# FORMULATION AND EVALUATION OF ALCOHOL RESISTANT MATRIX TABLETS OF QUETIAPINE FUMARATE BY USING VARIOUS POLYMERS: HPMC K 15M AND ETHYL CELLULOSE

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**ABSTRACT**

**Objective**: The present work is focused on the Formulation and Evaluation of Alcohol Resistant Dosage Forms of Quetiapine fumarate by various polymers.

METHOD: Oral controlled matrix tablet formulations of Quetiapine fumarate were prepared by wet granulation method. Matrix tablets provide specific advantages in controlling the drug release rate from the dosage form mainly by the type and proportion of polymers used in the preparation. The major drawback for these system is dose dumping which is prominent in presence of alcohol. In the present study attempt was made to prepare alcohol resistant tablet formulations of Quetiapine fumarate. Quetiapine fumarate is used as a model drug which is an anti-psychotic agent. Various polymers like Ethylcellulose, HPMC K50M, Xanthan gum were used for preparing the matrix tablets. The prepared matrix tablets were studied for drug release studies at various concentration of alcohol.

**RESULTS AND DISCUSSION**: The invitro drug release studies were carried out in phosphate buffer as well as phosphate buffer containing 5%, 10% and 15% alcohol. Drug release studies from these matrix tablets was by non – fickian diffusion and was comparable with that of marketed preparations. The polymer combination was also found to be an efficient alcohol resisting agent and the matrix tablets of Quetiapine fumarate had shown resistance to alcohol induced dose dumping.

**KEYWORDS**: Quetiapine fumarate, HPMC K50M, Ethylcellulose, Xanthan gum, Alcohol resistance, Matrix tablets.

## 1. INTRODUCTION:

The oral route is a route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. Sustained release formulations are preferred for such therapy because they maintain uniform drug levels, reduce dose and side effects, show better patient compliance, and increase safety margin for high potency drugs. Polymers which are used as release retarding materials in the design of matrix tablet dosage forms play a vital role in controlling the delivery of drug from these dosage forms.

Quetiapine is an antipsychotic that has the highest serotonin/dopamine binding ratio, being the serotonin type 2 (5-HT2)-receptor blocking effect about twice as strong as the dopamine D2-receptor blocking effect. Quetiapine Fumarate is readily absorbed from the gastrointestinal track with oral bioavailability of about 83% . Administration of Quetiapine Fumarate in the sustain release dosage form as once daily would be more desirable as this formulation is intended to be given to schizophrenic patients. The sustain release form would also control the mood for longer period of time by maintaining the plasma concentration of drug well above the therapeutic concentration. This characteristic makes Quetiapine well tolerated and effective in patients who are particularly susceptible to these severe side effects, including the elderly and adolescents and those with pre-existing dopaminergic pathologies, such as Alzheimer's disease and Parkinson's disease.

Controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of the activity and targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible. Polymers and release retarding materials play a vital role in controlling the drug release from the matrix tablets.

The objective of the present study is to evaluate combination of HPMC K15M, Xanthan gum, Ethyl cellulose as matrix and alcohol resistant material and to prepare matrix tablets of Quetiapine fumarate for controlled and alcohol resistant release. The matrix tablets containing Quetiapine fumarate were prepared by an industrially feasible wet granulation method and the tablets were evaluated for controlled release of Quetiapine fumarate.

## 2. MATERIALS AND METHODOLOGY:

MATERIALS:

Quetiapine fumarate received as a gift sample from APL, Hyderabad. Potato starch(hydrolysable) was prepared in the laboratory and all other materials used in the study were of Pharmacopoeial standards.

METHODOLOGY:

**1 PREPARATION OF TABLET**

Alcohol resistant Quetiapine fumarate tablets were prepared by wet granulation method. Wet granulation is the process by which the active ingredient, diluents and disintegrants are mixed and blended well. Solutions of the binding agent are added to the mixed powder with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow and then sieve the dove mass and dry them in the drying chamber. Then compression of tablets was done by automatic punching machine using 6mm flat punch.

**2 DRUG-EXCIPIENT COMPATABILITY STUDY**

FTIR spectroscopy is considered as important analytical technique for identification of drug substance as FTIR spectra reveals characteristic peaks, indicating presence of different functional group in drug substance. In order to evaluate the integrity and compatibility of drug in the formulation, drug and excipients were mixed in the ratio of 1:1 and analysed by Fourier-transform infrared spectroscopy (FTIR) using KBr pellet method.

**3 PRE-COMPRESSION PARAMETERS**

Prior to development of the dosage forms with a new drug candidate, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This information will dictate many of the subsequent events and possible approaches in formulation development. This first learning phase is known as preformulation.

- Angle of repose is measured by funnel method.The maximum angle possible between surface of a pile of powder and horizontal plane is known as Angle of Repose. It is the common way of expressing the flow characteristics of powders and granules.Through this the flow property of powder is measured.

**Tan Ø = h / r**

**Ø = Tan $^{-1}$ h / r**

'h' is the height of the powder heap and 'r' is the radius of the powder heap.

| **ANGLE OF REPOSE** | **FLOW PROPERTY** |
|---|---|
| 0-25° | Excellent |
| 25-35° | Good |
| 35-45° | Passable |
| >45° | Poor |

- **BULK DENSITY:**The bulk density of a material is the ratio of the mass to the volume (including the interparticulate void volume) of an untapped powder sample.

**Bulk density=weight of the powder/bulk volume**

- **TAPPED DENSITY:**It is the ratio of total mass of the powder to the tapped volume of the powder. It is measured by using tapped density apparatus.The tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until little further volume change is observed.

**Tapped density=mass of the powder/tapped volume of the powder**

- **TRUE DENSITY:**True density is measured using specific gravity bottle.First the empty specific bottle is weighed($W_1$).Then specific gravity bottle is filled with the powder and weighed, this weight is noted as ($W_2$).Specific gravity bottle is filled with powder and water, the weight is noted as ($W_3$).Weight of the bottle along with water is noted as ($W_4$).The values are substituted in the formula below to know the true density.

$$\text{TRUE DENSITY} = \frac{W2-W1}{(W4-W1)(W3-W2)}$$

- **CARR'S COMPRESSIBILITY INDEX:**Carr's index is an indication of the compressibility of the powder

**Compressability index = (Bulk density – Tapped density)100**
**Bulk density**

| Compressibility Index(%) | Type of flow |
|---|---|
| 1-10 | Excellent |
| 11-15 | Good |
| 16-20 | Fair |
| 21-25 | Passable |
| 26-31 | Poor |
| 32-37 | Very poor |

**HAUSNER RATIO:**It is the ratio of bulk density to tapped density.Hausner ratio is used to determine the nature of powder flow.

**Hausner ratio=Bulk density/Tapped density**

| HAUSNER RATIO | FLOW PROPERTY |
|---|---|
| 1.00-1.11 | Excellent |
| 1.12-1.18 | Good |
| 1.19-1.25 | Fair |
| 1.26-1.34 | Passable |
| 1.35-1.45 | Poor |
| 1.46-1.60 | Very poor |

**CALIBRATION CURVE**

PREPARATION OF STANDARD STOCK SOLUTION (1mg/ml or 1000µg/ml ): quetiapine fumarate equivalent to 10mg was weighed and transferred into 10ml volumetric flask, dissolved in methanol and the volume was made up with methanol.

PREPARATION OF SUB STOCK SOLUTION (100µg/ml ): From the standard stock solution 1ml was pipetted out into a 10ml volumetric flask and the volume was made up with 6.6 phosphate buffer.

PREPARATION OF SERIES OF STANDARDS: From the above solution 0.2,0.4,0.6,0.8,1ml was transferred into separate 10ml volumetric flasks and the volume was made up with buffer. This gives 2,4,6,8,10µg/ml solutions respectively.

The absorbance of the solutions was measured at 291 nm using UV-Visible spectrophotometer. A graph was plotted by taking concentration on x-axis and absorbance on y-axis.

**4. EVALUATION OF DOSAGE FORM: -**

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

**TABLET THICKNESS:** Thickness of tablets was important for uniformity of tablet size. Thickness was measured using Vernier Caliper on 3 randomly selected samples.

- **TABLET HARDNESS:**

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester.

- **FRIABILITY:**

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Friability was done as per USP specification.

