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# Preparation and Characterization of Hydrogel Based Drug Delivery System of Quetiapine Fumarate

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ABSTRACT

Quetiapine fumarate is an anti-psychotic with shorter half-life. The present research work aims to maintain sustained release of the pure drug by preparation of nine formulations of Hydrogel beads by using chitosan and sodium alginate and with different concentrations of HPMC, and Calcium chloride as counter ion. The physicochemical characterization like SEM, swelling index, and entrapment efficiency for the dried beads and Invitro dissolution studies were performed for all the formulations. Drug entrapment efficiency and water uptake of hydrogel beads increase with increase in percentage as well as grade of HPMC (K100,K15, K4).As the concentration of the polymer increased the drug release profile reduced.F4 formulation has shown good in-vitro dissolution profile with good correlation and reproducible results. These results showed that the introduction of polymeric network may offer simple and unique approaches for the preparation of new controlled drug delivery systems.

Key words: Quetiapine fumarate, Hydrogel beads, new controlled drug delivery systems.

## 1. INTRODUCTION

For many decades, medication of an acute or a chronic disease has been accomplished by delivering active pharmaceuticals to the patients via various pharmaceutical dosage forms like tablets etc. To achieve and then to maintain the concentration of drug administered within the therapeutically effective range, it is often necessary to take this type of conventional drug delivery systems several times a day. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. Recently several technical advancements have been developed for the drug-delivery[1,2]. Hydrogels are controlled drug delivery systems design for zero order release kinetic which ensure constant drug release over prolonged period of time[3,4]. It is a three dimensional network of hydrophilic polymer chains that are cross linked through either chemical or physical bonding[5,6]. Over the past decades advances in hydrogel technologies have spurred development in many biomedical applications including controlled drug delivery[7]. Hydrogels are reported to reduce the problem of not only conventional dosage forms but also of novel drug delivery systems[8].

Quetiapine is a new atypical dibenzothiazepine antipsychotic introduced that is expected to fulfil the main goals in treatment of schizophrenia that is amelioration of positive, negative, affective and cognitive symptoms, improves quality of the life and minimizes treatment related side effects. Above these, it has effect on affective symptoms for difficult cases of schizoaffective disorders, depression with psychosis and other mixed conditions.

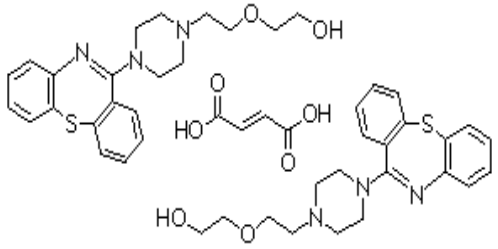

Figure No.1: Structure of Quetiapine fumarate

Quetiapine fumarate is a Competitive of selective histamine $H_1$ receptor antagonist, used as an antipsychotic drug, and is the drug of choice in treatment of schizophrenia; depressive episodes associated bipolar disorder, acute manic episodes. It's having shorter half-life (6hrs). The bioavailability of Quetiapine fumarate following oral administration is about 6 % which might be due to colonic degradation by colonic bacteria. High doses produce toxicity and hence dose could

be minimized. The minimal first pass metabolism of drug can be avoided in the form of hydrogels. By entrapment of drug in the form of Hydrogels the bioavailability can be increased[9].

The present research work aims to prepare hydrogel based drug delivery systems of Quetiapine fumarate with Chitosan, Sodium alginate and varying ratios of HPMC to achieve modified drug release for improving patient compliance.

## 2. Materials and Methods

### 2.1. Materials

Quetiapine fumarate and Chitosan were purchased from Yarrow ChemiePvt. Ltd, Mumbai. Hydroxy propyl methyl cellulose and Sodium alginate were purchased from S.D.Fine Chem. Ltd. All other chemicals used were of analytical grade.

