extended duration; (3) enhancement of activity duration for short half life drugs; (4) elimination of side effects, frequent dosing, and waste of drug; (5) optimized therapy and better patient compliance (Lee et al. 1987).

1.3 Oral delivery

Historically, the most convenient and commonly employed method of drug delivery has been oral ingestion. There are many obvious reasons for this, not the least of which would include acceptance by the patient and ease of administration. The types of sustained release and controlled release systems employed for oral administration include virtually every known theoretical mechanism for such applications. This is because there is more flexibility in dosage design, since constraints such as sterility and potential damage at the site of administration, are reduced (Banker et al. 1996).

1.4 Classification of controlled drug release polymeric systems

Because of the relative ease of production and cost, as compared with other methods of sustained or controlled delivery, dissolution and diffusion-controlled systems have classically been of primary importance in oral delivery of medication. Dissolution based systems have been some of the oldest and most successful oral systems in early attempts to market sustaining products. Controlled release systems have been classified into the following categories: (1) Diffusion controlled systems (2) Chemically controlled systems (3) Swelling controlled systems (4) Magnetically controlled systems (5) Osmotically controlled devices (Langer et al. 1981) (6) Bioadhesive systems and (7) Gastric retention devices to control GI transit (Florence et al. 1994).

DIFFUSION CONTROLLED SYSTEMS

These systems are further classified into reservoir systems and matrix systems.

Membrane-reservoir devices, where the drug core is surrounded by a rate-controlling membrane, are often employed in the area of controlled release pharmaceuticals. In the solution-diffusion mechanism, the drug transport occurs by first dissolving in the membrane at one interface followed by diffusion down a chemical potential gradient across the membrane and eventually released from the second interface into the external medium. Under steady state conditions, a membrane device having a saturated drug reservoir can maintain a constant thermodynamic activity gradient

across the membrane for an extended period of time. As a result, a constant rate of drug release is established. The rate of release from such a system is generally dependent on the device geometry and the nature, thickness, and area of the membrane, whereas the duration of the release is governed by the size of the drug reservoir.

Membrane reservoir systems based on solution-diffusion mechanism have been utilized in different forms for the controlled delivery of therapeutic agents. These systems include microcapsules, liposomes, and hollow fibers (Lee et al. 1987).

In the matrix type of diffusion control systems, the drug is uniformly distributed throughout the polymer matrix and is released from the matrix at a uniform rate as drug particles dislodge from the polymer network. Unlike the reservoir, there is no accidental rupture of the membrane (Ranade 1990). Some of the materials used for matrix systems are insoluble, erodible materials such as carnauba wax, stearyl alcohol, stearic acid, polyethylene glycol, castor wax (Lachman et al. 1987), hydrophilic materials such as methyl cellulose, hydroxypropyl methyl cellulose (Ford 1999), hydroxy ethylcellulose, sodium carboxymethyl cellulose, sodium alginate, carageenans and insoluble inert materials such as polyethylene, polyvinyl chloride, methyl acrylate, ethylcellulose, etc., (Lachman et al. 1987).

CHEMICALLY CONTROLLED SYSTEMS

These systems are classified in to two types (i) Bioerodible systems (ii) Pendant chain systems. In the Bioerodible system, the controlled release of drugs involves polymers

that gradually decompose. The drug is dispersed uniformly throughout the polymer and is slowly released as the polymer disintegrates. Two major advantages of bioerodible systems are (1) polymers do not have to be removed from the body after the drug supply is exhausted; and (2) the drug does not have to be water-soluble.

In Pendant chain systems a drug molecule is chemically linked to the backbone of the polymer. In the body, in presence of enzymes or fluids, chemical hydrolysis or enzymatic cleavage occurs with concomitant release of the drug at a controlled rate (Ranade. 1990).

SWELLING CONTROLLED SYSTEMS

Swelling controlled release of potent drugs may be achieved by employing the glassy/rubbery transition of polymers in the presence of a penetrant, and the macromolecular relaxations associated with this transition. In these systems the drug is dispersed in a glassy polymer. There is no drug diffusion in the solid phase. As the dissolution medium penetrates the matrix, the polymer swells and its glass transition temperature is lowered below the temperature of the experiment. Therefore, the swollen polymer is in a rubbery state and it allows the drug contained in it to diffuse outwards (Langer et al. 1981).

Hydrogels: Hydrogels are defined as a polymeric material, which have the ability to swell in water without dissolving and to retain water within its structure. They are

generally described as two compartment systems. One compartment being hydrophilic insoluble, three-dimensional network and other being water (Swarbick et al. 1988). The hydrophilicity of the polymer imparts water-attracting properties to the system. Their characteristic water-insoluble behavior is attributed to the presence of chemical or physical cross-links, which provide a network structure and physical integrity to the system. Hydrogels are elastic in nature because of the presence of a memorized reference configuration to which they return even after being deformed for a long period of time (Silberberg 1989). Preparation of a hydrogel-based drug product involves either cross-linking of linear polymers or simultaneous polymerization of monofunctional monomers and cross-linking with polyfunctional monomers (Bouwstra et al. 1993). Polymers from natural, synthetic or semi-synthetic sources can be used for synthesizing hydrogels. Usually, polymers containing hydroxyl, amine, amide, ether, carboxylate and sulfonate as functional groups in their side chains are used.

MAGNETICALLY CONTROLLED SYSTEMS

Magnetically controlled targeted drug delivery systems are aimed at concentrating drugs at defined site (Gupta et al 1989). In these systems, drug and small magnetic beads are uniformly dispersed within a polymer matrix. Upon exposure to aqueous media, drug is released in a fashion typical of diffusion-controlled matrix systems (Langer et al. 1981). Two major advantages of the magnetically responsive carrier system over other drug delivery systems are high efficiency for in *vivo* targeting and

its controllable release of drugs at the microvascular level. A magnetically controlled delivery mechanism has been used to deliver anti-tumor agents, antibiotics, insulin, and fibrinolytic agents (Ranade. 1990).

OSMOTICALLY CONTROLLED DEVICE

Osmotic pressure was first employed as an energy source to deliver active ingredients in the 1950s (Rose et al. 1955). Because pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure, there has been increasing interest in the development of osmotic devices in the past two decades. The elementary osmotic pump (EOP) was introduced by Theeuwes in the 1970s. The EOP consists of an osmotic core, with the drug surrounded by a semipermeable membrane drilled with a delivery orifice. In operation, the osmotic core acts by imbibing water from the surrounding medium via the semipermeable membrane. Subsequently, drug solution was generated within the device and delivered out of the device via the orifice. The EOP is very simple to prepare and releases drug at an approximate zero-order rate (Theeuwes et al. 1972). However, the generic EOP is only suitable for the delivery of water-soluble drugs.

To overcome the limit of EOP, a push-pull osmotic tablet was developed in the 1980s. Adalat® nifedipine tablet is a commercialized push-pull osmotic tablet product made by Pfizer. The push-pull osmotic tablet consists of two compartments, one containing drug and the other an osmotic agent and an expandable agent. A semipermeable membrane that regulates water influx into both compartments surrounds the system.

An orifice was drilled into the surface of the drug compartment to allow drug release (Theeuwes et al. 1984). While the push-pull osmotic tablet succeeds in delivering water-insoluble drug, it has two disadvantages: (1) the tablet core is prepared by compressing two kinds of compartments together, a complex technology as compared with that of monolithic tablets; and (2) after coating, a complicated laser-drilling technology should be employed to drill the orifice next to the drug compartment (Geerke 1997).

BIOADHESIVE SYSTEMS AND GASTRIC RETENTION DEVICES TO CONTROL GI TRANSIT

Floating drug delivery systems

Floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), are currently utilized in the prolongation of the gastric residence times (GRT). FDDS or hydrodynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in plasma drug concentrations in some cases (Singh et al. 1999).

Based on the mechanism of buoyancy, two distinctly different technologies, i.e., noneffervescent and effervescent systems, have been utilized in the development of FDDS.

Noneffervescent FDDS

The most commonly used excepients in noneffervescent FDDS are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier (Hilton et al 1986). The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier.

Effervescent FDDS

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel® or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid (Rubinstein et al. 1994). The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme (Rubinstein et al. 1994). The carbon dioxide generating components may be intimately mixed within the tablet matrix, in which case a single-layered tablet is produced (Hashim et

al. 1987), or a bilayered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a SR effect (Ingani et al. 1987).

Bio (mucoadhesive) gastrointestinal drug delivery systems:

Mucoadhesion involves the attachment of a natural or synthetic polymer to a biological substrate. It is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. In recent years there has been an increased interest in mucoadhesive polymers for drug delivery (Peppas et al. 1985).

A mucoadhesive controlled-release device can improve the effectiveness of a treatment by helping to maintain the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site.

Mucoadhesion also increases the intimacy and duration of contact between a drug-containing polymer and a mucous surface. It is believed that the mucoadhesive nature of the device can increase the residence time of the drug in the body. The combined effects of the direct drug absorption and the decrease in excretion rate allow for an increased bioavailability of the drug with a smaller dosage and less frequent administration (Huang et al. 2000).

An advantage of using a mucoadhesive polymer carrier for drug delivery is the prevention of first-pass metabolism of certain protein drugs by the liver through the introduction of the drug via a route bypassing the digestive tract. Drugs that are

absorbed through the mucosal lining of tissues can enter directly into the bloodstream and not be inactivated by enzymatic degradation in the gastrointestinal tract (Park et al 1984). A polymeric device allows for slow, controlled, and predictable drug release over a period of time and hence reduces the overall amount of drug needed.

1.5 Purpose of the study

The conventional tablets of trazodone hydrochloride available in the United States are 50mg, 100mg, 150mg, and 300mg. Controlled release tablets provide desired plasma levels within therapeutic window over a long period of time. The incidence of local and systematic side effects frequently observed after the intake of immediate release dosage forms will be reduced by controlled release tablets. The encapsulated matrix mini-tablet approach has the advantages of multiparticles (pellets) such as reduced risk of dose dumping, minimal food effect, and flexibility of adjusting dosage strengths. Further more, mini-tablets are easier to manufacture compared to the coated multiparticulate systems. Factorial design may be useful for screening purposes or as an aid in identifying individual effects in complex systems. The factorial design shows interaction between factors that a 'one at a time' model cannot reveal (Vastraj et al. 2002).

2. EXPERIMENTAL

2.1 MATERIALS

1. Trazodone Hydrochloride, Batch # 921473

   Orion Corporation, Espoo, Finland.

2. Hydroxypropyl methylcellulose K4M Premium CR, Lot # 0I25012N12

   The Dow Chemical Company, Midland, MI 48674

3. Avicel PH 102. Lot # 2205

   FMC Corporation, Newark, DE 19711.

4. Magnesium Stearate, Lot # 742748

   Fisher Scientific, Fair Lawn, NJ 07410.

5. Cab-O-Sil, Lot # 1I238

   Cabot Corporation, Tuscola, IL 61953.

6. Sodium Phosphate Tribasic, Lot # M50204

   Spectrum Quality Products Inc., New Brunswic, NJ 08901.

7. Hydrochloric Acid, Lot # 932379

   Fisher Chemical, Fair Lawn, NJ 07410

2.2 EQUIPMENT

1. USP Dissolution Apparatus I, Model # 11-7000

   Vankel Industries, Cary, NC 27513.

2. Hewlett Packard 8541 A Diode Array Spectrophotometer

   Hewlett Packard Company, Corvallis, OR.

3. Carver Laboratory Press, Model # C

   Fred. S. Carver Inc., Menomonee Falls, WI 53051

4. pH Meter, Model # IQ 240

   IQ Scientific Instruments Inc., San Diego, CA 92127

5. Magnetic Stirrer, Model # A 338436

   Fisher Scientific, Fair Lawn, NJ 07410.

6. Turbula Mixer, Model # 1PH

   Turbula, Basel, Switzerland.