%Friability = (Initial wt. of tablets – Final wt. of tablets) x 100 Initial wt. of tablets

- **WEIGHT VARIATION:**

Twenty tablets were weighed individually and the average weight was determined. The % deviation was calculated and checked for weight variation as per USP. The average weight of 20 tablets was calculated for each formulation

- **DRUG CONTENT:**

Tablet was weighed and powdered.10mg of the tablet powder was taken into 10ml volumetric flask and the volume was made up using methanol. It was sonicated for few minutes until the powder gets dissolved. From the above solution 1ml was transferred into another 10ml volumetric flask and volume was made-up with 6.6phosphate buffer. Further dilutions are made if necessary. The absorbance of resultant solution was measured at 291nm using UV-Visible spectrophotometer

- **IN-VITRO DISSOLUTION STUDY**

Dissolution Study of Tablets: -
Apparatus : USP type 2 apparatus (paddle)
Dissolution medium : 6.6 phosphate buffer
Volume of dissolution medium: 900ml
Ethyl alcohol(Ethanol) :45ml, 90ml, 135ml, 180ml according to the percentage of alcohol.
Temperature:37.5℃
Speed:75rpm

Procedure:The tablet was placed inside the dissolution vessel at 75 rpm, 5ml of sample were withdrawn at time intervals of 1, 2, 3, 4, 5, 6hr. The volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after every sample. Each sample was analyzed at 291nm, using double beam UV and Visible Spectrophotometer against blank.

## 5. MECHANISM OF DRUG RELEASE

Various models were tested for explaining the kinetics of drug release.
To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, Hixon- Crowell model and Korsmeyer-Peppas release model. Drug release rate kinetic of dosage form was calculated by using DDSover, A Microsoft Excel Add-in.

- **ZERO ORDER RELEASE RATE KINETICS:**

To study the zero–order release kinetics the release rate data are fitted to the following equation.
$\mathbf{F=K_0t}$
Where 'F' is the drug release, 'K' is the release rate constant and't' is the release time.
The plot of % drug release versus time is linear.

- **HIGUCHI RELEASE MODEL:**

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,
$\mathbf{F = k\ t^{1/2}}$
Where 'k' is the Higuchi constant.
In higuchi model, a plot of % drug release versus square root of time is linear.

- **KORSMEYER AND PEPPAS RELEASE MODEL:**

The release rate data were fitted to the following equation,
$\mathbf{M_t/M_\infty=K.t^n}$
Where, $M_t/M_\infty$ is the fraction of drug released, 'K' is the release constant,
't' is the release time.
'n' is diffusion exponent, if n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or nonfickian diffusion (swellable & cylinder Matrix).
In this model, a plot of log ($M_t/M_\infty$) versus log (time) is linear.
The dissolution data were fitted to Zero-order, First-order, Higuchi, and Korsmeyer-Peppas model to study the kinetics of drug release.

## 6. STABILITY STUDY:

In any rational design and evalution of dosage forms for drugs, stability of the active component must be a major criterion in determining their acceptance or rejection. Stabitily of the drug can be defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification (OR)
Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.
The international conference on Harmonization (ICH) guidelines titled 'stability testing of New Drug substance and products describes the stability test requirements for drug registration applications in the European union, japan and the USA.
ICH specifies the length of the study and storage conditions,
Long-Term Testing: 25℃ / 60% RH + 5% for 12 months.
Accelerated Testing: 40℃/ 75% RH + 5% for 6 months.
Stability studies were carried out at 40℃/ 75% RH for the selected formulation for three months.

Method: The selected formulation were packed in air tight plastic container. They were then stored at 40℃/ 75% RH, for three months and evaluated for their physical appearance, drug content, and drug release at specific interval of time per ICH guidelines.

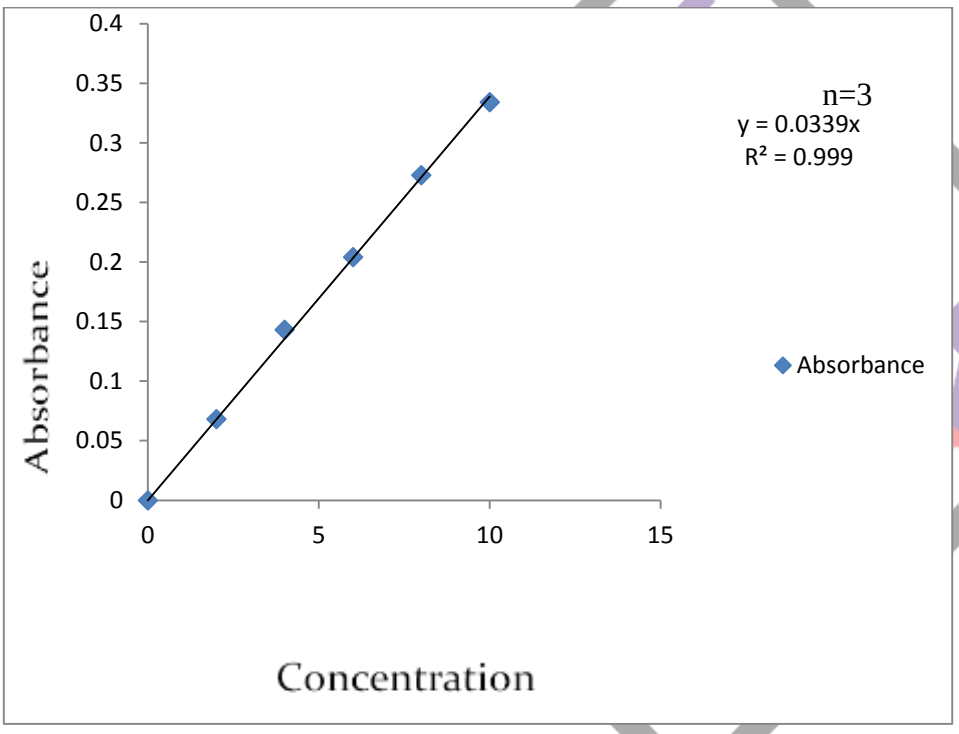
**RESULTS AND DISCUSSION:**
RESULTS AND DISCUSSIONS

3.1 Analytical estimation of Quetiapine Fumarate

Tab 3.1.1 Construction of standard plot for Quetiapine Fumarate in Ph 6.6 phosphate buffer

| Concentration (µg/ml) | Absorbance |
|---|---|
| 2 | 0.068 |
| 4 | 0.143 |
| 6 | 0.204 |
| 8 | 0.273 |
| 10 | 0.334 |

Fig 3.1.2 STANDARD PLOT OF QUETIAPINE FUMARATE:




The UV-Spectrophotometric caliberation curve for analysis in Ph 6.6 phosphate buffer was developed. The plot was drawn between concentrations versus absorbance which is in the above figure. The linear relationship between the concentrations of Quetiapine fumarate on the corresponding absorbance values have confirmed that they obey Beers Law in the concentration range 2-10µg/ml. The regression equation was obtained using Microsoft Excel by setting Y intercept 0.

Y mx + C

Where Y = absorbance (nm)

X = concentration of drug.

A positive correlation between the concentration of Quetiapine fumarate and the corresponding absorbance values were observed (correlation coefficient $R^2 = 0.998$) in buffer.

3.2 PREPARATION OF TABLETS:

FORMULATIONS PREPARED BY USING HPMC K15M + ETHYL CELLULOSE

Tab 3.2.1: HPMC K15M + ETHYL CELLULOSE

| INGREDIENTS(mg) | FA1 | FA2 | FA3 | FA4 | FA5 |
|---|---|---|---|---|---|
| QUETIAPINE FUMARATE | 50 | 50 | 50 | 50 | 50 |
| ETHYL CELLULOSE | 5 | 6 | 7.5 | 7.5 | 7.5 |
| HPMC K15M | 2.5 | 2.5 | 2.5 | 2 | 1.5 |
| MICROCRYSTALLINE CELLULOSE | 36.5 | 35.5 | 34 | 34.5 | 35 |
| CROSSCARMELLOSE SODIUM | 5 | 5 | 5 | 5 | 5 |
| TALC | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| MAGNESIUM STEARATE | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

DRUG EXCIPIENT COMPATIBILITY STUDIES:

FTIR OF PURE DRUG:

Determination of interaction between drug and excipient were performed using FTIR. FTIR of pure drug of Quetiapine fumarate shown in fig 4.3.1 showed spectra of HPMC K15M shown in figure 4.3.2 showed O-H sreching at 3315.63cm$^{-1}$ and AR-H stretching at 3072.60cm$^{-1}$ , C-N stretching at 1600.92cm$^{-1}$ and aromatic C=C stretching at 1458.18cm$^{-1}$ , C-H bending at 1338.60cm$^{-1}$ and C-O-C group at 1031.92 cm$^{-1}$, substituted benzene ring at 794.67 cm$^{-1}$.