### 2.2. Methods

### 2.3.3. Preparation of Hydrogel beads

Hydrogel beads of Quetiapine fumarate were prepared by Ionotropic gelation technique. In the present work nine sets of Hydrogel beads were prepared by using chitosan and sodium alginate and with different concentrations of HPMC, and Calcium chloride as counter ion. The detailed composition of the various formulations prepared is as mentioned in Table No.1.

Table No. 1: Formulation Design of Hydrogel beads

| Formulation | Drug | Na. alginate | K100 | K15 | K4 |
|---|---|---|---|---|---|
| F1 | 1% | 1% | 1% | - | - |
| F2 | 1% | 1% | 2% | - | - |
| F3 | 1% | 1% | 3% | - | - |
| F4 | 1% | 1% | - | 1% | - |
| F5 | 1% | 1% | - | 2% | - |
| F6 | 1% | 1% | - | 3% | - |
| F7 | 1% | 1% | - | - | 1% |
| F8 | 1% | 1% | - | - | 2% |
| F9 | 1% | 1% | - | - | 3% |

In the all batches of drug-loaded Hydrogel beads were prepared (F1 to F9) by Ionotropic gelation technique.

A solution of Chitosan (1%), sodium alginate (1%), with respective concentration of HPMC and weighed drug was dissolved in 50 ml of deionized water. Bubble free dispersion was dropped through a syringe into 50 ml aqueous calcium chloride solution and stirred at 100rpm. After stirring for 10minutes, the gelled beads were separated by filtration, washed with distilled water, air dried and then finely dried at $40^0$C for 6 hr in an oven.

### 2.4. Characterization of Beads

### 2.4.1. Fourier Transform Infrared spectroscopy (FTIR)

FT-IR spectroscopy was conducted using a FTIR Spectrophotometer (Thermo-IR 200) and Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The spectrum of Quetiapine fumarate, Chitosan, Sodium alginate and HPMC was recorded in the wavelength region of 4000–400 $cm^{-1}$.

### 2.5. Drug Entrapment Efficiency

Drug entrapment efficiency of Quetiapine fumarate was performed by accurately weighing 100 mg of Hydrogel beads and suspended in 100 ml of pH 7.4 phosphate bufferand then it was kept for 24 hrs. Stirred for 15 mins, and subjected for filtration. After suitable dilution, Quetiapine fumarate content in the filtrate was analyzed spectrophotometrically at 290 nm using Shimadzu 1201 UV-visible spectrophotometer.

The absorbance found from the UV-spectrophotometer was plotted on the standard curve to get the concentration of the entrapped drug. Calculating this concentration with the dilution factor we get the percentage drug encapsulated in Hydrogel beads.

### 2.6. Particle Size

Particle size of drug-loaded hydrogel beads was performed by optical microscopy.

### 2.7. Flow Property

The flow properties were investigated by measuring the angle of repose of drug-loaded Hydrogel beads using fixed-base cone method to assess the flowability. The fixed-base cone method, a funnel was secured with its tip at a 1cm height (H) above the graph paper that was placed on a flat horizontal surface. Hydrogel beads were carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. Measure the height of the pile (h) and theradius of the base (r) with ruler. The angle of repose was determined by using the equation.

$$\theta = \tan^{-1}\left[\frac{h}{r}\right]$$

Where θ = angle of repose,

R = radius of the base of pile,

H = height of pile.

2.8. Swelling Properties

Swelling of hydrogels was carried out in triplicate by gravimetric method. Known weight of hydrogels were taken and immersed in pH 7.4 phosphate buffer solution at 37 ºC. Then the hydrogels were removed at particular time intervals, wiped with tissue paper to remove excess of solvent and weighed immediately. The difference in weight has given the amount of pH 7.4 phosphate buffer solution uptake by hydrogels after definite time intervals (60 min) for 6 hr.

$$\text{Swelling ratio} = \frac{W_t - W_0}{W_0}$$

Where, $w_t$ =weight of hydrogels at time.

$w_o$ = initial weight of hydrogels.