7. Analytical Balance, Model # AE-240S

   Mettler Instrument Corporation, Hightown, NJ

2.3 METHODS

2.3.1 CONSTRUCTION OF THE CALIBRATION CURVE OF TRAZODONE HYDROCHLORIDE

Serial concentrations of trazodone hydrochloride in 0.1 N HCl buffer (pH 1.2), phosphate buffers (pH 5 and pH 7.4) having concentrations between 0-150 mcg/ml were prepared. The absorbance of the prepared solutions was measured spectrophotometrically at λ_{max} 312 nm. The absorbance was plotted against the concentration and regression lines were calculated.

2.3.2 PREPARATION OF TRAZODONE HYDRCHLORIDE TABLETS

Mixing: Trazodone hydrochloride, hydroxy propyl methylcellulose (HPMC), Avicel PH 102 and Cab-O-Sil were weighed and sieved through a sieve of mesh size 40. The ingredients of the formulation were mixed in the desired ratio, according to the formulation (Table 1) for 15 minutes in a turbula mixer to achieve a homogeneous mixture.

Lubrication: Magnesium stearate was weighed and passed through a sieve of mesh size 80 and added to the above powder blend for lubrication purpose and mixed for an additional 5 minutes in the turbula mixer.

Compaction: Two kinds of tablets were prepared from each of the eight formulations. One kind was matrix-mini tablets (round concave, punch size 6 mm in diameter) and

Table 1: List of ingredients and their quantities used for eight formulations

Ingredients	Form # 1	Form # 2	Form # 3	Form # 4	Form # 5	Form # 6	Form # 7	Form # 8
Trazodone.HCl	50	75	50	50	75	50	75	75
HPMC K4M	40	40	50	40	50	50	40	50
Avicel PH 102	5	5	5	10	5	10	10	10
Magnesium Stearatre	1	1	1	1	1	1	1	1
Cab-O-Sil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	96.5	121.5	106.5	101.5	131.5	111.5	126.5	136.5

All the quantities are in mg

the other was matrix tablets (round concave, punch size 9 mm in diameter). Two matrix-mini tablets from each formulation were encapsulated into a hard gelatin capsule size #2 and put in to basket of USP Dissolution apparatus 1. The matrix tablet was prepared by weighing exactly double the quantity of matrix-mini tablet from each formulation. Tablets were prepared by direct compression on a Carver Laboratory press machine. The compression pressure was adjusted at 3000lb. The hardness was ranged from 6.4-6.9 kg for matrix-mini tablets and 5.1-6.0 kg for matrix tablets. Friability was ranged from 0.8-0.9% for matrix-mini tablets and 0.5-0.6% for matrix tablets. The surface areas of tablets prepared from eight formulations were given in Table 2.

2.3.3 TABLET EVALUATION

In vitro Dissolution:

The *in vitro* drug release was studied in various pH media in order to simulate *in vivo* dissolution behavior. The solution pH values selected were 1.2, 5 and 7.4. The dissolution was carried out using USP apparatus I (basket method). Six tablets were tested from each formulation. The volume of the media was 900 ml in each cylinder and 50 rotations per minute (rpm) was maintained. The temperature of the dissolution medium was maintained at 37±0.5° C. The dissolution tests were carried out for total of 24 hrs, in which pH was maintained at 1.2 for first 1 hr, pH 5 for next 5 hrs (pH was increased using 4.6 gms of sodium phosphate tribasic/900 ml) and pH 7.4 for remaining 16 hrs (pH was increased using 4.8 gms of sodium phosphate tribasic/900 ml). Samples of 4ml were taken from each cylinder at the interval of 0.5, 1, 2, 4, 6, 8,

Table 2: Surface area (mm^2) of tablets

Formulation #	Matrix-mini tablets	Matrix tablets
1	263.97	220.87
2	268.89	224.10
3	265.33	221.65
4	268.65	221.27
5	269.68	224.44
6	265.53	221.68
7	269.31	224.15
8	272.02	224.70

12, 18, and 24 hr. The collected samples were filtered and analyzed at λ_{max} 312 nm using spectrophotometer.

2.3.4 EXPERIMENTAL DESIGN

A 2^3 full factorial design was employed to study the effect of different formulation variable on tablet release. The three independent variables were selected after primary screening for the study are summarized in Table 3. X_1 represents the amount of trazodone, X_2 is amount of HPMC and X_3 is the amount of Avicel PH 102. All other processing and formulation variables remained constant throughout the study. Table 4 lists a total of 8 experiments required for a 2^3 full factorial design. All the three variables are kept at two levels- high (+) and low (-). The response parameters are Y_1, T_{50} (time required to release 50% of the drug from the formulation); Y_2, T_{90} (time required to release 90% of the drug from the formulation).

Table 3: List of factors and their range

Factors:	+1 Max	-1 Min
X_1: Amount of drug (mg)	**75**	**50**
X_2: Amount of HPMC K4M (mg)	**50**	**40**
X_3: Amount of Avicel PH 102 (mg)	**10**	**5**

Table 4: 2^3 full factorial design

Form #	X_1 (trazodone)	X_2 (HPMC)	X_3 (Avicel)
1	-	-	-
2	+	-	-
3	-	+	-
4	-	-	+
5	+	+	-
6	-	+	+
7	+	-	+
8	+	+	+

2.3.5 ANALYSIS OF DATA

All the statistical and regression analysis procedures for the response parameters were performed using a Minitab software package. Statistical analysis includes the determination of coefficients of regression equation for each response variable, analysis of variance (ANOVA) to determine the significance of each independent variable (X1, X_2, and X_3), two-way interactions (X_1 X_2, X_2X_3, and X1 X_3) and three-way interactions (X_1 X_2 X_3), main effect plots and interaction plots. Contour plots are also generated to study the effect of different formulation variables on the response parameters. (Vastraj et al. 2002). All the experiments were carried out twice to perform ANOVA.

The general linear model used for the experimental design was:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_1 X_2 + \beta_5 X_2 X_3 + \beta_6 X_1 X_3 + \beta_7 X_1 X_2 X_3$$

3. RESULTS AND DISCUSSION

3.1 CALIBRATION CURVE OF TRAZODONE HYDROCHLORIDE IN DIFFERENT BUFFERS

Table 5 illustrates the absorbencies of the serial concentrations of trazodone hydrochloride in HCl buffer pH 1.2. Figure 2 shows the standard curve of trazodone hydrochloride at pH 1.2. The concentration of trazodone hydrochloride in this buffer was calculated using the following equation.

$$\text{Concentration (mcg/ml)} = (\text{Absorbance} - 0.016) / 0.0082 \qquad \text{(Eqn. 1)}$$

Table 6 illustrates the absorbencies of the serial concentrations of trazodone hydrochloride in phosphate buffer pH 5.0. Figure 3 shows the standard curve of trazodone hydrochloride at pH 5.0. The concentration of trazodone hydrochloride in this buffer was calculated using the following equation.

$$\text{Concentration (mcg/ml)} = (\text{Absorbance} - 0.002) / 0.0086 \qquad \text{(Eqn. 2)}$$

Table 7 illustrates the absorbencies of the serial concentrations of trazodone hydrochloride in phosphate buffer pH 7.4. Figure 4 shows the standard curve of trazodone hydrochloride at pH 7.4. The concentration of trazodone hydrochloride in this buffer was calculated using the following equation.

$$\text{Concentration (mcg/ml)} = (\text{Absorbance} + 0.0099) / 0.0084 \qquad \text{(Eqn. 3)}$$

Table 5: Standard calibration data for trazodone hydrochloride in HCl buffer (pH 1.2)

Concentration (mcg/ml)	Absorbance
0	0
25	0.223
50	0.439
75	0.651
100	0.839
125	1.036
150	1.245

Figure 2: Standard curve of trazodone hydrochloride in HCl buffer (pH 1.2)

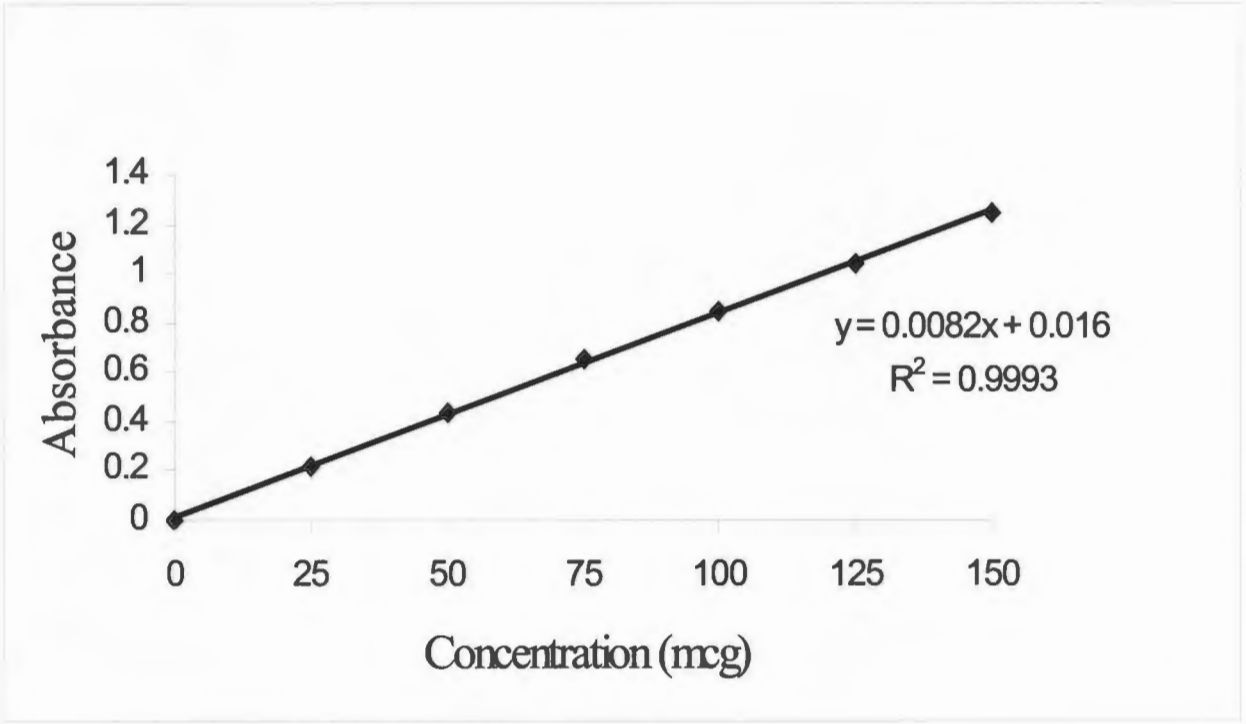


Table 6: Standard calibration data for trazodone hydrochloride in phosphate buffer (pH 5.0)

Concentration (mcg/ml)	Absorbance
0	0
25	0.213
50	0.438
75	0.649
100	0.86
125	1.051
150	1.299

Figure 3: Standard curve of trazodone hydrochloride in phosphate buffer (pH 5.0)