DRUG AND EXCIPIENTS COMPATIBILITY:

FTIR spectra of HPMC K15M shown in figure 4.3.2 showed O-H sreching at 3317.56cm$^{-1}$ and AR-H stretching at 3072.60cm$^{-1}$ , C-N stretching at 1600.92cm$^{-1}$ and aromatic C=C stretching at 1458.18cm$^{-1}$ , C-H bending at 1338.60cm$^{-1}$ and C-O-C group at 1031.92 cm$^{-1}$, substituted benzene ring at 794.67 cm$^{-1}$.

FIG:3.3.1 QUETIAPNE FUMARATE PURE DRUG

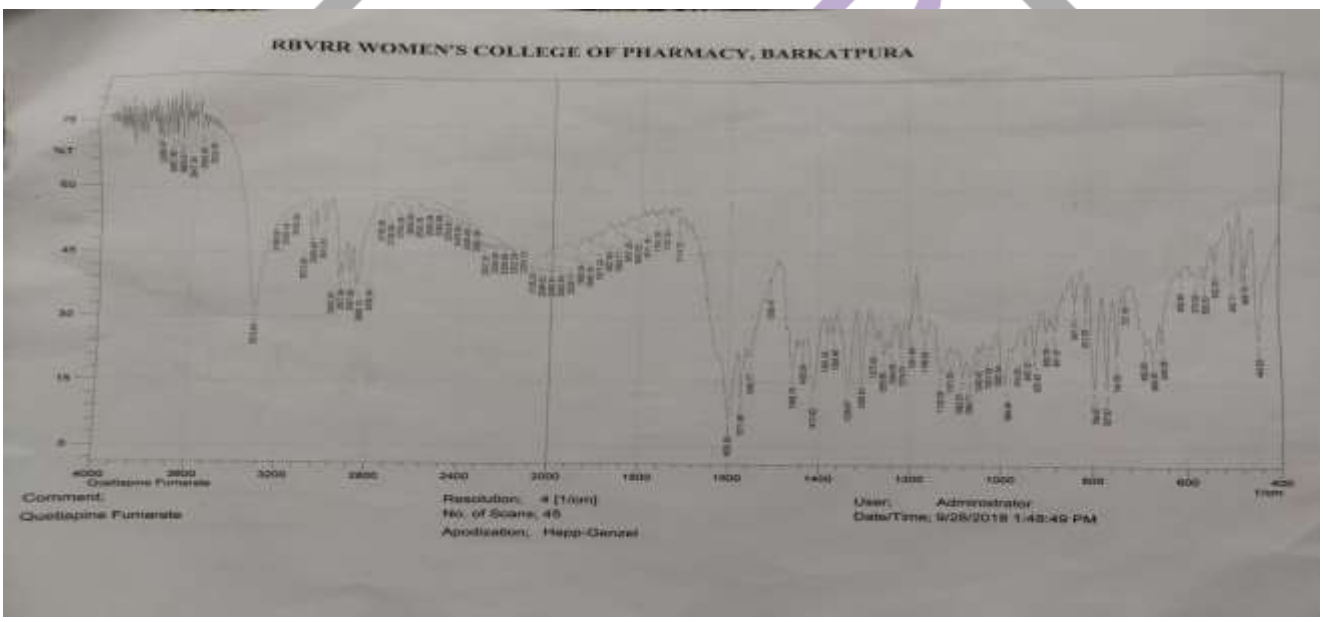
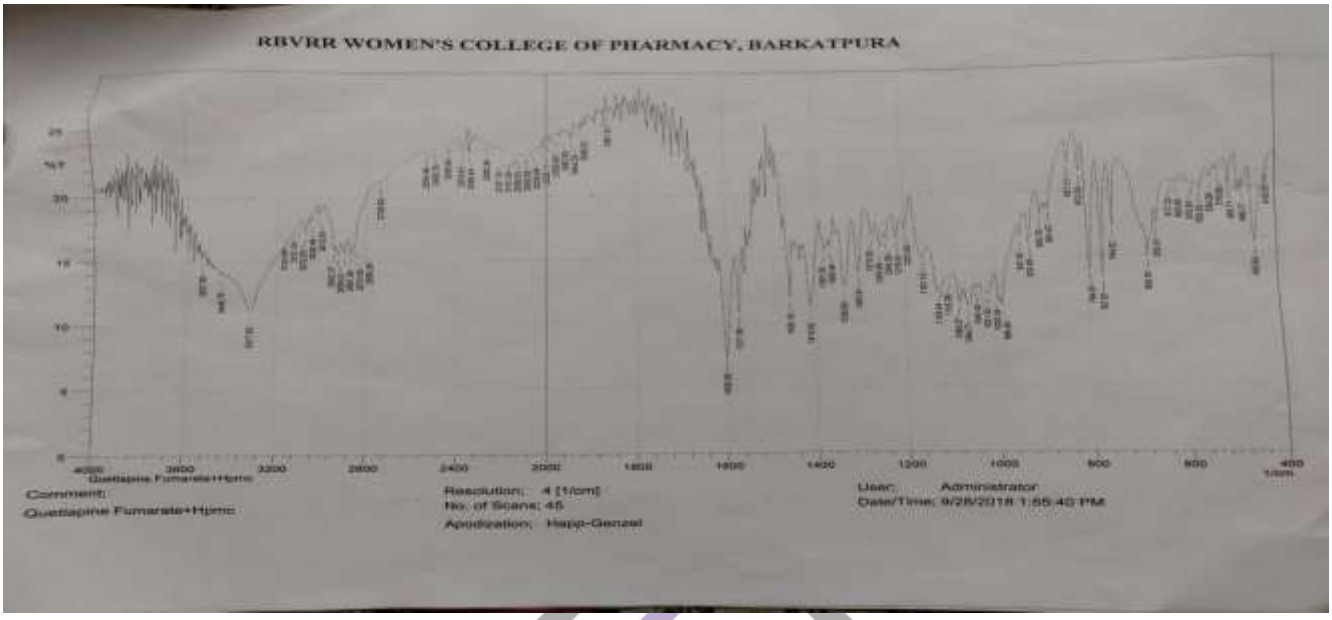


FIG:3.3.2 DRUG + HPMC K15M




The FTIR studies of formulations shows that the characteristic peaks of drug and excipient were retained which shows that there are no compatibility issues between drug and excipient.

Tab 3.4 PRE – FORMULATION PARAMETERS:

| PARAMETERS | FA1 | FA2 | FA3 | FA4 | FA5 |
|---|---|---|---|---|---|
| ANGLE OF REPOSE(tanΘ) | 26.5 | 26.7 | 26.8 | 27 | 26.6 |
| BULK DENSITY(g/ml) | 0.27 | 0.29 | 0.32 | 0.28 | 0.26 |
| TAPPED DENSITY(g/ml) | 0.29 | 0.32 | 0.31 | 0.35 | 0.31 |
| CARR'S INDEX(%) | 13.6 | 13.4 | 14 | 13.2 | 14.1 |
| HAUSNER'S RATIO | 1.14 | 1.12 | 1.11 | 1.13 | 1.14 |

- Angle of repose for all the formulations were examined. The values were found to be within the range from $25^0$ to $29^0$. This indicated that the powder blend has good flow property.
- The bulk density and tapped density values were found to be within range from 0.26g/ml to 0.37g/ml and 0.26g/ml to 0.39g/ml respectively.
- Carr's comprresibilty index was found to be within the range from 13% to 16%. This indicate that the powder blend has good flow property.
- The Hausner's ratio values were found to be within the range from 1.11 to 1.19. This indicated that the powder blend has good flow property.

4. EVALUATION TESTS OF QUETIAPINE FUMARATE MATRIX TABLETS:

The prepared formulations of Quetiapine fumarate matrix tablets were evaluated for the tests like friabilty, hardness, assay, thickness, weight variation and all the formulations showed results within the limits as shown in table: Tab 4.5.1: Evaluation parameters of Quetiapine fumarate matrix tablets:

Tab 4: Evaluation tests of quetiapine fumarate matrix tablets

| PARAMETERS | FA1 | FA2 | FA3 | FA4 | FA5 |
|---|---|---|---|---|---|
| Friability(%) | 0.26 | ˆ0.32 | 0.37 | 0.43 | 0.28 |
| Hardness(kg/cm) | 2.8 | 3 | 2.7 | 3 | 3 |
| Wight variation(mg) | 0.3 | 0.2 | 0.2 | 0.5 | 0.4 |
| Thickness(cm) (±SD) | 0.53± 0.12 | 0.52± 0.16 | 0.53± 0.1 | 0.52± 0.16 | 0.52± 0.18 |
| Drug content(%) | 98 | 99 | 98 | 97 | 98 |

The weight variation of tablets was uniform in all formulations the % deviation was below 7.5 which is acceptable and within limits.