2.9. Water uptake

Known weight of hydrogels for were taken and immersed in excess of distilled water at 37ºc. Then the hydrogels were removed at particular time intervals, wiped with tissue paper to remove excess of solvent and weighed immediately. The difference in weight has given the amount of water uptake by hydrogels for definite period of time.

$$\text{Water uptake} = \frac{W_S}{W_D}$$

Where, $W_S$= weight of swollen hydrogels.

$W_D$=weight of dried hydrogels.

2.10. In-vitro Dissolution Studies

In-vitro release profile of the Hydrogel beads was evaluated in triplicate using rotating basket dissolution USP II apparatus. 900 ml of acid buffer (pH1.2) for 2hr and phosphate buffer (pH 6.8) for 6 hr, maintained at 37±0.5$^0$C were used as dissolution Medias respectively, and the basket was rotated at a constant speed of 50 rpm. Accurately weighed amount of Hydrogel beads equivalent to 200 mg of drug were placed in the baskets.

Aliquotes of samples were withdrawn at the interval of every 1 hour for pH 1.2 and for 6.8 pH. The samples withdrawn were filtered, diluted suitably and analyzed at 290 nm spectrophotometrically for drug release.

3. Results and Discussion

3.1. Drug compatibility Studies by FTIR

To check the compatibility of the drug with various polymers, IR spectra of drugs, polymers and combination of the drug and polymers were taken. The IR spectra of the drug and polymer combinations were compared with the spectra of pure drug and individual polymers. The principle peaks obtained for the combinations were almost similar to that of the drug. The IR spectra of the Drug-HPMC, Drug – chitosan, and Drug-Sodium alginate, did not show any changes. The possibility of interaction was ruled out as there was no major shift in the absorption bands of drug and the formulations as shown in figure no 2.

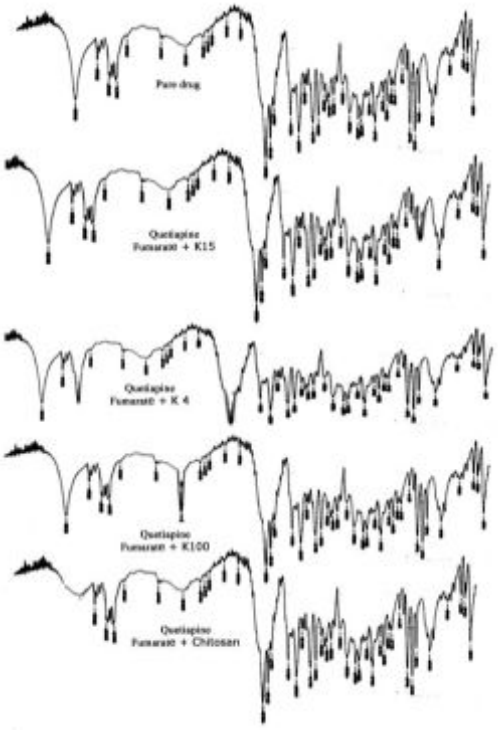


Figure No.2: Comparative FTIR spectrum of (a) Quetiapine fumarate- Chitosan (b) Quetiapine fumarate- K-15 (c) Quetiapine fumarate- K-4 (d) Quetiapine fumarate- K-100 physical mixture.

## 3.2. SEM analysis:

The SEM of the hydrogel beads prepared from Chitosan, HPMC sodium alginate were spherical in shape, exhibits uniformity and rough surface has a sandy appearance, This was due to coalescence and fusion to the colloidal aqueous polymer dispersions in the alginate matrix. The average diameter of the particles increases and decreases the porosity accounts for slow release of drug. SEM photographs of prepared beads shown in Figure no. 1.

3.3. Drug Entrapment Efficiency:

The drug entrapment efficiency of all the batches are shown in Table no 2, Drug entrapment efficiency of hydrogel beads increase with increasing in the percentage as well as by grade of HPMC ( K100,K15, K4).These may be due to

drug adhering property of the polymers and also reduced the loss of drug in the curing medium and formation of dense matrix structure shows increase in the drug entrapment efficiency of the hydrogel beads. The amount of calcium chloride has probably no significant effect on the drug entrapment efficiency.