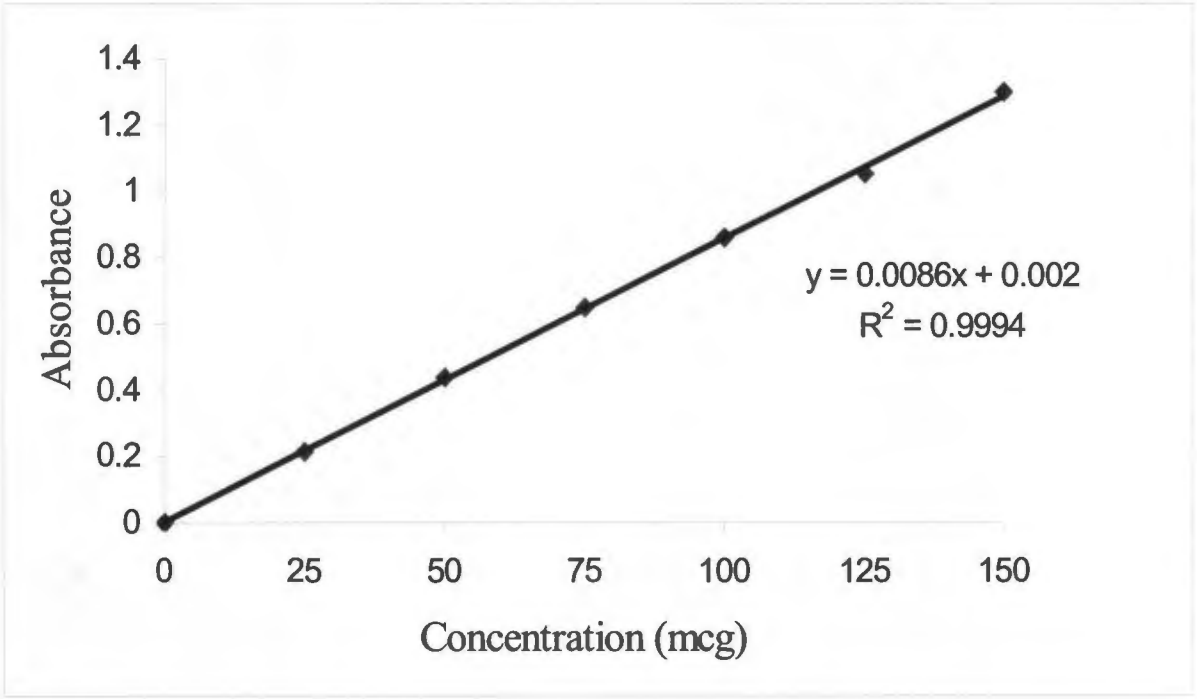
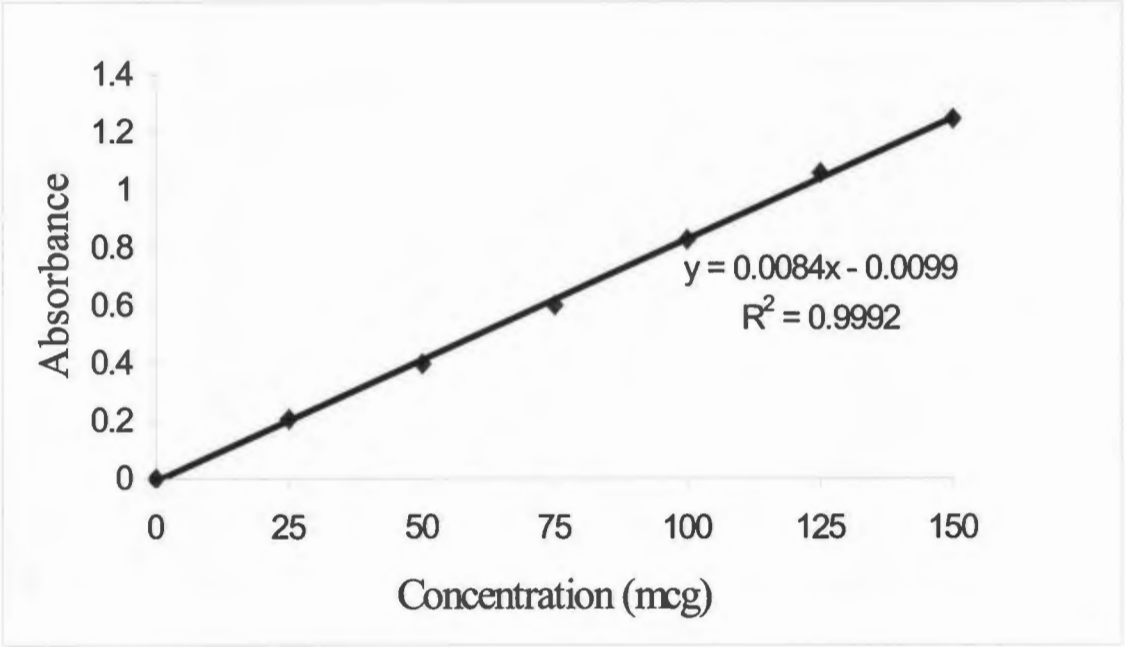


Table 7: Standard calibration data for trazodone hydrochloride in phosphate buffer (pH 7.4)

Concentration (mcg/ml)	Absorbance
0	0
25	0.205
50	0.397
75	0.601
100	0.827
125	1.056
150	1.245

Figure 4: Standard curve of trazodone hydrochloride in phosphate buffer (pH 7.4)



3.2 DIFFUSIONAL COEFFICIENT

Hydroxypropylmethyl cellulose (HPMC) is a polymer, which is frequently used in sustained release matrices. The mechanism by which it retards drug release center on its ability to rapidly form a gel layer around the surface of a matrix exposed to aqueous fluids (Alderman, 1984). As the matrix contacts the dissolution medium, the polymer undergoes a relaxation process and two fronts are established around the matrix: the penetration front and the dissolution front. The penetration front is defined as the interface between the non-relaxed polymer and the gel; the dissolution front is defined as the interface between the gel and the dissolution medium. At the penetration front, the hydration, swelling and coalescence of polymer particles occur, whereas at the dissolution front, polymer chain disentanglement and dissolution of the hydrated matrix occur (Lee and Peppas, 1987: Harland et al., 1988: Skoug et al., 1993: Pham and Lee, 1994: Gao et al., 1995).

For drugs with low water solubility, drug release is mainly via erosion; for a soluble drug, the drug can dissolve and diffuse through the hydrated gel layer and diffusion is predominant (Alderman, 1984; Doelker, 1987; Skoug et al., 1993).

Korsmeyer et al. (1983) used a simple empirical equation, Eqn 4, to describe general solute release behavior from controlled release polymeric matrices.

$$Mt/M\infty = k\, t^{n} \qquad \text{(Eqn.4)}$$

Where $Mt/M\infty$ is the fraction of drug released, k is the drug release constant, t is the time and n is the diffusional exponent. Peppas (1985) stated that n is 0.5 for Fickian diffusion, $0.5 < n > 1.0$ for non-Fickian transport and 1.0 for case II transport.

Figure 5 shows the dissolution curve for all eight batches of matrix-mini tablets. Table 8 shows the dissolution data for eight batches of matrix-mini tablets. T_{50} and T_{90} of formulations # 2, 5, 7 and 8, which have higher drug load, are longer than remaining formulations. Figure 6 shows the dissolution curve for all eight batches of matrix tablets. Table 9 shows the dissolution data for eight batches of matrix tablets.

T_{50} and T_{90} of formulations # 2, 5, 7 and 8, which have higher drug load, longer than remaining formulations.

Table 10 compares T_{50} and T_{90} of matrix-mini tablets and matrix tablets. Matrix tablets released drug slowly compared to matrix-mini tablets with higher T_{50} and T_{90}, which is a desirable characteristic for controlled release formulations. This may be due to higher surface area of matrix-mini tablets (Table 2).

Table 11&12 show the values of n, k and R^2 for matrix-mini tablets and matrix tablets respectively. The correlation coefficient was greater than 0.95 in most cases indicating a good fit of the equation (the results of early drug release 0.5, 1, 2 hr were omitted, because at the beginning of the dissolution study, the drug present on the surface of the tablet rapidly comes in to dissolution medium and which is not the case later on). All the n values lie between 0.5-1.0 indicating a non-Fickian transport (Peppas., 1985).

Even though n values of matrix tablets were close to 0.89 indicating a zero-order release, the total drug release was in the range of 90.00-98.70%. In the case of matrix-mini tablets, the total drug release was in the range of 93.02-100%.

Figure 5: Dissolution curve of eight batches of trazodone hydrochloride matrix-mini tablets

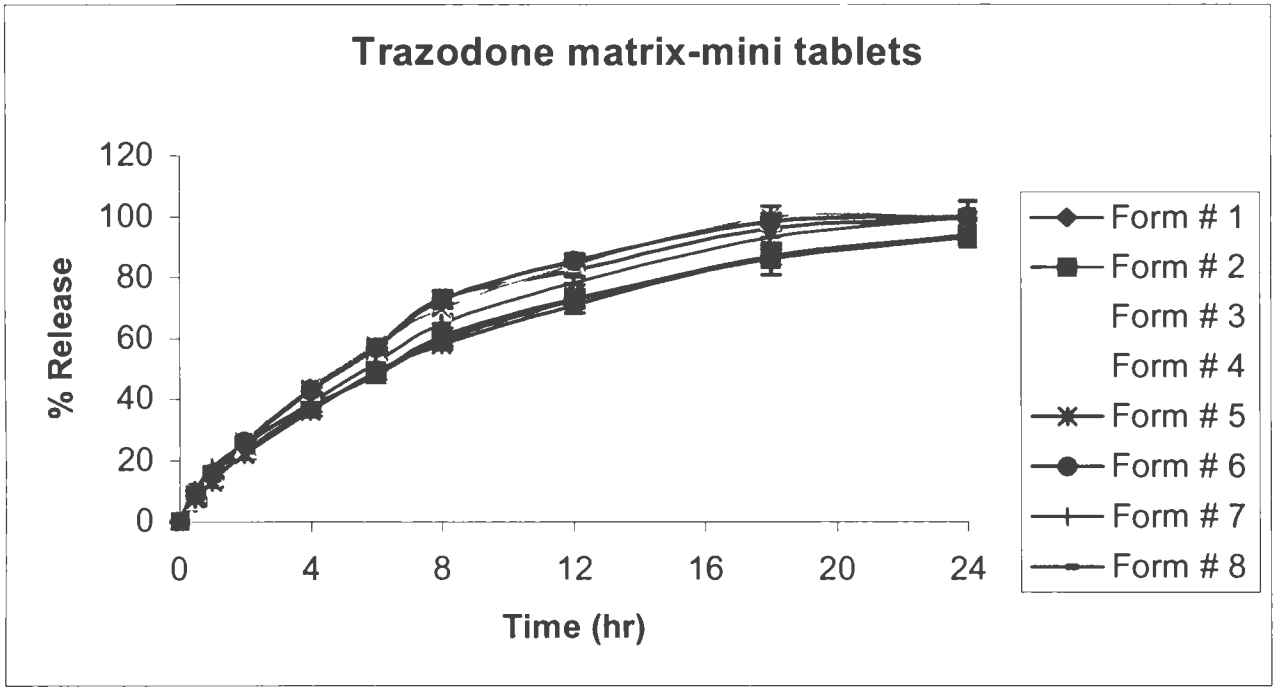


Table 8: Dissolution data for eight batches of trazodone hydrochloride matrix-mini tablets

Time (hr)	Form # 1	Form # 2	Form # 3	Form # 4	Form # 5	Form # 6	Form # 7	Form # 8
0	0	0	0	0	0	0	0	0
0.5	6.26 ± 1.17	9.54 ± 0.62	7.19 ± 0.53	9.40 ± 1.33	7.61 ± 1.73	8.98 ± 1.00	10.41 ± 0.56	9.46 ± 0.71
1	14.73 ± 0.78	15.33 ± 1.00	15.07 ± 0.49	15.99 ± 1.39	13.15 ± 1.68	15.49 ± 1.26	17.62 ± 0.56	16.40 ± 0.90
2	24.98 ± 0.98	23.26 ± 0.66	23.88 ± 0.57	26.49 ± 1.11	22.02 ± 1.60	26.23 ± 1.56	25.20 ± 1.97	23.12 ± 1.02
4	43.50 ± 1.83	37.13 ± 0.94	42.28 ± 1.61	43.90 ± 1.70	36.14 ± 1.71	43.10 ± 2.32	38.98 ± 0.99	37.20 ± 1.18
6	57.19 ± 2.11	48.10 ± 1.35	55.10 ± 1.82	57.87 ± 1.81	48.98 ± 1.72	56.83 ± 1.72	51.84 ± 1.07	47.77 ± 1.20
8	73.03 ± 2.56	60.68 ± 1.39	68.97 ± 2.25	69.76 ± 1.87	58.06 ± 1.79	72.56 ± 2.51	64.65 ± 1.38	58.92 ± 1.49
12	82.29 ± 4.64	73.12 ± 2.47	85.19 ± 2.55	84.17 ± 1.78	70.78 ± 2.39	85.56 ± 1.76	78.10 ± 2.21	72.27 ± 2.21
18	96.06 ± 7.24	86.21 ± 5.17	98.38 ± 2.67	100 ± 3.53	86.87 ± 2.73	98.20 ± 1.62	92.28 ± 2.56	86.67 ± 2.54
24	99.33 ± 5.75	93.02 ± 2.85	100 ± 1.08	100 ± 1.10	93.87 ± 3.36	100 ± 0.94	99.79 ± 2.52	93.74 ± 2.23