The hardness of the prepared tablets was ranged from 2.7 to 3kg/cm$^2$, friabilty values were ranged from 0.24 to 0.38 which fallen within the limit of standard (0.1 to 0.9%).

Drug content of tablets was ranged from 96 to 99%. Thickness of tablets was uniform and Values are ranged from 0.52 to 0.53cm.

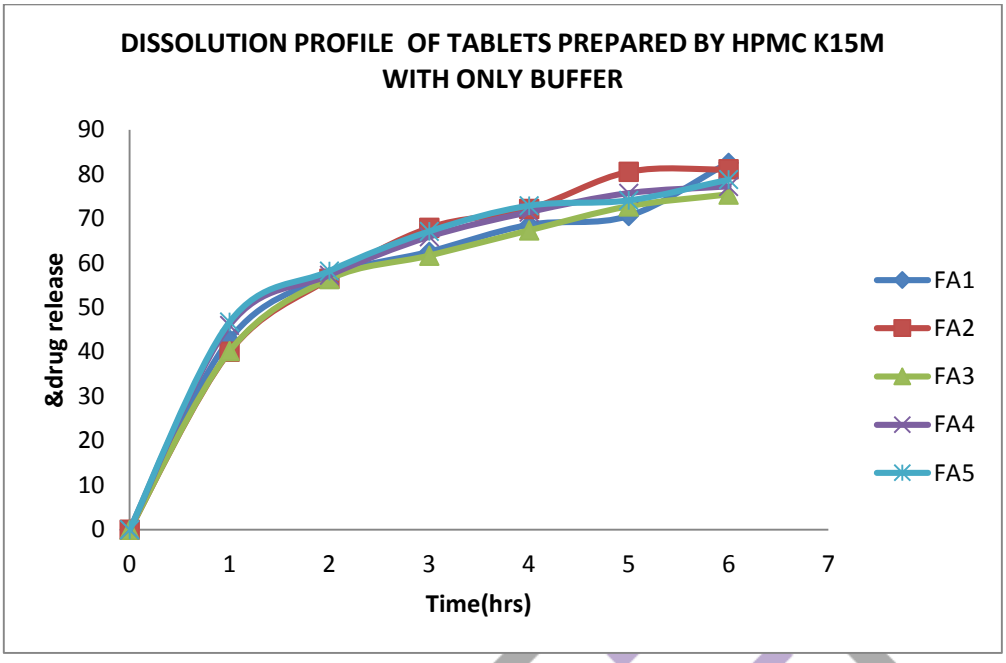
4.2 INVITRO DRUG RELEASE OF QUETIAPINE FUMARATE MATRIX TABLETS:

All the prepared formulations of quetiapine fumarate employing HPMC K15M were evaluated by drug release studies by normal buffer, 5% , 10% and 15% ethanol.

Tab 4.2.1 DISSOLUTION PROFILE OF TABLETS PREPARED BY HPMC K15M WITH ONLY BUFFER

| **TIME (hrs)** | **FA1** | **FA2** | **FA3** | **FA4** | **FA5** |
|---|---|---|---|---|---|
| 1 | 42.794 | 40.06 | 40.143 | 45.97 | 46.719 |
| 2 | 56.887 | 56.46 | 56.358 | 57.235 | 58.214 |
| 3 | 62.512 | 67.93 | 61.656 | 65.886 | 67.125 |
| 4 | 68.564 | 72.194 | 67.33 | 71.430 | 72.917 |
| 5 | 70.558 | 80.55 | 72.76 | 75.692 | 74.103 |
| 6 | 82.548 | 81.08 | 75.433 | 77.215 | 78.784 |

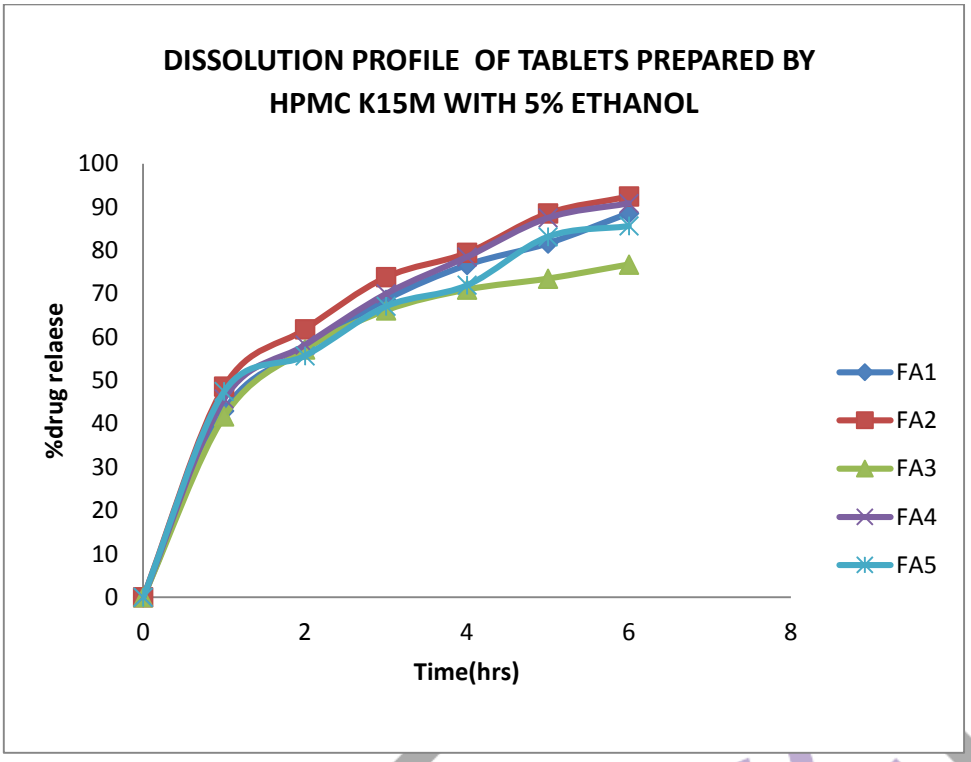
Fig :4.2.1 DISSOLUTION PROFILE OF TABLETS PREPARED BY HPMC K15M WITH ONLY BUFFER




Tab 4.2.2 DISSOLUTION PROFILE OF TABLETS PREPARED BY HPMC K15M WITH 5% ETHANOL

| TIME(hrs) | FA1 | FA2 | FA3 | FA4 | FA5 |
|---|---|---|---|---|---|
| 1 | 43.005 | 48.564 | 41.717 | 45.769 | 47.452 |
| 2 | 57.097 | 61.815 | 57.128 | 58.184 | 55.713 |
| 3 | 68.620 | 73.810 | 66.179 | 69.969 | 67.125 |
| 4 | 76.615 | 79.43 | 70.964 | 78.492 | 71.976 |
| 5 | 81.605 | 88.534 | 73.489 | 87.487 | 83.174 |
| 6 | 88.543 | 92.421 | 76.748 | 90.851 | 85.648 |