Figure No.1: Hydrogel beads and SEM surface image of nine formulations

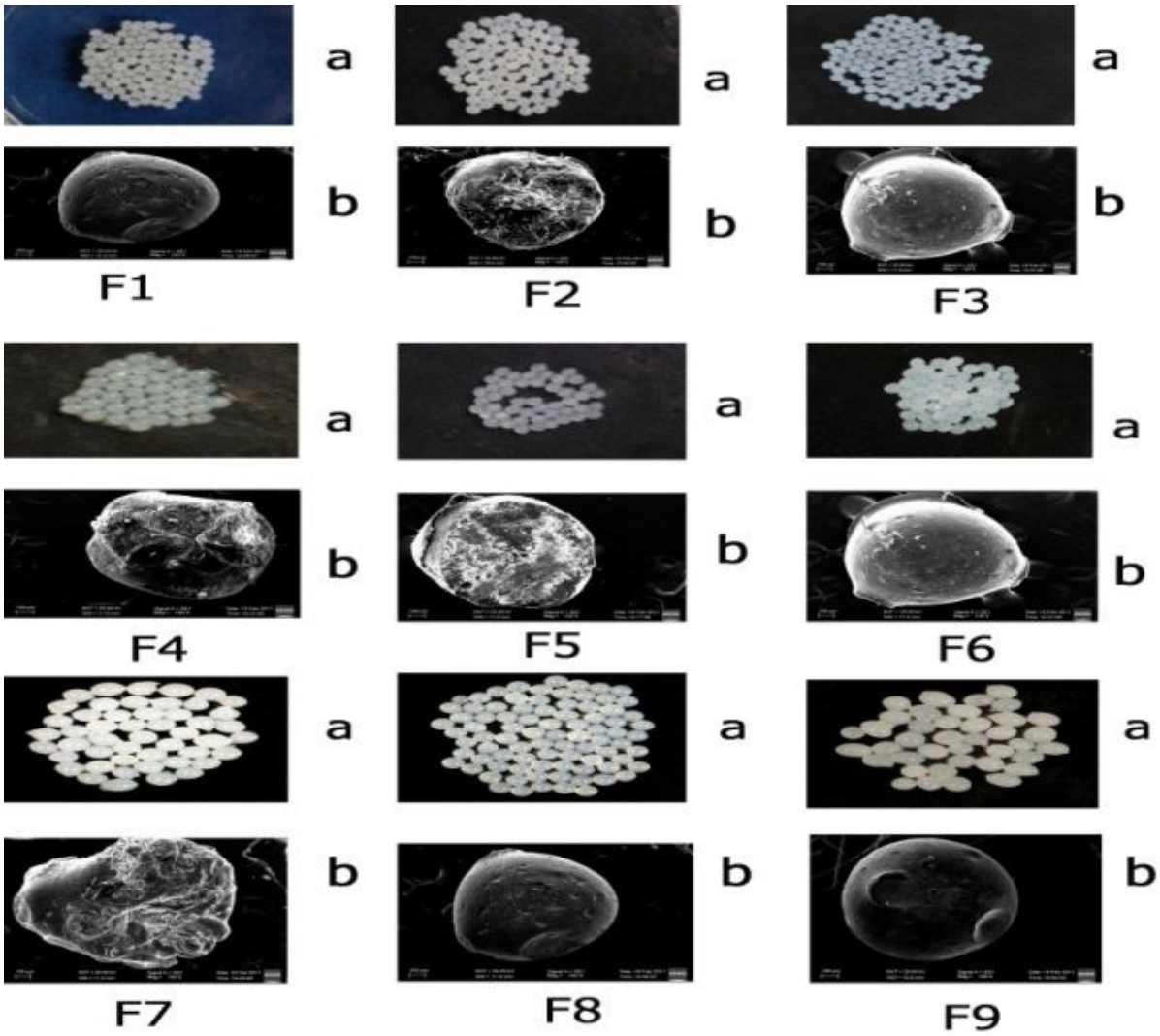


Table No. 2: Drug entrapment, flow analysis and size analysis of efficiency

| Formulation CODE | Percentage of yield | Drug entrapment | Angle of repose | Size analysis | |
|---|---|---|---|---|---|
| | | | | Dried beads | Wet beads |
| F1 | 50.50 | 14.1±1.8% | 23±0.52 | 1.20±0 .32 | 2.30±0.01 |
| F2 | 65.32% | 15.6±1.7% | 24±0.44 | 1.38 ±0.12 | 2.43±0 .12 |
| F3 | 66.50% | 16.4±1.9% | 24.25±0.12 | 1.48± 0.02 | 2.66±0 .32 |
| F4 | 50.50% | 25.3±1.8% | 24.58±0.38 | 1.20 ±0.11 | 2.32±0 .17 |
| F5 | 65.90% | 27.5±2.1% | 25.74±0.62 | 1.50±0 .14 | 2.40± 0.51 |
| F6 | 69.10% | 29.8±2.3% | 25.21±0.65 | 1.65± .051 | 2.51± 0.21 |
| F7 | 67.50% | 20.1±1.8% | 24.02±0.45 | 1.28 ±0.05 | 2.41± 0.09 |
| F8 | 69.30% | 35.3±1.6% | 24.58±0.54 | 1.65±0 .04 | 2.52± 0.02 |
| F9 | 75.80% | 39.4±1.7% | 25.32±0.64 | 1.83±0 .04 | 2.93± 0.19 |