Dissolution data in % average release ± SD

Figure 6: Dissolution curve for eight batches of trazodone hydrochloride matrix tablets

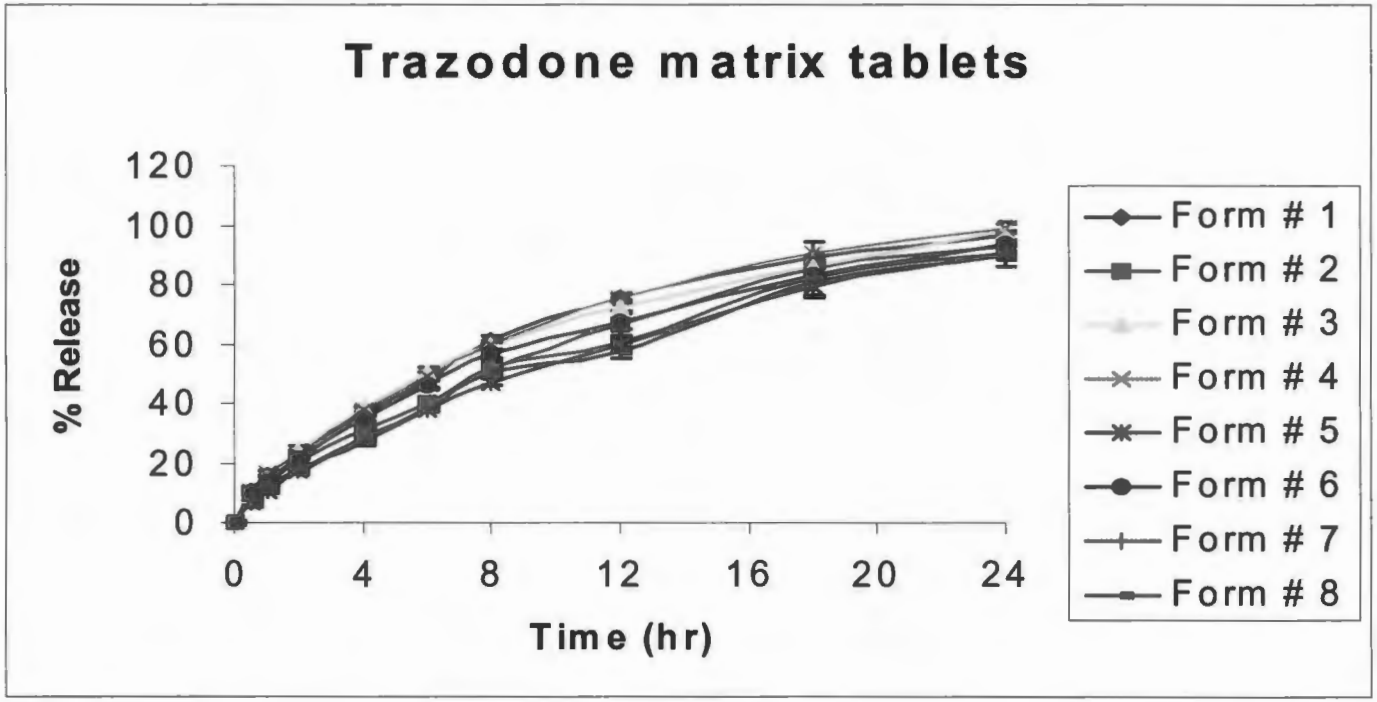


Table 9: Dissolution data for eight batches of trazodone hydrochloride matrix tablets.

Time (hr)	Form # 1	Form # 2	Form # 3	Form # 4	Form # 5	Form # 6	Form # 7	Form # 8
0	0	0	0	0	0	0	0	0
0.5	10.32 ± 0.43	8.39 ± 0.32	9.24 ± 1.71	10.85 ± 1.14	7.04 ± 1.38	9.44 ± 1.06	7.56 ± 0.28	7.02 ± 0.85
1	15.53 ± 0.19	13.01± 0.6	13.57 ± 0.72	16.70 ± 0.95	10.66 ± 0.36	13.10 ± 1.14	11.77 ± 1.50	10.90 ± 0.37
2	22.87 ± 0.44	20.06± 1.00	24.38 ± 1.30	22.92 ± 0.97	17.31 ± 0.41	20.88 ± 1.08	17.64 ± 0.37	16.63 ± 0.38
4	36.19 ± 0.93	30.58 ± 0.94	38.28 ± 1.06	37.60 ± 0.78	28.88 ± 0.79	34.88 ± 1.26	28.17 ± 0.76	27.02 ± 1.56
6	47.22 ± 2.01	40.36 ± 0.62	50.28 ± 1.92	49.34 ± 0.98	37.79 ± 1.06	46.31 ± 1.57	38.63 ± 1.26	38.03 ± 1.33
8	61.49 ± 0.97	51.37± 1.05	59.76 ± 1.94	59.65 ± 1.52	46.99 ± 1.23	56.53 ± 1.87	51.89 ± 2.83	50.92 ± 2.84
12	75.28 ±1.77	66.39 ± 1.35	72.35 ± 2.03	75.40 ± 1.22	59.97 ± 1.43	66.81 ± 4.22	60.43 ± 1.64	57.53 ± 2.59
18	88.78 ± 1.30	85.35 ± 1.46	86.17 ± 2.04	90.53 ± 3.79	79.14 ± 3.35	83.15 ± 2.45	81.93 ± 1.47	80.97 ± 4.47
24	96.83 ± 1.58	92.81 ± 1.57	97.79 ± 3.05	98.70 ± 1.43	90.83 ± 2.41	93.95 ± 4.27	90.90 ± 2.07	90.00 ± 3.71

Dissolution data in % average release± SD

Table 10: Comparison of T_{50} & T_{90} of matrix-mini tablets and matrix tablets

Time (hr)	Form # 1		Form # 2		Form # 3		Form # 4		Form # 5		Form # 6		Form # 7		Form # 8	
	M.M Tab	Mat Tab	M.M Tab	Mat Tab	M.M Tab	Mat Tab	M.M Tab	Mat Tab	M.M Tab	Mat Tab	M.M Tab	Mat Tab	M.M Tab	Mat Tab	M.M Tab	Mat Tab
T_{50}	4.95	6.3	6.1	6.3	5.2	6.0	4.8	6.1	5.95	8.1	4.9	6.3	5.7	7.3	4.5	8.5
T_{90}	14.9	16.3	18.7	23.0	14.25	17.4	13.95	16.7	19.5	23.5	13.7	17.3	16.1	18.0	20.05	22.5

M.M. Tab- matrix-mini tablet, Mat.Tab- matrix tablet

Table 11: Values of kinetic constant (k), release exponent (n) and correlation coefficient (R^2) following linear regression of dissolution data analyzed by equation 4 for matrix-mini tablets.

Form. #	n	Log k (hr^{-1})	R^2
1	0.558	1.291	0.948
2	0.566	1.229	0.980
3	0.550	1.258	0.958
4	0.549	1.306	0.963
5	0.588	1.202	0.983
6	0.554	1.300	0.956
7	0.568	1.257	0.982
8	0.571	1.222	0.985

Table 12: Values of kinetic constant (k), release exponent (n) and correlation coefficient (R^2) following linear regression of dissolution data analyzed by equation 4 for matrix tablets

Form. #	n	Log k (hr^{-1})	R^2
1	0.553	1.252	0.972
2	0.638	1.117	0.989
3	0.513	1.295	0.990
4	0.544	1.268	0.985
5	0.647	1.078	0.998
6	0.540	1.239	0.989
7	0.652	1.082	0.982
8	0.663	1.060	0.979

3.3 EFFECT OF FORMULATION VARIABLES ON T_{50} OF MATRIX-MINI TABLETS

T_{50} indicates the time required to release 50% of the drug from the formulation. T_{50} ranged from 4.5–6.1 hr, in the conducted eight batches of dissolution experiments. Figure 7 shows the main effects plot for T_{50}. T_{50} was higher at a high concentration of drug (75mg) and low concentrations of HPMC (40mg) and Avicel (5mg). Figure 8 shows the interaction plot of T_{50} for the matrix mini-tablets, there is an interaction between the pairs of all the three variables since the lines in the plot are either intersecting with each other or they are not parallel to each other. If the lines are parallel to each other, it means there is no interaction between the factors. In order to statistically determine the significance of each of the three formulation variables in dissolution of the matrix-mini tablets, an ANOVA (analysis of variance) was performed. Table 13 shows ANOVA results for T_{50}. The ANOVA table shows that the amount of drug, HPMC and Avicel were statistically significant at alpha 0.05. All the dual interactions (drug*HPMC, drug*Avicel, HPMC*Avicel) and the three way interactions (drug*HPMC*Avicel) also significantly affected the rate of release of drug from the mini tablets. Figure 9 shows the surface wire plot for T_{50} of the amount of drug and the amount of HPMC. The time taken to release 50% of drug was highest when the amount of drug was 75 mg and the amount of HPMC was 40 mg. Figure 10 shows the surface wire plot for T_{50} of the amount of drug and the amount of Avicel. The time taken to release 50% of drug was highest when the amount of drug was 75 mg and the amount of Avicel was 5 mg. Tukey test was performed for the T_{50} values