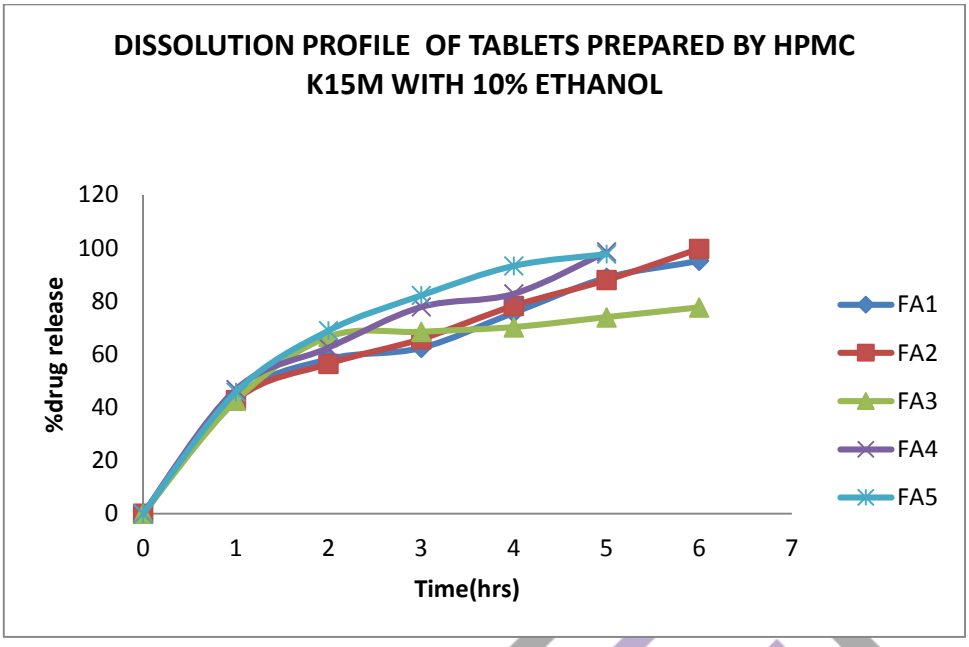
Fig :4.2.2 DISSOLUTION PROFILE OF TABLETS PREPARED BY HPMC K15M WITH 5% ETHANOL




4.2.3 DISSOLUTION PROFILE OF TABLETS PREPARED BY HPMC K15M WITH 10% ETHANOL

| TIME (hrs) | FA1 | FA2 | FA3 | FA4 | FA5 |
|---|---|---|---|---|---|
| 1 | 43.797 | 42.769 | 42.510 | 46.733 | 45.768 |
| 2 | 58.146 | 56.394 | 66.504 | 62.461 | 68.869 |
| 3 | 62.405 | 65.712 | 68.391 | 77.769 | 82.134 |
| 4 | 75.664 | 78.235 | 70.174 | 82.758 | 93.265 |
| 5 | 88.818 | 87.912 | 73.909 | 98.534 | 97.689 |
| 6 | 95.174 | 99.69 | 77.587 | - | - |

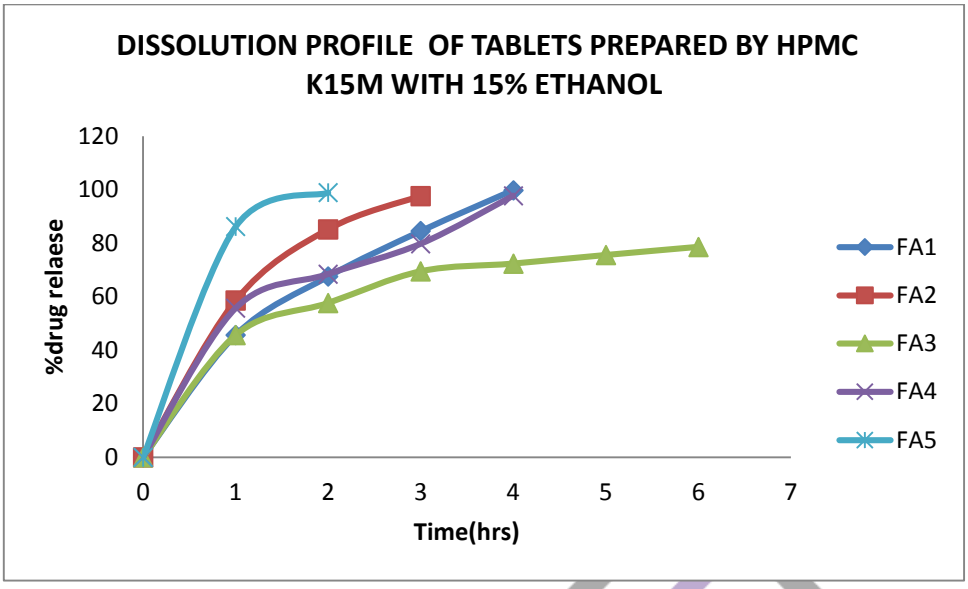
Fig :4.2.3 DISSOLUTION PROFILE OF TABLETS PREPARED BY HPMC K15M WITH 10% ETHANOL




4.2.4 DISSOLUTION PROFILE OF TABLETS PREPARED BY HPMC K15M WITH 15% ETHANOL

| **TIME (hrs)** | **FA1** | **FA2** | **FA3** | **FA4** | **FA5** |
|---|---|---|---|---|---|
| 1 | 45.685 | 58.559 | 45.664 | 55.733 | 86.190 |
| 2 | 67.517 | 85.188 | 57.657 | 68.461 | 98.897 |
| 3 | 84.510 | 97.634 | 69.496 | 79.769 | - |
| 4 | 99.818 | - | 72.384 | 97.758 | - |
| 5 | - | - | 75.587 | - | - |
| 6 | - | - | 78.636 | - | - |

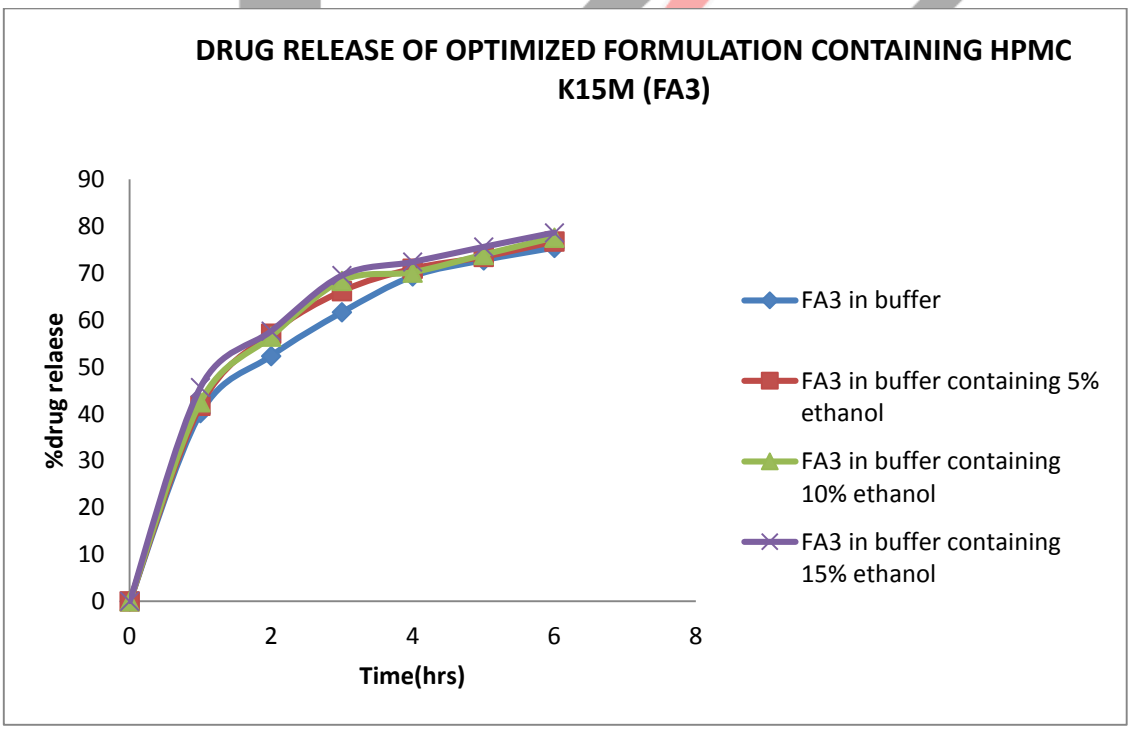
Fig :4.2.4 DISSOLUTION PROFILE OF TABLETS PREPARED BY HPMC K15M WITH 15% ETHANOL




Tab 4.2.5: % DRUG RELEASE OF OPTIMIZED FORMULATION CONTAINING HPMC K15M (FA3)

| TIME (hrs) | FA3 in buffer | FA3 in buffer containing 5% ethanol | FA3 in buffer containing 10% ethanol | FA3 in buffer containing 15% ethanol |
|---|---|---|---|---|
| 1 | 40.143 | 41.717 | 42.510 | 45.664 |
| 2 | 52.358 | 57.128 | 56.504 | 57.657 |
| 3 | 61.656 | 66.179 | 68.391 | 69.496 |
| 4 | 69.33 | 70.964 | 70.174 | 72.384 |
| 5 | 72.76 | 73.489 | 73.909 | 75.587 |
| 6 | 75.433 | 76.748 | 77.587 | 78.636 |