Table No.3: Swelling ratio data for all formulations at different time intervals

| Formulation code | Time in mins | | | | | |
|---|---|---|---|---|---|---|
| | 60 | 120 | 180 | 240 | 300 | 360 |
| F1 | 1.2±0.05 | 2.6± 0.1 | 4.5 ±0.1 | 5.4± 0.15 | 7.2± 0.05 | 7.6± 0.05 |
| F2 | 2.2± 0.05 | 3.6 ±0.05 | 4.4 ±0.05 | 6.4± 0.05 | 7.3± 0.05 | 8.2 ±0.05 |
| F3 | 2.7± 0.11 | 4.3± 0.05 | 6.2± 0.11 | 7.5± 0.1 | 10.7± 0.05 | 10.7± 0.05 |
| F4 | 0.5± 0.15 | 2.6± 0.15 | 3.6± 0.05 | 4.3± 0.05 | 6.6± 0.05 | 6.6± 0.05 |
| F5 | 1.3± 0.1 | 3.4± 0.15 | 4.7± 0.05 | 5.4± 0.05 | 7.3± 0.11 | 7.3± 0.11 |
| F6 | 1.7 ±0.1 | 4.6± 0.1 | 6.5± 0.15 | 7.5± 0.05 | 9.6± 0.05 | 9.6± 0.05 |
| F7 | 1.0±0.1 | 2.6± 0.1 | 5.3 ±0.11 | 9.4± 0.05 | 9.6 ±0.05 | 9.6±0.05 |
| F8 | 1.6 ±0.1 | 3.3± 0.15 | 7.4± 0.05 | 8.2± 0.05 | 10.6± 0.05 | 10.6± 0.05 |
| F9 | 2.5 ±0.1 | 4.7± 0.05 | 7.5 ±0.05 | 9.5± 0.05 | 12.6± 0.05 | 12.6± 0.05 |