Figure 7: Main effects plot of data means of T_{50} of matrix mini-tablets

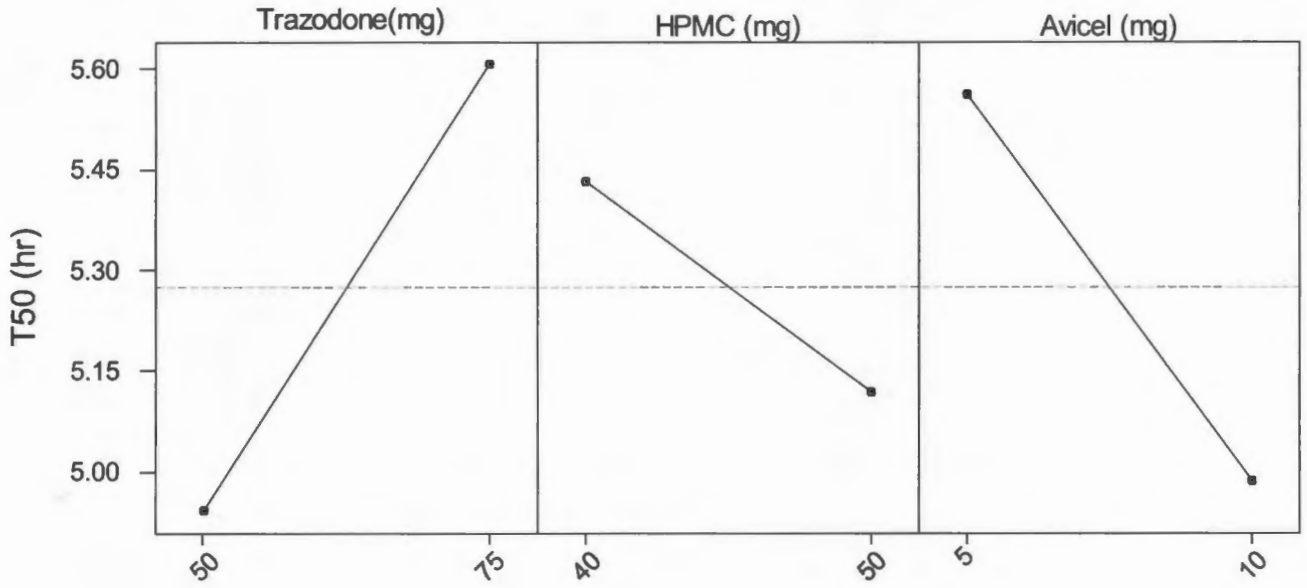


Figure 8: Interaction plot for data means of T_{50} of matrix mini-tablets

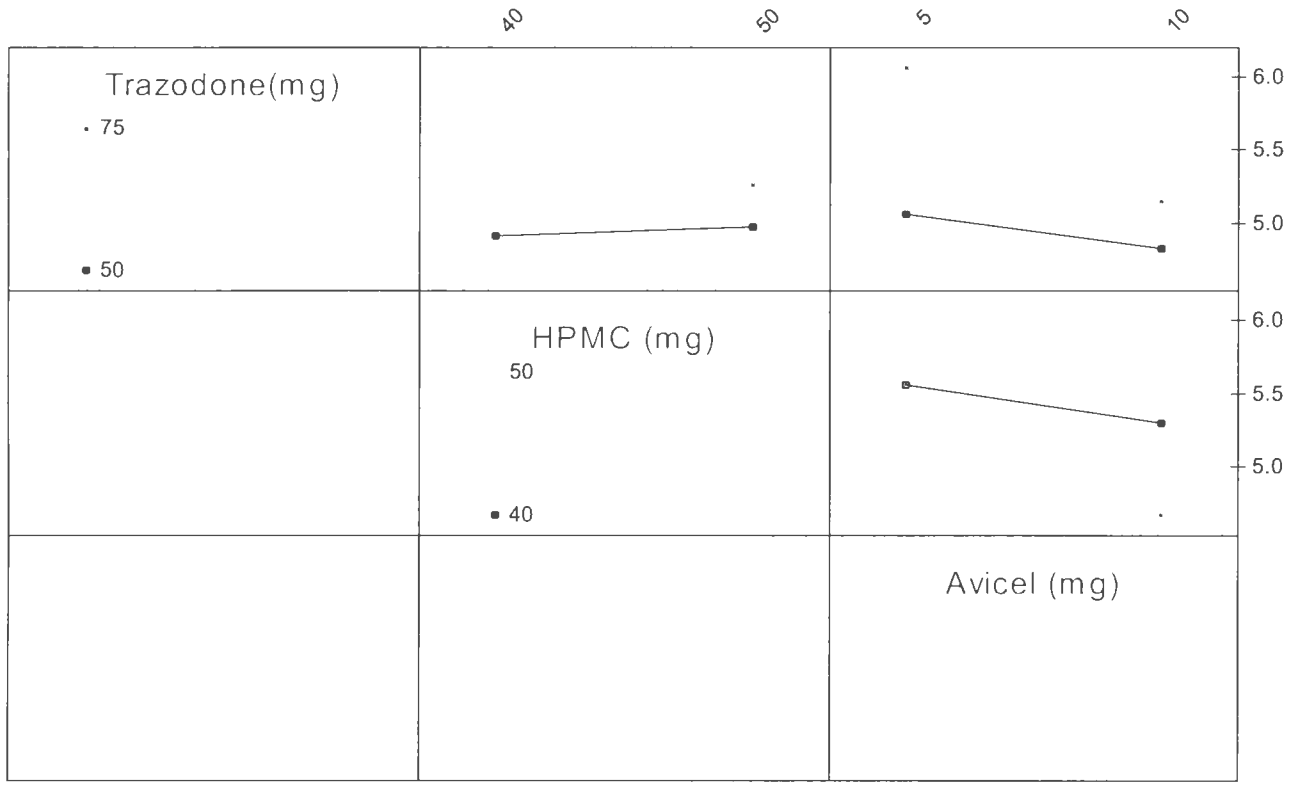


Table 13: Analysis of variance (ANOVA) of T_{50} of matrix-mini tablets.

Source	DF	Seq SS	Adj SS	Adj MS	F	P
drug	1	1.75562	1.75562	1.75562	295.68	0.000
HPMC	1	0.39062	0.39062	0.39062	65.79	0.000
Avicel	1	1.32250	1.32250	1.32250	222.74	0.000
drug*HPMC	1	0.56250	0.56250	0.56250	94.74	0.000
drug*Avicel	1	0.45562	0.45562	0.45562	76.74	0.000
HPMC*Avicel	1	0.39062	0.39062	0.39062	65.79	0.000
drug*HPMC*Avicel	1	0.16000	0.16000	0.16000	26.95	0.001
Error	8	0.04750	0.04750	0.00594		
Total	15	5.08500				

Figure 9: Surface wire plot of trazodone vs HPMC for T_{50} of matrix mini-tablets

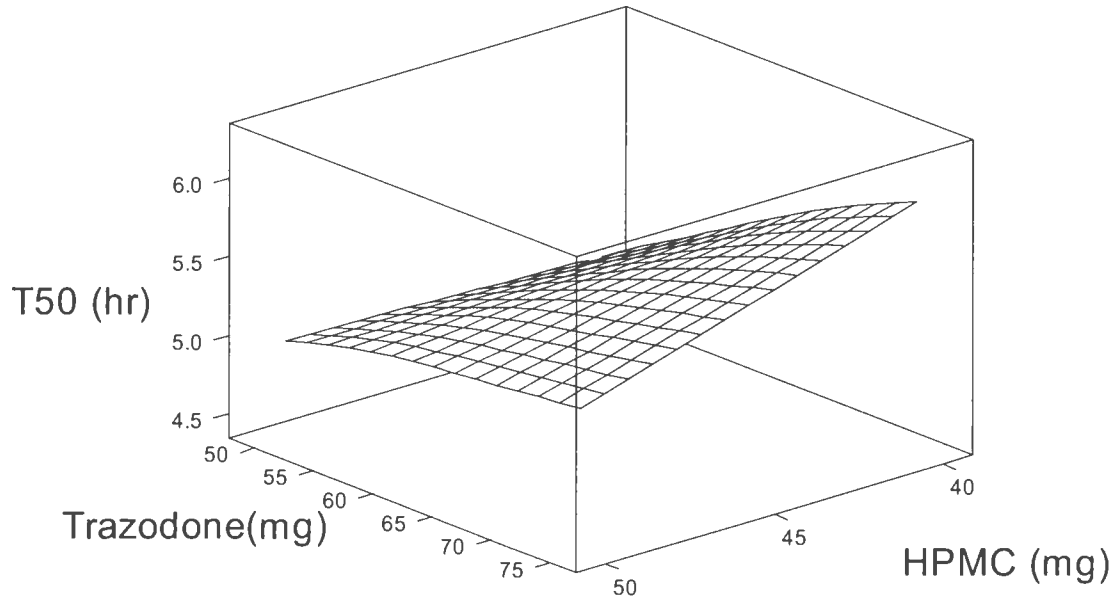
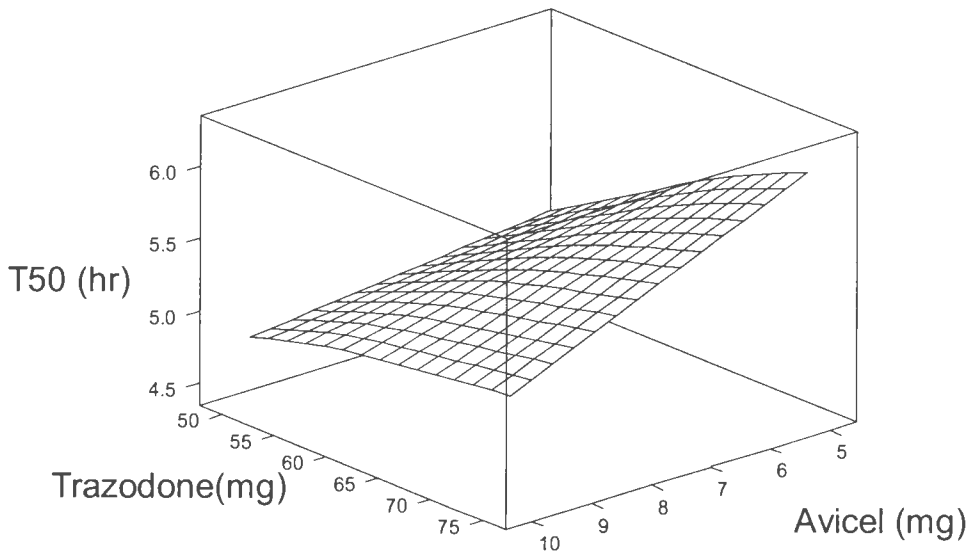


Figure 10: Surface wire plot of trazodone vs Avicel for T_{50} of matrix mini-tablets



of matrix-mini tablets prepared from eight formulations and the result was given in Table 14. The basis of grouping was attributed to the closeness of T_{50} values.

3.4 EFFECT OF FORMULATION VARIABLES ON T_{90} MATRIX-MINI TABLETS

T_{90} indicates the time required to release 90% of the drug from the formulation. T_{90} ranged from 13.7–20.05 hr, in the eight batches tested during dissolution experiments. Figure 11 shows the main effects plot for T_{90}. T_{90} was higher at high concentrations of drug (75mg) and of HPMC (50 mg) and at low concentration of Avicel (5 mg). Figure 12 shows the interaction plot for T_{90}, there is an interaction between pair of X_1, X_2 (amount of drug and HPMC respectively) as the lines are not parallel, X_2, X_3 (amount of HPMC and Avicel respectively) as the lines are intersecting with each other. There is no interaction between pair X1, X3 (amount of Drug and Avicel respectively) as the lines are almost parallel. Table 15 shows ANOVA results of the T_{90} .The ANOVA table shows that the amount of drug, HPMC and Avicel were statistically significant at alpha 0.05. All the two-way interactions (drug*HPMC, drug*Avicel, HPMC*Avicel) and the three way interactions (drug*HPMC*Avicel) also significantly affected the rate of release of drug from the matrix-mini tablets. Figure 13 shows the surface wire plot for T_{50} of the amount of drug and the amount of HPMC. The time taken to release 90% of drug was highest when the amount of drug was 75 mg and the amount of HPMC was 50 mg. Figure 14 shows the surface wire plot for T_{50} of the amount of drug and the amount of Avicel. The time taken to release 90% of drug was highest when the amount of drug was 75 mg and the amount of Avicel was 5 mg. Tukey test was performed for the T_{90} values of matrix-mini tablets prepared from eight

Table 14: Tukey test for T_{50} of matrix-mini tablets

Means with the same letter are not significantly different*.

Tukey Grouping	Mean (T_{50})	N	Formulation #
A	6.150	2	2
A			
B A	5.975	2	5
B			
B	5.750	2	7
C	5.150	2	3
C			
D C	4.975	2	1
D			
D	4.850	2	4
D			
D E	4.800	2	6
E			
E	4.525	2	8