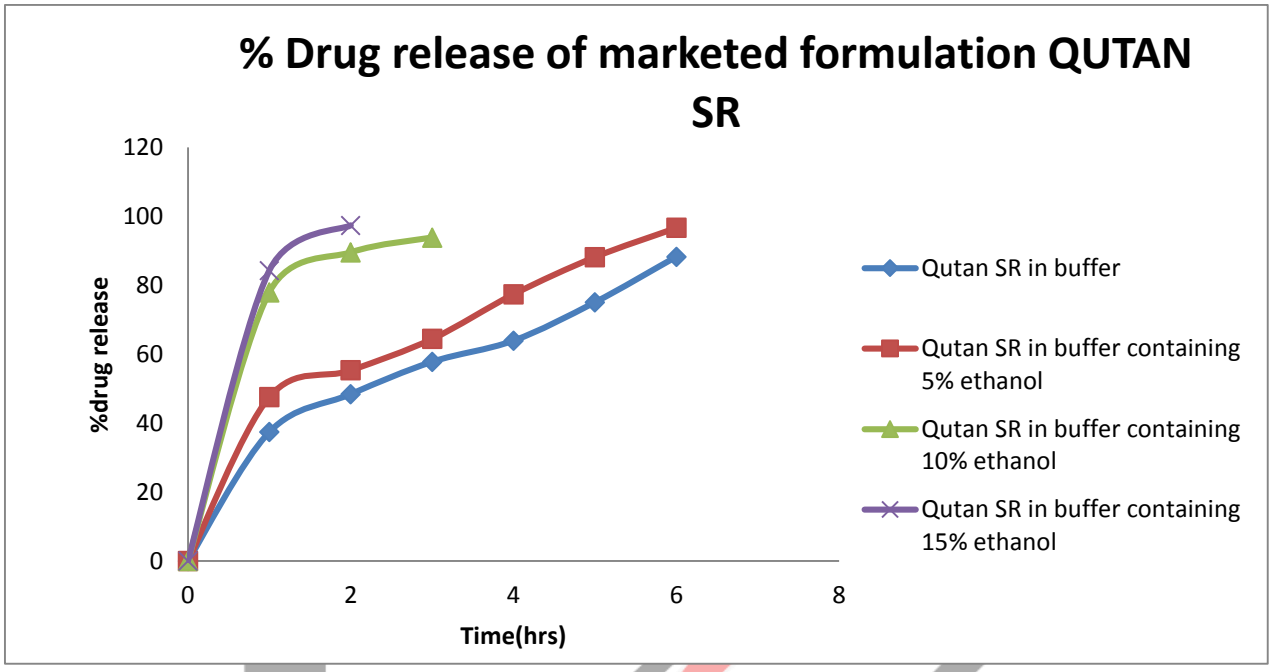
Fig :4.2.5 % DRUG RELEASE OF OPTIMIZED FORMULATION CONTAINING HPMC K15M (FA3)



Tab 4.2.6 DISSOLUTION PROFILE OF MARKETED FORMULATION OF QUETIAPINE FUMARATE (QUTAN SR)

| TIME (hrs) | Qutan SR in buffer | Qutan SR in buffer containing 5% ethanol | Qutan SR in buffer containing 10% ethanol | Qutan SR in buffer containing 15% ethanol |
|---|---|---|---|---|
| 1 | 37.405 | 47.573 | 77.964 | 84.265 |
| 2 | 48.405 | 55.314 | 89.507 | 97.335 |
| 3 | 57.776 | 64.440 | 93.811 | - |
| 4 | 63.916 | 77.398 | - | - |
| 5 | 75.027 | 88.181 | - | - |
| 6 | 88.237 | 96.657 | - | - |

Fig 4.2.6 : **%** Drug release of marketed formulation QUTAN SR




The drug release profiles of selected formulations were also tested using 5%, 10% and 15% alcohol in buffer as the dissolution medium. The selected matrix tablets shown similar drug release profile in phosphate buffer with and without alcohol indicating alcohol resistant release of the drug from the prepared tablets as shown in figure.3 and 4. When compared to marketed preparation the drug release from the prepared matrix tablets was slow and sustained without dose dumping in presence of alcohol.

5 MECHANISM OF DRUG RELEASE:

KINETIC PLOTS – FORMULATION FA3

Fig 5.1 Zero order of formulation FA3

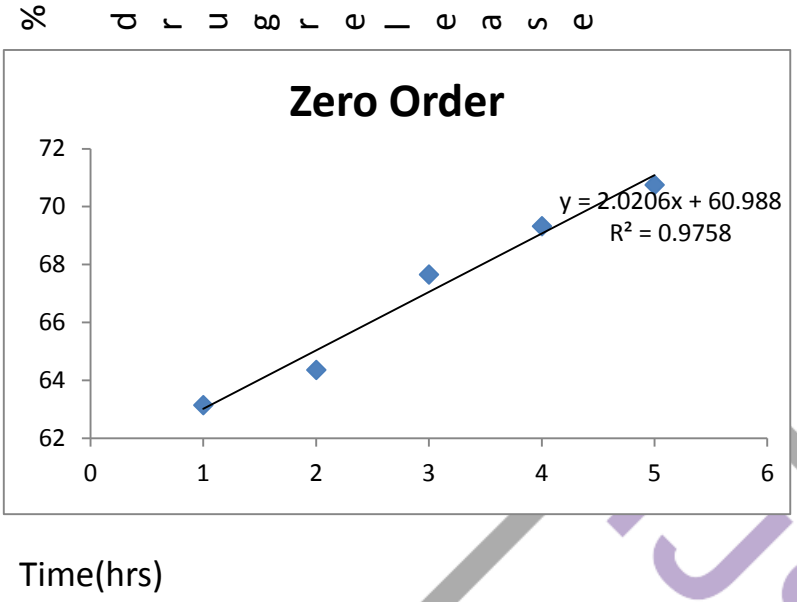



Fig 5.2 First order of formulation FA3

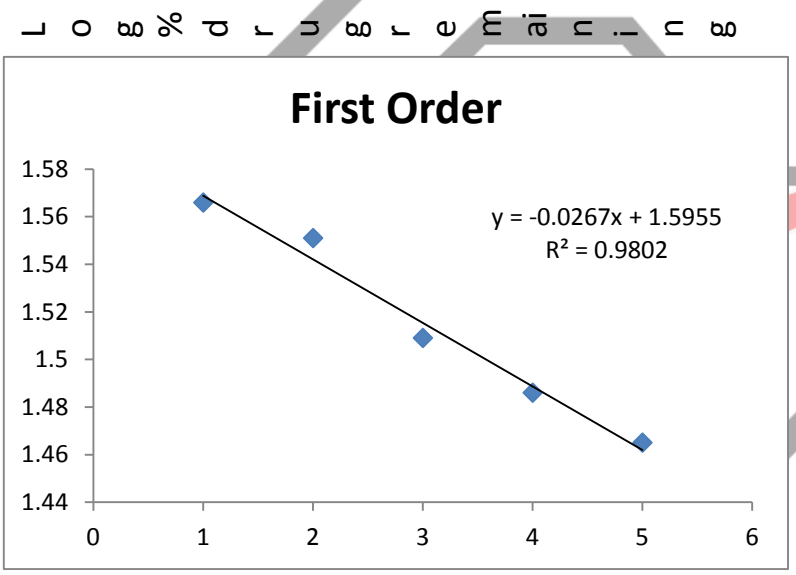


Fig 5.3 Korsemeyer peppas plot of formulation FA3

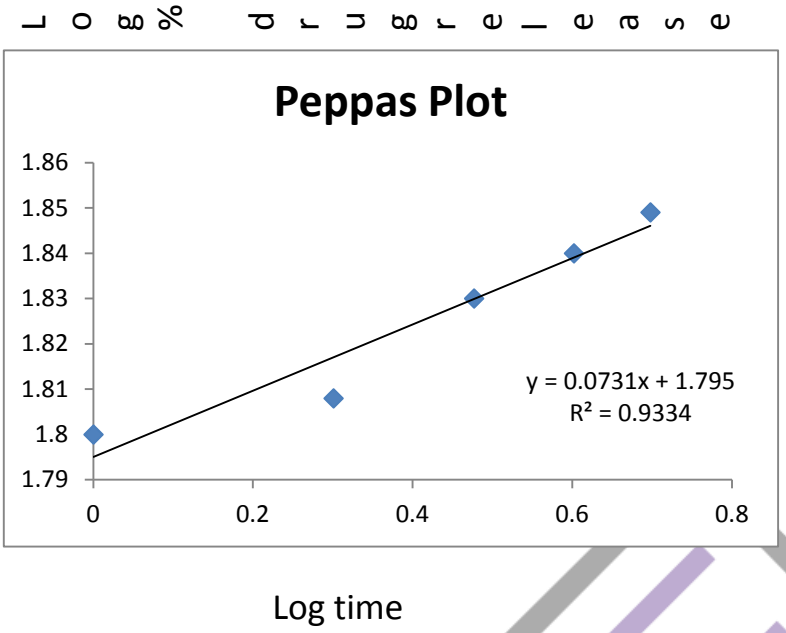
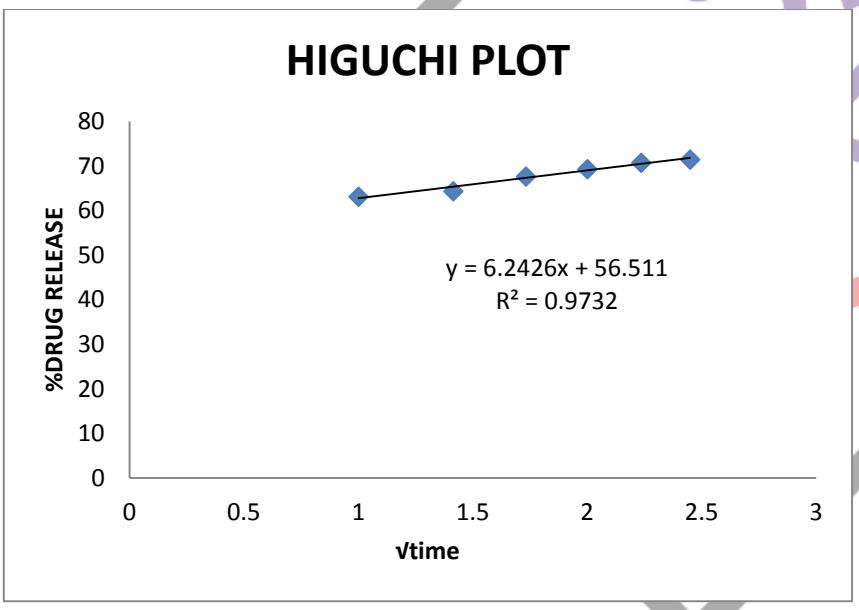