Table No. 5 Water uptake data for all formulations

| Formulation code | Time in mins | | | | | |
|---|---|---|---|---|---|---|
| | 60 | 120 | 180 | 240 | 300 | 360 |
| F1 | 2.2±0.05 | 3.7± 0.1 | 5.6± 0.1 | 6.6 0.05 | 8.3± 0.05 | 8.5± 0.05 |
| F2 | 3.3±0.05 | 4.5 ±0.05 | 5.4± 0.05 | 7.2± 0.05 | 8.6± 0.05 | 9± 0.05 |
| F3 | 3.7 ±0.11 | 5.3± 0.05 | 7.3± 0.11 | 8.3± 0.1 | 11.8± 0.57 | 11.8± 0.57 |
| F4 | 1.6± 0.15 | 3.6± 0.15 | 4.4± 0.05 | 5.3± 0.05 | 7.6± 0.05 | 7.6± 0.05 |
| F5 | 2.3± 0.1 | 4.5± 0.15 | 5.8± 0.05 | 6.4± 0.05 | 8.3± 0.11 | 8.3± 0.11 |
| F6 | 2.7± 0.1 | 5.6± 0.1 | 7.6± 0.15 | 8.5± 0.05 | 10.6± 0.05 | 10.6± 0.05 |
| F7 | 2.1± 0 | 3.7± 0.1 | 6.4± 0.11 | 10.5± 0.05 | 10.5± 0.05 | 10.5± 0.05 |
| F8 | 2.5± 0.1 | 4.3± 0.15 | 8.6± 0.05 | 9.2± 0.05 | 11.6± 0.05 | 11.6± 0.05 |
| F9 | 3.5 ±0.1 | 5.6± 0.05 | 8.5± 0.05 | 10.5± 0.05 | 13.6 0.05 | 13.6± 0.05 |