* Minimum significant difference was 0.2926

Figure 11: Main effects plot of data means of T_{90} of matrix mini-tablets

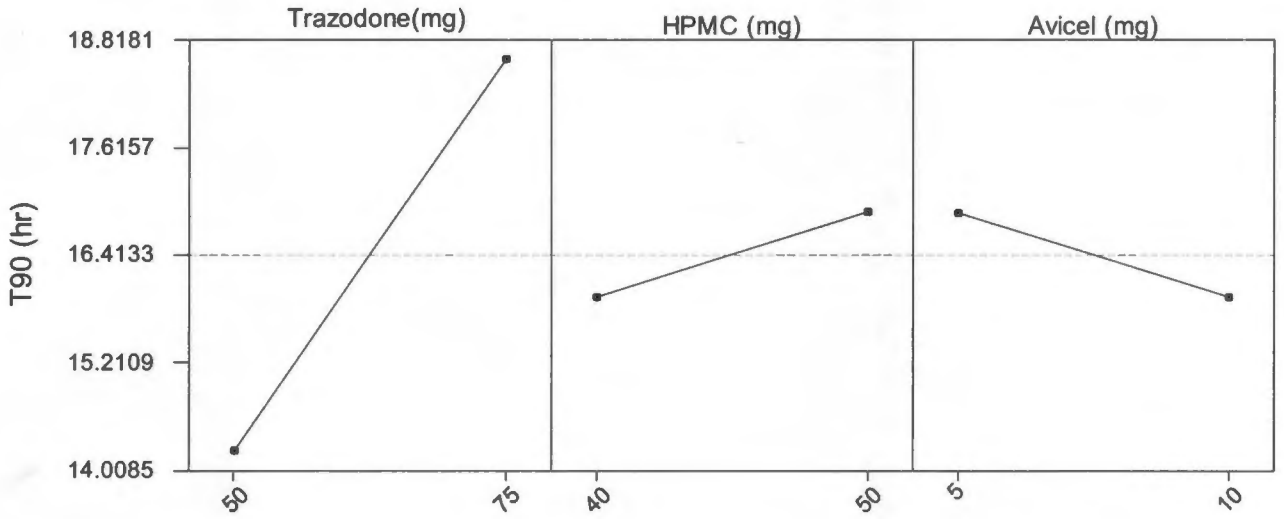


Figure 12: Interaction plot of data means of T_{90} of matrix mini-tablets

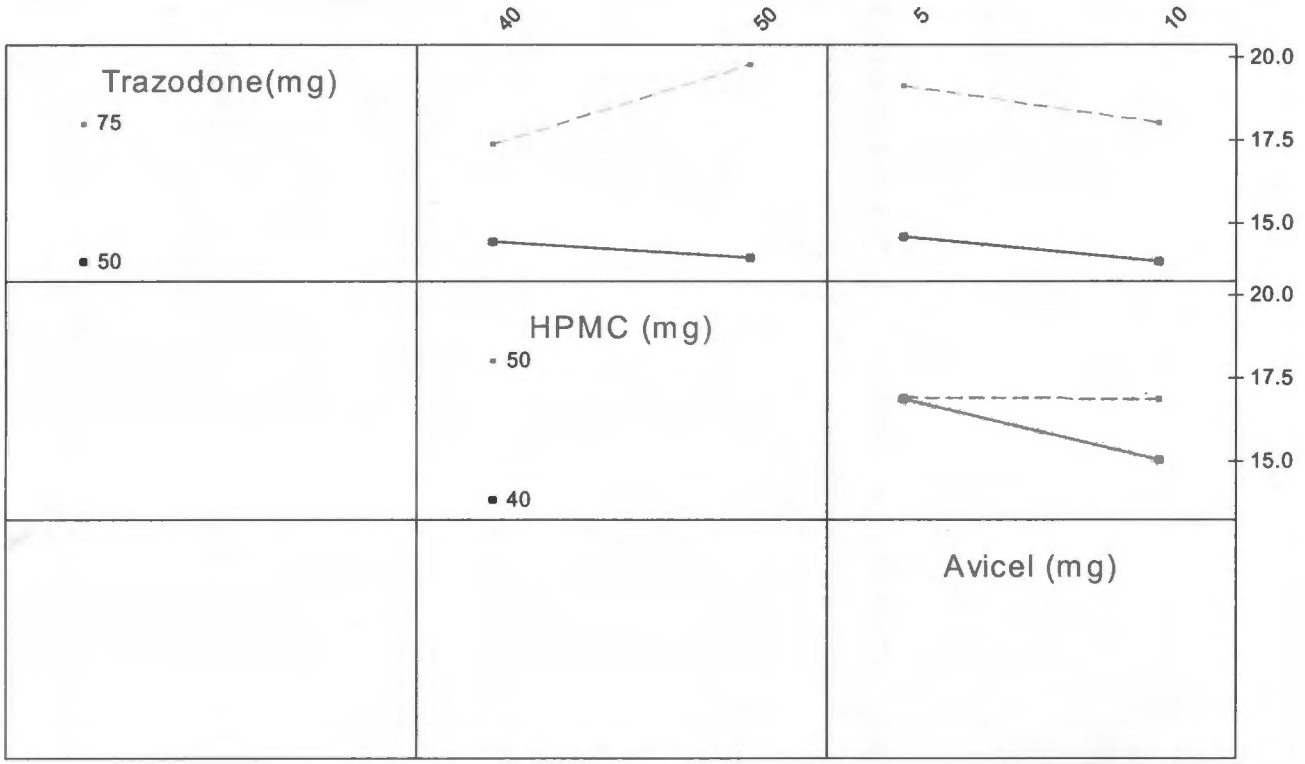


Table 15: Analysis of variance (ANOVA) of T_{90} of matrix-mini tablets

Source	DF	Seq SS	Adj SS	Adj MS	F	P
drug	1	76.126	76.126	76.126	1.5E+04	0.000
HPMC	1	3.610	3.610	3.610	722.00	0.000
Avicel	1	3.516	3.516	3.516	703.12	0.000
drug*HPMC	1	8.410	8.410	8.410	1682.00	0.000
drug*Avicel	1	0.141	0.141	0.141	28.12	0.001
HPMC*Avicel	1	3.063	3.063	3.063	612.50	0.000
drug*HPMC*Avicel	1	1.960	1.960	1.960	392.00	0.000
Error	8	0.040	0.040	0.005		
Total	15	96.864				

Figure 13: Surface wire plot of trazodone vs HPMC for T_{90} of matrix mini-tablets

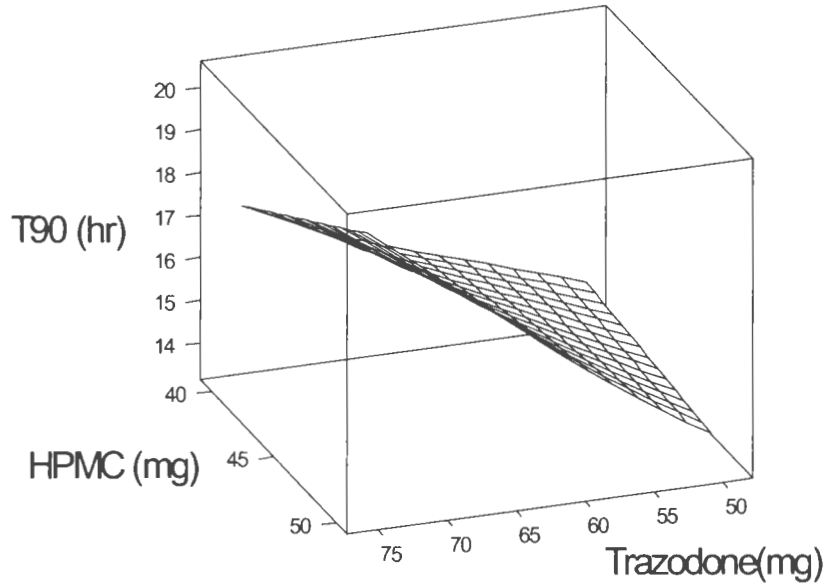
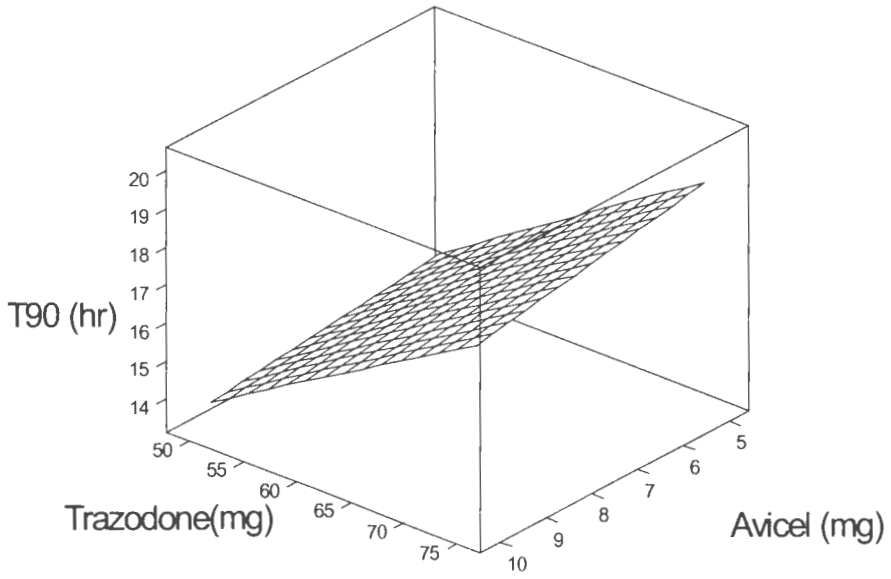


Figure 14: Surface wire plot of trazodone vs Avicel for T_{90} of matrix mini-tablets



formulations and the result was given in Table 16. The basis of grouping was attributed to the closeness of T_{90} values.

3.5 EFFECT OF FORMULATION VARIABLES ON T_{50} OF MATRIX TABLETS

T_{50} indicates the time required to release 50% of the drug from the formulation. T_{50} ranged from 6.0–8.9 hr, in the conducted eight batches of dissolution experiments. Figure 15 shows the main effects plot for T_{50}. T_{50} was higher at high concentrations of drug (75mg) and of HPMC (50mg) and at low concentration of Avicel (5mg). Figure 16 shows the interaction plot for T_{50}, for the matrix tablets, there is an interaction between the pairs of X_1, X_2 (amount of drug and HPMC respectively) as the lines are not parallel, X_2, X_3 (amount of HPMC and Avicel respectively) as the lines are intersecting with each other. There is no interaction between pair X1, X3 (amount of drug and Avicel respectively) as the lines are almost parallel. In order to statistically determine the significance of each of the three formulation variables, an ANOVA (analysis of variance) was performed. Table 17 shows ANOVA results for T_{50}. The ANOVA table shows that the amount of drug and HPMC were statistically significant at alpha 0.05. All the dual interactions (drug*HPMC, drug*Avicel, HPMC*Avicel) and the three way interactions (drug*HPMC*Avicel) also significantly affected the rate of release of drug from the matrix tablets.

Figure 17 shows the surface wire plot for T_{50} of the amount of drug and the amount of HPMC. The time taken to release 50% of drug was highest when the amount of drug was 75 mg and the amount of HPMC was 50 mg. Figure 18 shows the surface wire plot for T_{50} of the amount of drug and the amount of Avicel. The time taken to release

Table 16: Tukey test for T_{90} of matrix-mini tablets

Means with the same letter are not significantly different*.

Tukey Grouping	Mean (T_{90})	N	Formulation #
A	20.025	2	8
B	19.575	2	5
C	18.750	2	2
D	16.050	2	7
E	14.950	2	1
F	14.275	2	3
F			
F	14.025	2	4
G	13.700	2	6