Fig 5.4 Higuchi plot of formulation FA3




6. STABILITY STUDIES:

The accelerated stability studies were carried out according to ICH guidelines. Optimised formulations FAIII and FBII were packed and stored in stability chambers maintained at 40℃ ± and 75%RH (zone III as per ICH guidelines) for 3 months. The tablets were evaluated before and after one month for change in appearance, the drug content and invitro release.

After a period of each month, the samples were observed for any change in general appearance. It was observed that tablet was devoid of any change in colour or appearance of any kind of spot on it. It was also noted that tablet was free of any kind of microbial or fungal growth or bad odour.

The formulation batch showed circular shape with no cracks. The in-vitro drug release showed no significant changes in drug release pattern before, during and after stability period.

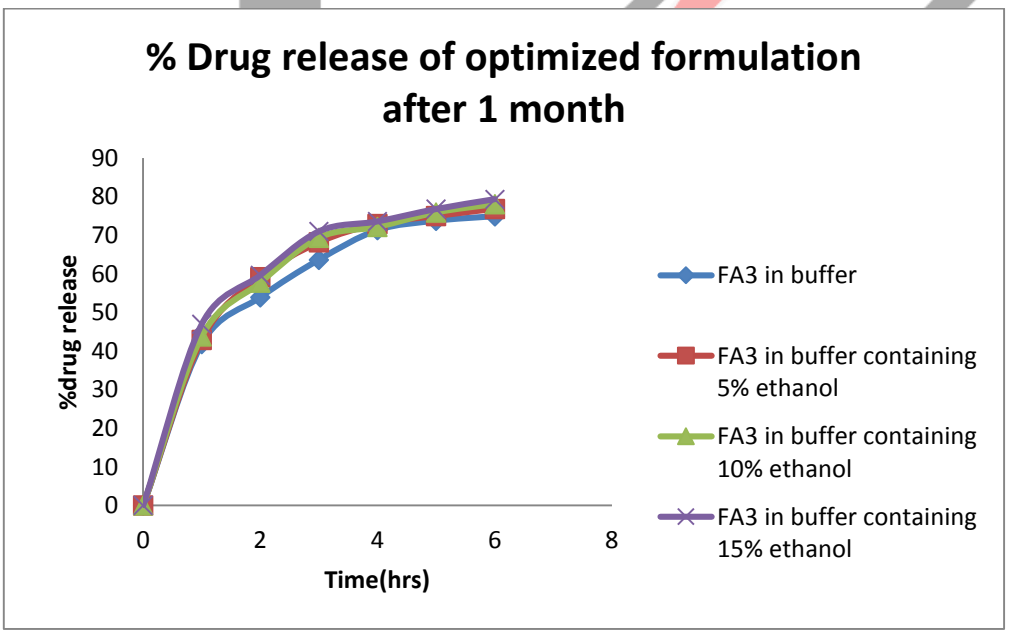
Tab 6.1: STABILITY STUDY OF FORMULATION FA3

| PARAMETERS | 1 MONTH | 2 MONTHS | 3 MONTHS |
|---|---|---|---|
| PHYSICAL APPEARENCE | No change was observed | No change was observed | No change was observed |
| WEIGHT VARIATION | 100.5± 0.3 | 100.5± 0.34 | 100.5± 0.4 |
| HARDNESS | 3kg/cm$^2$ | 3kg/cm$^2$ | 3kg/cm$^2$ |
| FRIABILTY | 0.32 | 0.32 | 0.31 |
| DRUG CONTENT | 98 | 98 | 97.5 |
| % DRUG RELEASE | 73.659 | 72.384 | 71.643 |

Tab 6.2: % Drug release of optimized formulation after 1 month

| TIME (hrs) | FA3 in buffer | FA3 in buffer containing 5% ethanol | FA3 in buffer containing 10% ethanol | FA3 in buffer containing 15% ethanol |
|---|---|---|---|---|
| 1 | 41.843 | 42.917 | 43.810 | 46.964 |
| 2 | 53.958 | 59.128 | 57.750 | 59.657 |
| 3 | 63.656 | 68.179 | 69.391 | 70.996 |
| 4 | 71.33 | 72.964 | 72.174 | 73.584 |
| 5 | 73.76 | 74.989 | 75.909 | 76.787 |
| 6 | 74.933 | 76.848 | 78.087 | 79.336 |

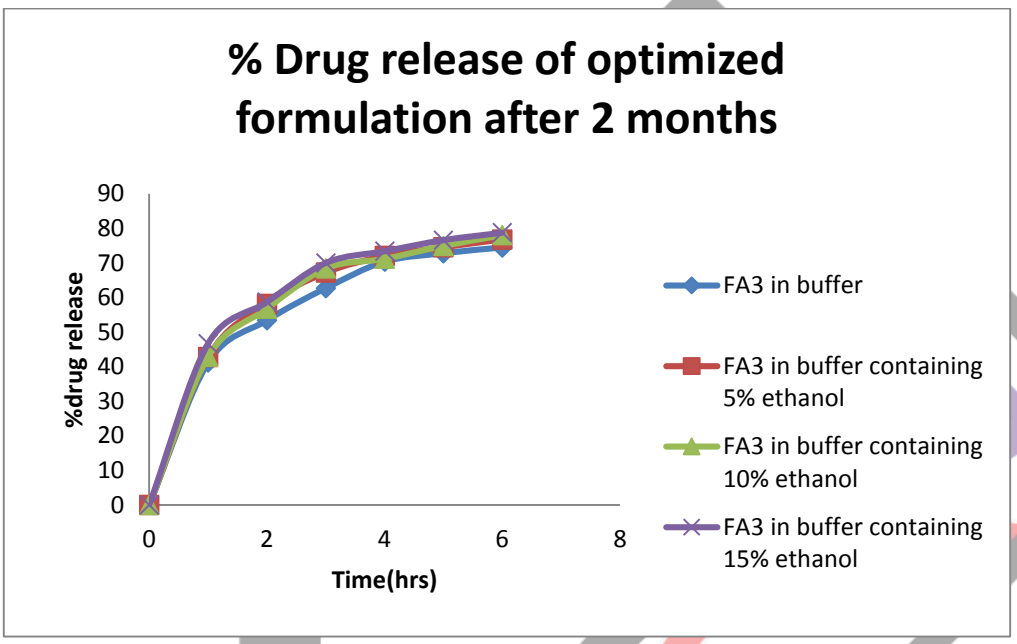
Fig 6.2 : % Drug release of optimized formulation after 1 month



Tab 6.3 : % Drug release of optimized formulation after 2 months

| TIME (hrs) | FA3 in buffer | FA3 in buffer containing 5% ethanol | FA3 in buffer containing 10% ethanol | FA3 in buffer containing 15% ethanol |
|---|---|---|---|---|
| 1 | 41.143 | 42.717 | 42.810 | 46.664 |
| 2 | 53.358 | 58.128 | 567504 | 58.657 |
| 3 | 62.656 | 67.179 | 68.391 | 69.996 |
| 4 | 70.33 | 71.964 | 71.174 | 73.384 |
| 5 | 72.76 | 74.489 | 74.909 | 76.587 |
| 6 | 74.433 | 76.748 | 77.987 | 78.736 |