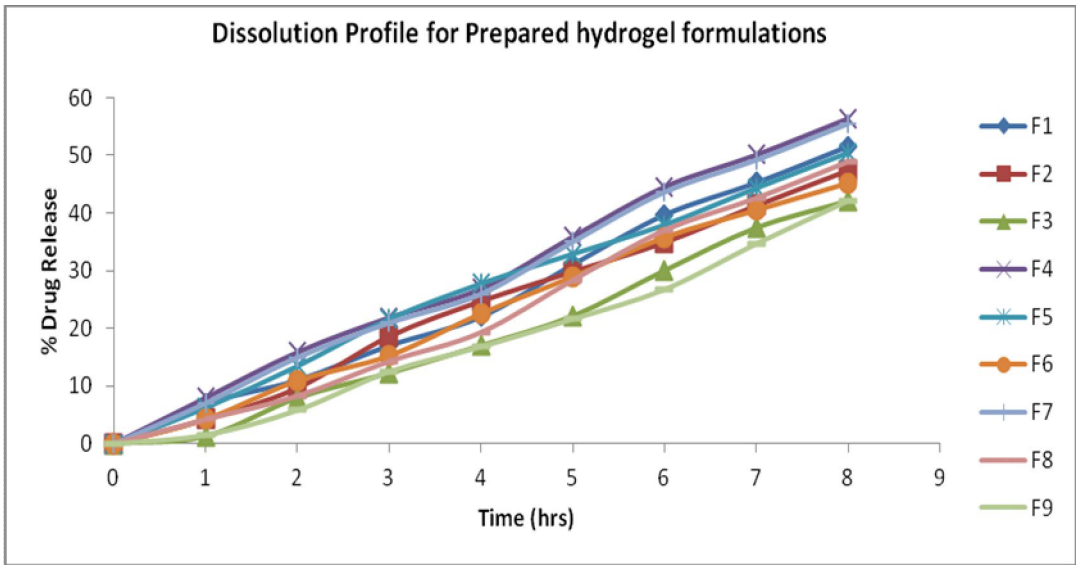

Table No. 6 Dissolution profile for the prepared hydrogel formulations

| Time | % Drug Release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F-1 | F-2 | F-3 | F-4 | F-5 | F-6 | F-7 | F-8 | F-9 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 6.97 | 4.24 | 1.26 | 7.97 | 6.25 | 4.27 | 7.03 | 4.23 | 1.54 |
| 2 | 11.02 | 9.68 | 7.93 | 15.89 | 13.45 | 10.94 | 14.95 | 8.28 | 5.81 |
| 3 | 17.02 | 18.61 | 12.24 | 21.89 | 21.62 | 15.25 | 20.95 | 14.28 | 12.48 |
| 4 | 22.02 | 24.74 | 17.02 | 26.89 | 27.75 | 22.56 | 25.95 | 19.28 | 16.79 |
| 5 | 31.06 | 29.88 | 22.14 | 35.93 | 32.89 | 28.93 | 34.99 | 28.32 | 21.57 |
| 6 | 39.69 | 34.94 | 30.04 | 44.56 | 37.95 | 35.76 | 43.62 | 36.95 | 26.69 |
| 7 | 45.27 | 41.32 | 37.46 | 50.14 | 44.33 | 40.47 | 49.2 | 42.53 | 34.59 |
| 8 | 51.56 | 47.42 | 42.13 | 56.43 | 50.43 | 45.14 | 55.49 | 48.82 | 42.01 |

### 3.4. Particle Size Analysis

Particle size of drug-loaded hydrogel beads was performed by optical microscopy. The size of the beads was obtained in the range 1.2 to 2.93 mm. The mean diameter of the particles was found to increase by increasing in the concentration of HPMC polymer as well as grade. The mean diameter of the hydrogel beads was reported in Table No.2.

### 3.5. Flow Property

All prepared hydrogel beads of Quetiapine fumarate showed good flowability. Angle of repose values with SD were mentioned in Table no. 2.

### 3.6. Swelling Properties

The "Swelling-dissolution-erosion" process is highly complex. In systems based on sodium alginate cross-linked with calcium chloride, the osmotic pressure gradient that exists between the alginate gel and the environment comprises an important factor in the swelling process. The observations of swelling properties of the prepared hydrogel beads in pH 7.4 phosphate buffer were shown in Table no.3.

### 3.7. Water uptake studies

Water uptake studies of prepared hydrogel beads of Quetiapine fumarate were done in triplicate. As the polymer concentration and grade increases, the water uptake of formulated beads increases and results mentioned in Table no 5.

### 3.8. In-vitro Dissolution Studies

The Dissolution studies had been performed for the prepared hydrogel beads in 0.1 n HCl for first 2 hours and remaining 6 hours in pH 6.8 phosphate buffer. The results were shown in the Table no.6 and graph was given in Figure No. 4. The percentage drug release from F1 formulation at the end of 8 hours is 51.56 % where as the drug release from F2, F3 formulation is 47.42% and 42.13% respectively. The three formulations contain K100 in the 1%, 2%, 3% ratios respectively. The decrease in the release of drug from F3 might be due to increased polymer concentration resulting in prolonged drug release. F4, F5, F6 formulations contain K 15 in the ratios 1%, 2% and 3% and the drug release was 56.43%, 50.43% and 45.14% respectively. The drug release from F7, F8, F9 formulations at the end of 8 hours is 55.49%, 48.82%, 42.015% respectively.

As the concentration of the polymer increases the drug release is sustained, this might be due to high networking of polymer. F4 formulation has shown higher dissolution rate over others with 56.43% drug release. All the formulations are following first order release kinetics indicating a dose dependent release from a matrix system, which is formed by the cross linking of polymers.

## 4. CONCLUSION

The Quetiapine fumarate hydrogel beads were prepared by ionic cross linkage method. Nine formulations were prepared with the polymers sodium alginate, Chitosan and varying concentrations (in 1%, 2%, 3%) of HPMC of grades K 100, K 15, K 4. The polymers chosen showed no significant interaction with drug which was evident from FTIR studies. The physicochemical characterization like SEM, swelling index, and entrapment efficiency for the dried beads was performed for all the formulations. As the polymer concentration and grade increases, the water uptake and entrapment efficiency of formulated beads increases. The *in-vitro* dissolution studies have been performed all the formulations. Good correlation and reproducible results were obtained with F4 formulation showing good *in-vitro* dissolution profile. As the concentration of the polymer increased the drug release profile reduced with

increased entrapment efficiency. The sustained drug release profile has been maintained.So the present technique is successful in developing a sustained release formulation for the Quetiapine fumerate.

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