* Minimum significant difference was 0.2798

Figure 15: Main effects plot of data means of T_{50} of matrix tablets

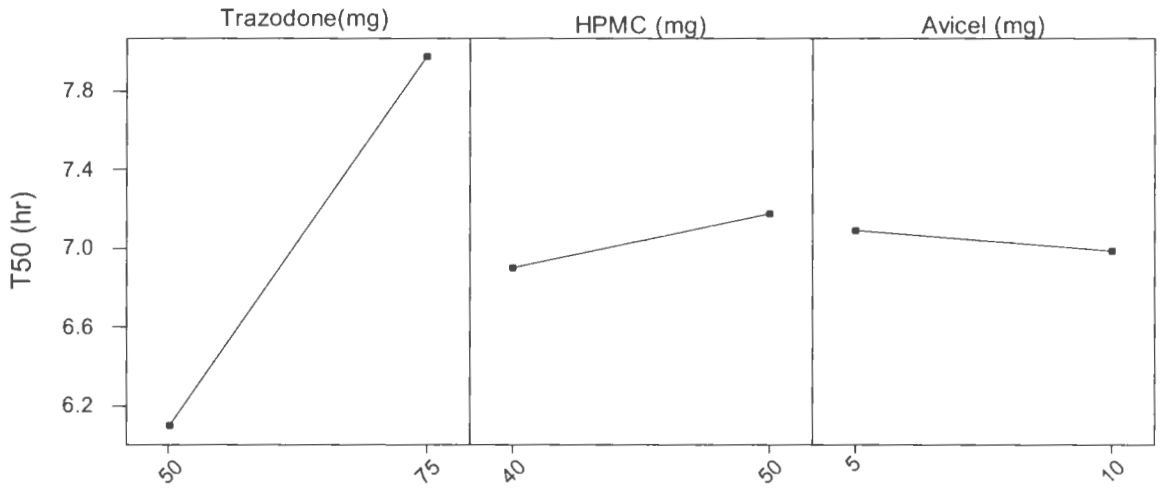


Figure 16: Interaction plot of data means of T_{50} of matrix tablets

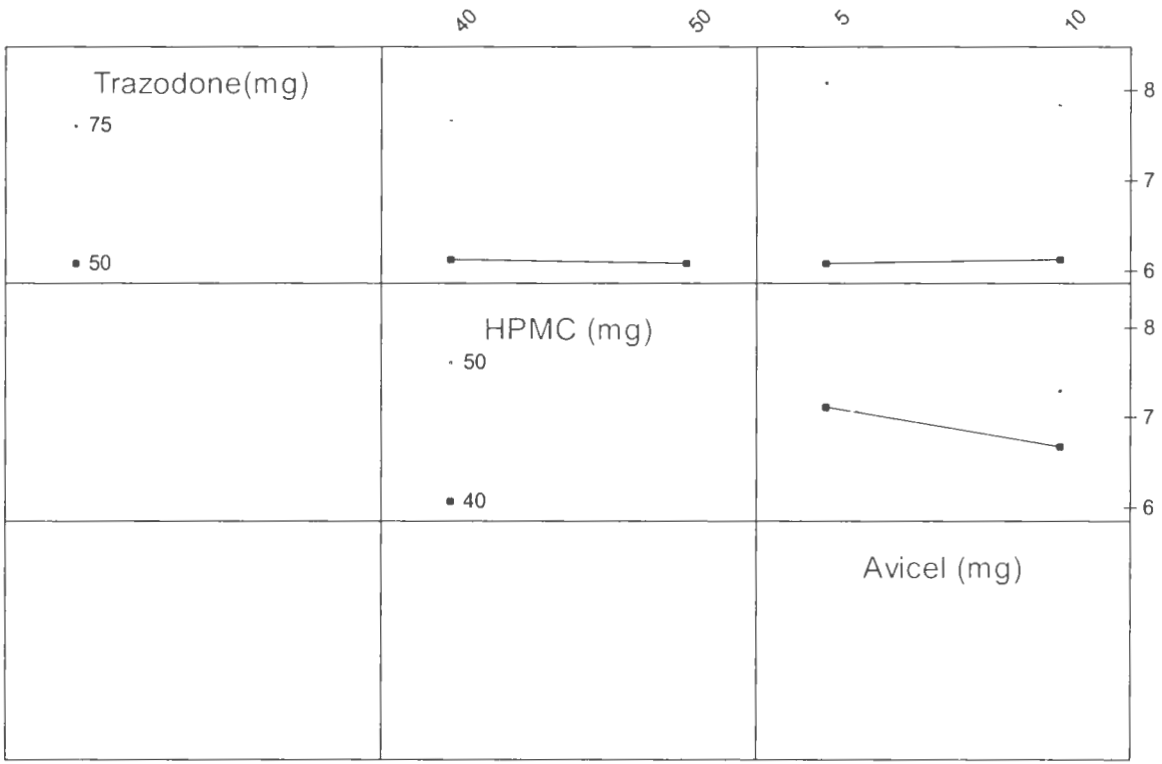


Table 17: Analysis of variance (ANOVA) for T_{50} of matrix tablets

Source	DF	Seq SS	Adj SS	Adj MS	F	P
drug	1	14.0625	14.0625	14.0625	1406.25	0.000
HPMC	1	0.3025	0.3025	0.3025	30.25	0.001
Avicel	1	0.0400	0.0400	0.0400	4.00	0.081
drug*HPMC	1	0.4225	0.4225	0.4225	42.25	0.000
drug*Avicel	1	0.0900	0.0900	0.0900	9.00	0.017
HPMC*Avicel	1	0.4900	0.4900	0.4900	49.00	0.000
drug*HPMC*Avicel	1	0.0900	0.0900	0.0900	9.00	0.017
Error	8	0.0800	0.0800	0.0100		
Total	15	15.5775				

Figure 17: Surface wire plot of trazodone vs HPMC for T_{50} of matrix tablets

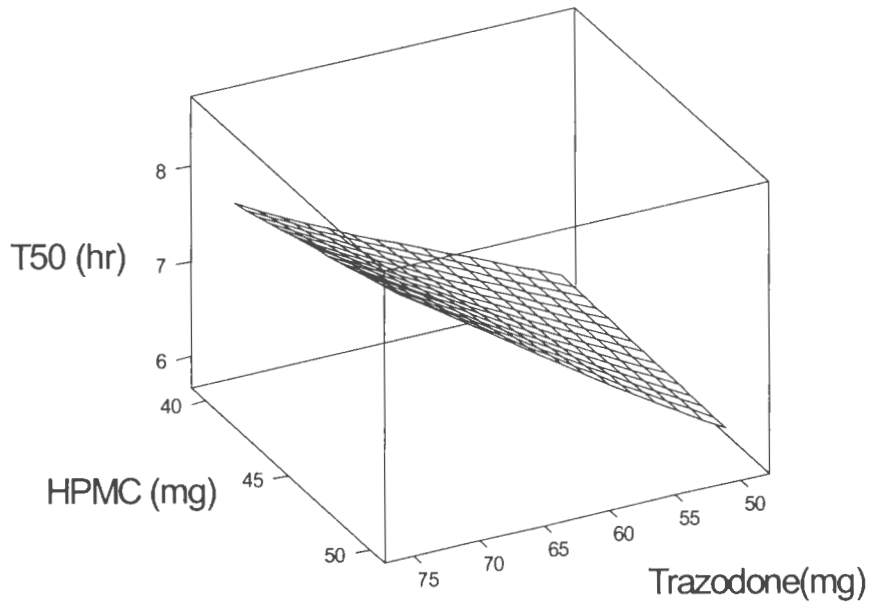
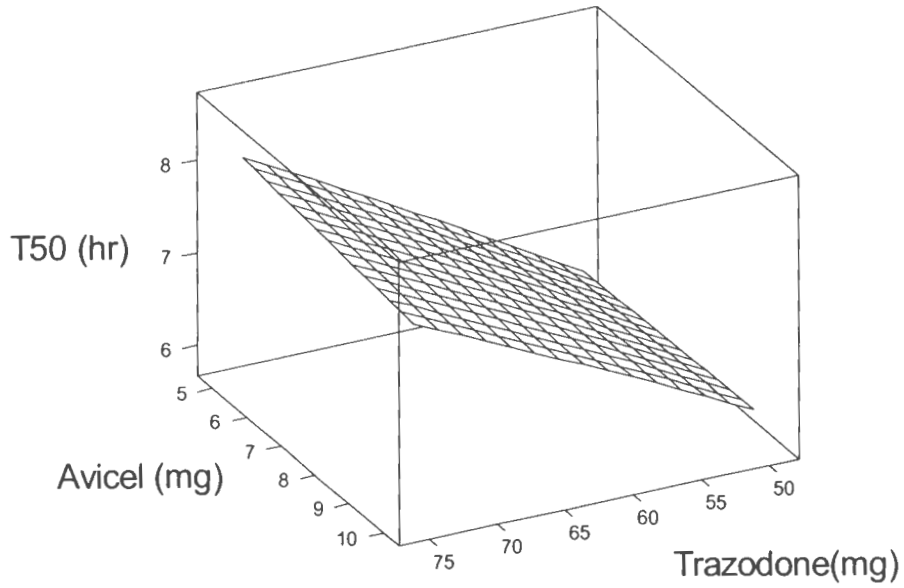


Figure 18: Surface wire plot of trazodone vs Avicel for T_{50} of matrix tablets



50% of drug was highest when the amount of drug was 75 mg and the amount of Avicel was 5 mg. Tukey test was performed for the T_{50} values of matrix tablets prepared from eight formulations and the result was given in Table 18. The basis of grouping was attributed to the closeness of T_{50} values.

3.6 EFFECT OF FORMULATION VARIABLES ON T_{90} MATRIX TABLETS

T_{90} indicates the time required to release 90% of the drug from the formulation. T_{90} ranged from 17.3–23.5 hr, in the eight batches tested during dissolution experiments. Figure 19 shows the main effects plot for T_{90}. T_{90} was higher at high concentrations of drug (75mg) and of HPMC (50 mg) and at low concentration of Avicel (5 mg). Figure 20 shows the interaction plot for T_{90}, there is an interaction between all the three variables since the lines in the plot are either intersecting with each other or they are not parallel to each other. If the lines are parallel to each other, it means there is no interaction between the factors. Table 19 shows ANOVA results of the T_{90} .The ANOVA table shows that the amount of drug, HPMC and Avicel were statistically significant at alpha 0.05. All the two-way interactions (drug*HPMC, drug*Avicel, HPMC*Avicel) and the three way interactions (drug*HPMC*Avicel) also significantly affected the rate of release of drug from the mini tablets. Figure 21 shows the surface wire plot for T_{50} of the amount of drug and the amount of HPMC. The time taken to release 90% of drug was highest when the amount of drug was 75 mg and the amount of HPMC was 50 mg. Figure 22 shows the surface wire plot for T_{50} of the amount of drug and the amount of Avicel. The time taken to release 90% of drug was highest when the amount of drug was 75 mg and the amount of Avicel was 5 mg.

Table 18: Tukey test for T_{50} of matrix tablets

Means with the same letter are not significantly different*.

Tukey Grouping	Mean (T_{50})	N	Formulation #
A	8.400	2	8
A			
A	8.150	2	5
A			
A	8.050	2	2
B	7.300	2	7
C	6.200	2	1
C			
C	6.200	2	6
C			
C	6.050	2	4
C			
C	5.950	2	3