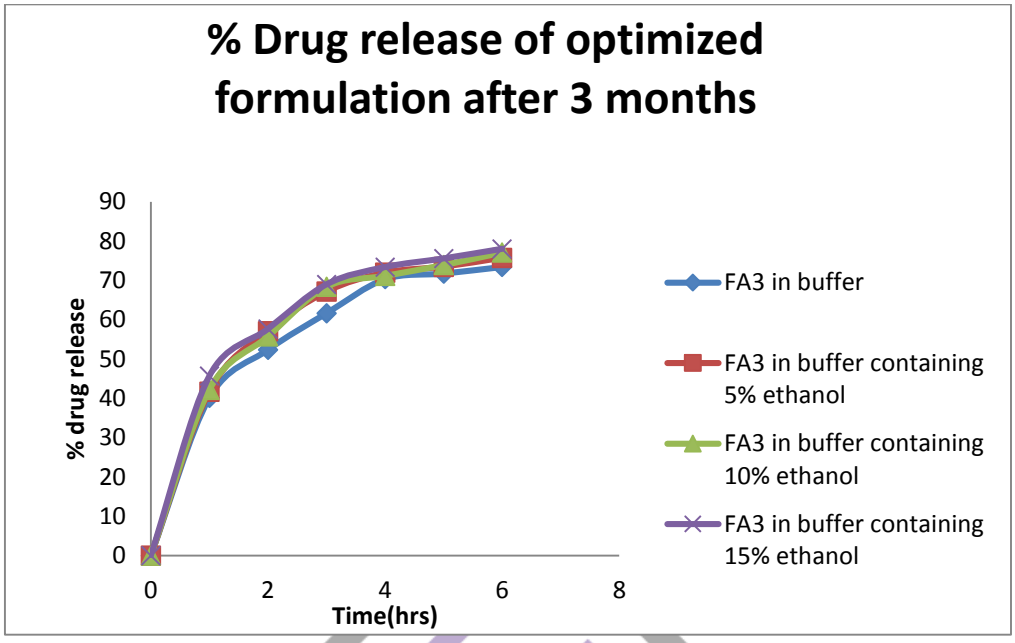
Fig 6.3 : % Drug release of optimized formulation after 2 months




Tab 6.4 : % Drug release of optimized formulation after 3 months

| TIME (hrs) | FA3 in buffer | FA3 in buffer containing 5% ethanol | FA3 in buffer containing 10% ethanol | FA3 in buffer containing 15% ethanol |
|---|---|---|---|---|
| 1 | 40.843 | 41.917 | 42.210 | 45.964 |
| 2 | 52.958 | 57.128 | 56.750 | 57.657 |
| 3 | 61.656 | 67.179 | 68.091 | 68.996 |
| 4 | 70.33 | 71.964 | 71.174 | 73.584 |
| 5 | 72.76 | 74.089 | 75.109 | 74.187 |
| 6 | 73.933 | 75.848 | 77.087 | 78.036 |

Fig 6.4: % Drug release of optimized formulation after 3 months




## 7. DISCUSSIONS:

- Quetiapine fumarate is an atypical antipsychotic agent. Antipsychotic drugs are used for the treatment of several mood and mental disorders including bipolar disorders, episodes of mania and depression associated with bipolar and schizophrenia. It rebalances the concentration of certain neurotransmittors in the brain.
- Aim of the present study is to formulate and evaluate alcohol resistant matrix tablets of Quetiapine fumarate using polymers such as HPMC K15 and Ethyl cellulose.
- The tablets wer prepared by wet granulation method using hydroxyl propyl methyl cellulose K15(HPMC K15), ethylcellulose. Results indicate the release from optimized formulation of alcohol resistant matrix tablets of Quetiapine fumarate can enhance the release of drug for extended period and also there is no dose dumping in presence of alcohol.
- From the results, we can summarize:
- From the IR and physical observation it was observed that there was no significant Drug-Excipient interaction.
- The bulk density, tapped density and true density were found to be 0.4g/ml, 2.745g/ml, 0.5g/ml respectively.
- The angle of repose was found to be 26.5º. the powder has good flow property.
- Hausner's ratio was found to be 1.20(fair flow property).
- The results of carr's compressibility index show that the powder has fair flow property.
- Tablet thickness(n=2) were almost uniform in all the formulations and values ranges from 0.50cm to 0.60cm.
- The weight uniformity of tablets ranges from 108±5mg to 208±5mg.
- The hardness of all formulations was in the range of 2 to 3kg/cm$^2$.
- The values of friability of all the formulations ranged from 0.10 to 0.4%.
- The % drug content of all the formulated tablets was calculated and it was observed that the drug release was sustained upto 6 hours.
- The optimized formulation follow zero order with non fickian diffusion on the basis of regression coefficient of the kinetic data of cumulative drug release from the dosage form.
- The drug release profiles of the prepared tablets were comparable with that of the marketed preparation.

- When compared to marketed preparation the drug release from the prepared matrix tablets was slow and sustained without dose dumping in presence of alcohol.
- The results of accelerated stability study showed that there was no change in the formulatipn after 3 months.

**8. CONCLUSION:**

- In the present study, attempt was made to prepare alcohol resistant tablet formulation.
- Quetiapine fumarate sustained release tablets were prepared by wet granulation method by using HPMC k50, ethylcellulose, magnesium stearate, talc, microcrystalline cellulose and cross carmellose sodium.
- Bulk density, tapped density, compressibility index, true density, angle of repose were performed and the results indicate that the powder blend has good flow property.
- Quetiapine fumarate matrix tablets prepared employing HPMC K15 and Ethyl cellulose in combinations, the drug release was sustained over a long period of time and the drug release was depended on the concentration of polymers used.
- The drug release profiles of the prepared tablets were comparable with that of the marketed preparation.
- When compared to marketed preparation the drug release from the prepared matrix tablets was slow and sustained without dose dumping in presence of alcohol
- The matrix tablets prepared employing HPMC K15 and Ethyl cellulose in the formulation FA3 were showing similar release profile of the drug in plain buffer and buffer containing alcohol upto 15% , indicating alcohol resistant release of the drug without dose dumping.

REFERENCES:

1. Chandira M, Venkateswarlu B.S., Anup J, Shankarrao, Formulation and Evaluation of Extended Release Tablets containing Metformin HCl, International Journal of ChemTech Research, 2(2), 2010, 1320-1329.

2. Hamdani J., Moes J. A., Amigh, K., Physical and thermal characterisation of Precirol® and Compritol® as lipophilic glycerides used for the preparation of controlledrelease matrix pellets International Journal of Pharmaceutics, 260(1), 2003, 47–57.

3. Kottke M. K., Chuech H. R. and Rhodes C. T., Comparison of Disintegrant and Binder Activity of Three Corn Starch Products, Drug Development and Industrial Pharmacy, 18, 1992, 2207.

4. Herman J. and Remon J. P., Modified starches as hydrophilic matrices for controlled oral delivery III. Evaluation of sustained-release theophylline formulations based on thermal modified starch matrices in dogs, International Journal of Pharmaceutics, 63, 1990,201.

5. Jagdale S.C., Patil S.A., Kuchekar B.S., Chabukswar A.R., Preparation and characterization of metformin hydrochloride - compritol 888 ATO solid dispersion, Journal of Young Pharmacists, 3(3), 2011, 197-204.

6. Patel J.K., Patel N.V., Shah S.H., In vitro controlled release of colon targeted mesalamine from compritol ATO 888 based matrix tablets using factorial design, Research In Pharmaceutical Sciences, 4(2),2009, 63-75.

7. Rang H. P., Dale M. M and Ritter J. M., in Pharmacology, 4th Edn., Churchil,l Living Stone, London, 1999, 230.

8. Masazumi K, Hiroaki N. Development of controlled release matrix pellets by annealing with micronized water-insoluble or enteric polymers, J. Contr. Rel., 2002; 82: 335-343.

9. Ponghanaghakul T, Puttipipatkhachorn S. Alginate-magnesium aluminum silicate film: Effect of plasticizer film properties, drug permeation and drug release from coated tablets. Int. J. Pharm., 2007; 333: 34-44.

10. Mustafa SinanKaynak, H. SüheylaKaş, LeventÖner, Formulation of Controlled Release Glipizide Pellets Using Pan Coating Method Hacettepe University Journal of the Faculty of Pharmacy 27; 2:2007, 93-106.