* Minimum significant difference was 0.3957

Figure 19: Main effects plot of data means of T_{90} of matrix tablets

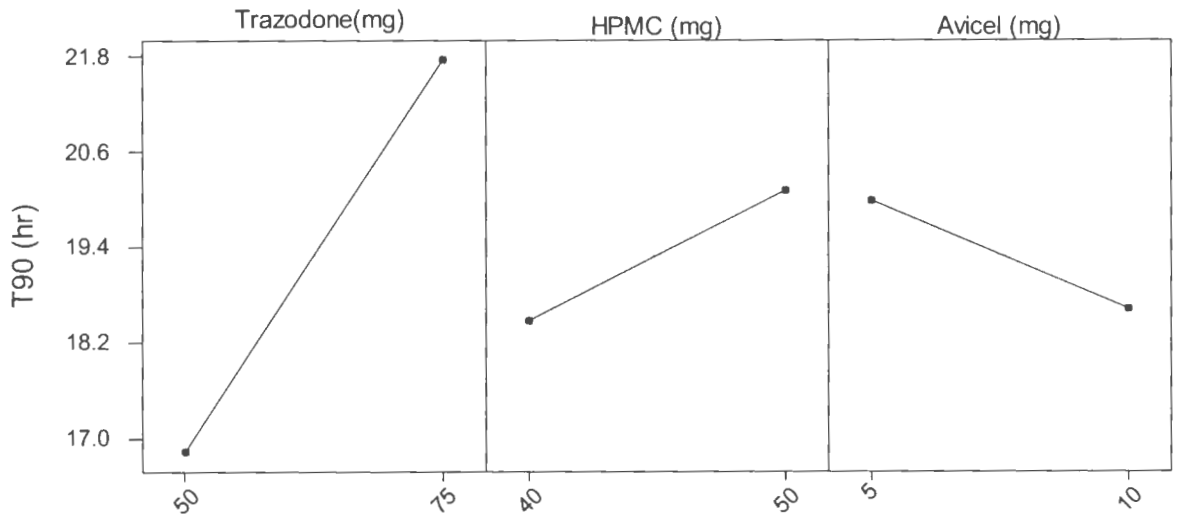


Figure 20: Interaction plot of data means of T_{90} of matrix tablets

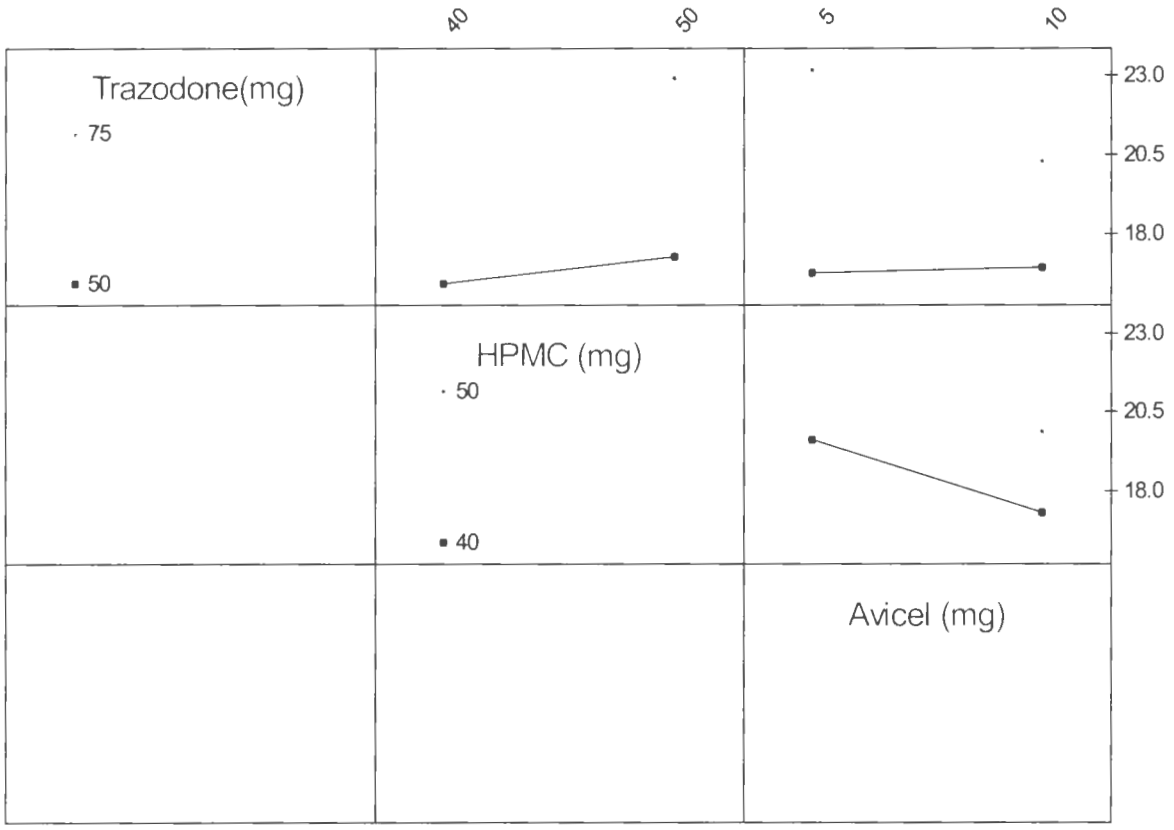


Table 19: Analysis of variance (ANOVA) for T_{90} of matrix tablets

Source	DF	Seq SS	Adj SS	Adj MS	F	P
drug	1	96.531	96.531	96.531	6177.96	0.000
HPMC	1	10.726	10.726	10.726	686.44	0.000
Avicel	1	7.426	7.426	7.426	475.24	0.000
drug*HPMC	1	2.326	2.326	2.326	148.84	0.000
drug*Avicel	1	9.456	9.456	9.456	605.16	0.000
HPMC*Avicel	1	3.516	3.516	3.516	225.00	0.000
drug*HPMC*Avicel	1	5.406	5.406	5.406	345.96	0.000
Error	8	0.125	0.125	0.016		
Total	15	135.509				

Figure 21: Surface wire plot of trazodone vs HPMC for T_{90} of matrix tablets

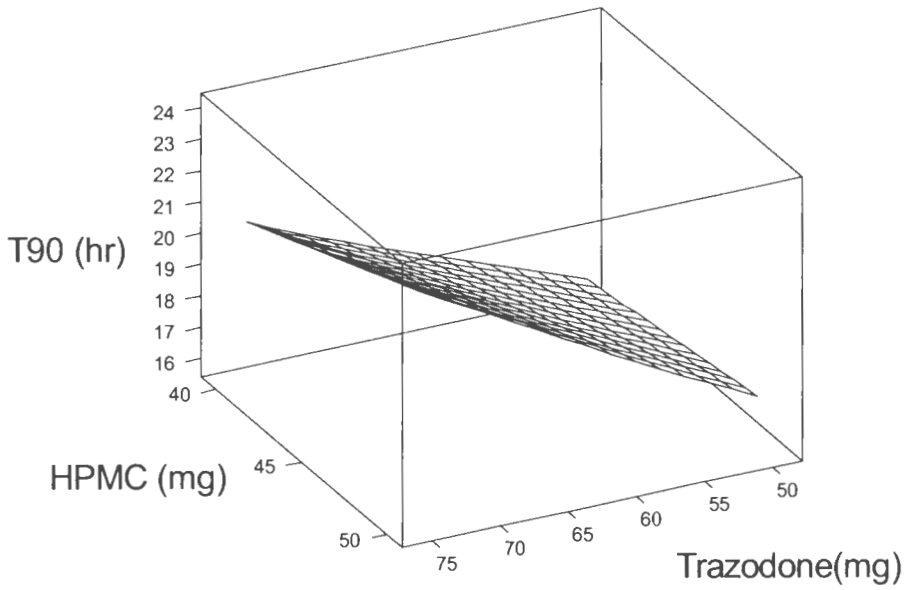


Figure 22: Surface wire plot of trazodone vs Avicel for T_{90} of matrix tablets

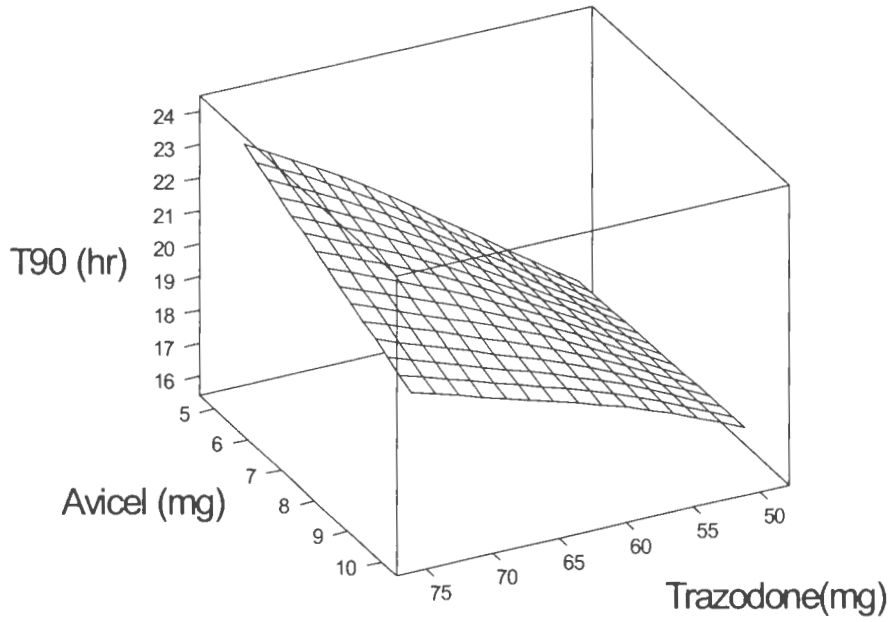


Table 20: Tukey test for T_{90} of matrix tablets

Means with the same letter are not significantly different*.

Tukey Grouping	Mean (T_{90})	N	Formulation #
A	23.350	2	5
A			
A	23.050	2	2
B	22.550	2	8
C	18.050	2	7
D	17.300	2	3
D			
D	17.250	2	6
E	16.600	2	4
E			
E	16.200	2	1

* Minimum significant difference was 0.4946

Tukey test was performed for the T_{90} values of matrix tablets prepared from eight formulations and the result was given in Table 20. The basis of grouping was attributed to the closeness of T_{90} values.

4. CONCLUSIONS

The results of this investigation can be summarized as follows:

1. Controlled release matrix-mini tablets and matrix tablets of trazodone-hydrochloride may be prepared by direct compression of the formulation ingredients.

2. Factorial experimental design was demonstrated to be an efficient and effective tool for the evaluation of effects of factors and their interaction on the drug release from the matrix.

3. Matrix tablets have longer T_{50}s and T_{90}s than matrix-mini tablets, may be because of lower surface areas.

4. Hydroxypropylmethylcellulose (HPMC) seems to be a good polymer for the preparation of controlled release tablets of trazodone hydrochloride.

BIBLIOGRAPHY

Alderman, D.A., A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms, International Journal of Pharmaceutical Technology Production and Manufacturing, 5: 1-9 (1984).

Banker, G. S. and Rhodes, C. T. "Modern Pharmaceutics" 3 rd Edition, Marcel Dekker Inc., NY. 1996.

Bouwastra, J.A.. and Junginger, H.E., Hydrogels. Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc. 441-65 (1993).

Doelker, E.L., Water-swollen cellulose derivatives in pharmacy, In Peppas, N.A, (Ed), Hydro gels in Medicine and Pharmacy, Volume II: Polymers, CRC Press, Boca Raton, FL, 1987.

Florence, A.T. and Jani, P.U., Novel oral drug formulations. Their potential in modulating adverse effects. Drug Safety, 10 (3): 233-66 (1994).

Gao, P., Nixon, P.R and Skoug, J.W., Diffusion in HPMC gels. Ii Prediction of drug release rates from hydrophilic matrix extended-release dosage forms. Pharmaceutical Reasearch, 12: 965-971 (1995).

Gupta, P.K. and Hung, C.T., Magnetically controlled targeted micro-carrier systems, Life Sciences, 44 (3): 175-86 (1989).

Harland, R.S., Gazzaniga, A., Sangalli, M.E., Colombo,P. and Peppas, N.A., Drug polymer matrix swelling and dissolution. Pharmaceutical Reasearch, 5: 488-494 (1988).

Hashim, H. and Li Wan Po, A., Improving the release charcterstics of water-soluble drugs from hydrophilic sustained release matrices by in situ as generation, International Journal of Pharmacy, 35: 201-09 (1987).

Hilton, A,K. and Deasy, P.B., In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate, International Journal of Pharmacy, 86: 79-88 (1992).

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A., Mechanisms of solute release from porous hydrophilic polymers, International Journal of Pharmacy, 15: 25-35 (1983).

Lachman, L., Liberman, H.A. and Kang, J.L., The Theory and Practice of Industrial Pharmacy. 3rd Edition, Lee & Febiger (1987).

Langer, R.S. and Peppas, N.A., Present and future applications of biomaterials in controlled drug delivery systems. Biomaterials (2): 201-214 (1981).

Lee. P.I., and Peppas. N.A., Prediction of polymer dissolution in swellable controlled-release systems, Journal of Controlled Release, 6: 207-215 (1987).

Lee, P.I. and Good, W. R., Controlled-Release Technology, Pharmaceutical Applications, American Chemical Society, Washington, DC (1987).

Peppas, N.A., Analysis of Fickian and non-Fickian drug release from polymers, Pharmaceutica Acta Helvetiae, 60: 110-111 (1985).

Pham, A.T. and Lee, P.I., Probing the mechanisms of drug release from hydroxypropylmethylcellulose matrices, Pharmaceutical Reasearch, 11: 1379-1384 (1994).

Ranade, V. V., Drug delivery systems: 3A. Role of Polymers in Drug Delivery, Journal of Clinical Pharmacology. 30: 10-23 (1990).

Ranade, V. V., Drug delivery systems: 5A. Oral Drug Delivery, Journal of Clinical Pharmacology, 31: 2-16 (1991).

Rawls, W. N., Trazodone (Desyrel, Mead-Johnson Pharmaceutical Divison: Drug Intelligence & Clinical Pharmacy, 16: 7-13 (1982).

Rubinstein, A. and Friend, D.R., Specific delivery to the gastrointestinal tract, Polymeric site specific Pharmacotherapy, Wiley, Chichester: 282-83 (1994).

Silberberg. A., Network deformation in flow. Molecular basis of Polymer networks, 147-51 (1989).

Skoug. J.W., Mikelsons, M.V., Vigneron, C.N. and Stemm, N.L., Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurment of polymer release. Journal of Controlled Release, 27: 227-245 (1993).

Singh, B.N. and Kim, K.H., Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, Journal of Controlled release, 63: 235-259 (2000).

Swarbick, J. and Boylan, J., Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc. (1998).

Vastraj, N., Zia, H. and Needham, T.E., Formulation and Optimazion of a sustained-release Tablet of Ketorolac Tromethamine, Drug Delivery, 9: 153-59 (2002)