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Research Article

FORMULATION AND DESIGN OF TASTE MASKED QUETIAPINE FUMARATE ORALLY FAST DISINTEGRATING TABLETS

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ABSTRACT

Quetiapine Fumarate bioavailability is 9%. Used in the treatment of schizophrenia. It is preferable to administer in the form of fast disintegrating tablets used for depressive episodes, acute manic episodes associated with bipolar I disorder at a short time. In present research work an attempt has been made to prepare taste masked fast dissolving tablets of Quetiapine Fumarate were prepared by using direct compression method. IR spectral analysis study showed that there was no drug interaction with formulation additives of the tablet. The blend was examined for the pre-compressional parameters results were within prescribed limits and indicated good free flowing property. The prepared tablets formulations were evaluated for post-compressional parameters. All the post-compressional parameter are evaluated were prescribed limits and results were within IP acceptable limits. Taste evaluation was performed on six healthy human volunteers. The pure drug was felt bitter immediately after it was kept on the tongue and the sense was even carried upto 5 min. However the bitterness of the drug was reduced or even masked after complexation with Eudragit EPO in different ratios (1:0.5, 1: 1, 1:2, 1:3). In case of 1: 0.5 ratio it was felt slightly bitter after 1 min and it is apparent from the results that the increasing concentrations of the polymer have completely masked the bitter taste of the drug. The disintegration time of 72 to 241 sec, and *in-vitro* drug release showed 96.88 - 98.92% within 9 min. Formulation A3 showed 98.91% release after 30 min, B3 and C3 showed 102.83, 99.44 % drug release in release in 30 min and 19 min for both formulations respectively. The initial drug release for formulation C3 at 08 min is 79.62 %. From the above observations, it is concluded that crospovidone 15 % shows better drug release profile compared with other super disintegrants. So crospovidone was selected as best formulation. The stability study conducted as per the ICH guidelines and the formulations were found to be stable. The results concluded that bitterness of the drug was masked and showing enhanced dissolution, improved effectiveness and hence better patient compliance.

Keywords: Taste masked fast dissolving tablets, Quetiapine Fumarate, Croscarmellose sodium, sodium starch glycolate, crospovidone, Disintegration time.

INTRODUCTION

Quetiapine Fumarate bioavailability is 9%. Half-life of drug is Approximately 6 hrs. Quetiapine Fumarate is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. Used in the treatment of schizophrenia. It is preferable to administer in the form of fast disintegrating tablets used for depressive episodes, acute manic episodes associated with bipolar I disorder at a short time [1-3].

Most pharmaceutical forms for oral administration are formulated for direct ingestion, for chewing, for prior dispersion and /or dissolution in water; some of them are absorbed in mouth (sublingual or buccal tablets). Elderly individuals have difficulty in swallowing when prescribed in conventional tablet and capsule form [4-6]. The problem of swallowing is also evident in pediatrics, psychiatric as well as travelling patients who may not have ready access to water [7].The rapidly disintegrating tablet in mouth or oro dispersible tablets overcome all the above problems and thus offer an alternate form of oral medication, which provide patient s with a more convenient means of taking their medication [8]. Addition of super disintegrating agent in the formulation is one of the approaches to formulate oro dispersible tablets [9-15].

Orally Disintegrating tablets (ODTs) rapidly disintegrate in the mouth without chewing upon oral administration and without the need for water, unlike other drug delivery systems and conventional oral solid immediate-release dosage form. ODT dosage forms, also commonly known as fast melt, quick melts, fast disintegrating and orodispersible systems have the unique property of disintegrating the tablet in the mouth in sec.

The desired criteria for the FDT they should Have a pleasing mouth feel, Leave minimal or no residue in the mouth after oral administration and not require water to swallow, but it should dissolve or disintegrate in the mouth in a matter of sec [16-17].

In present research work an attempt has been made to prepare taste masked fast dissolving tablets of Quetiapine Fumarate were prepared by using direct compression method. The objective of the present study is to mask the metallic taste of QUETIAPINE FUMARATE. Taste masking of Quetiapine Fumarate was done by complexation with the Eudragit E100 at different ratios. To study the effect of different superdisintegrants, subliming agent and effervescence producing agents on the Disintegration time (DT), Wetting time (WT), and *in vitro* drug release profile of Quetiapine fumarate orally fast disintegrating tablets.

MATERIALS AND METHODOLOGY

Materials

Quetiapine Fumarate was procured from Gift sample from Aan Pharma Ltd. Gujarat. Croscarmellose sodium was procured as a gift sample from Signet (Mumbai), mannitol, MCC, aspartame, talc and magnesium stearate purchased from S.D. Fine chem., Mumbai. All other materials were of analytical reagent grade.

Preparation of Drug Polymer Complex

Quetiapine Fumarate and Eudragit E100 complex was prepared by solvent evaporation method (Kawtikwar et al., 2009). Saturated stock solutions of Quetiapine Fumarate and Eudragit E100 were prepared in absolute Ethanol. Aliquots of drug and polymer solutions were taken to obtain various ratios (1:0.5, 1:1, 1:2, 1:3) and mixed continuously at 150 rpm on a magnetic stirrer. Stirring was allowed to continue until the solvent is completely evaporated. After this mixture was kept at 35°C for 2 hours and dried under vacuum for 24 hrs to obtain a hard matrix. Then the hard matrix is subsequently pulverized and screened through 60 mesh to obtain the uniform sized fine powder of drug polymer complex (DPC) and it was finally stored in a tightly closed container for further studies.

Taste evaluation: Taste evaluation was performed on six healthy human volunteers for pure drug, and for four different ratios of drug: polymer. Bitterness was recorded immediately and at several intervals for 5 min according to the bitterness intensity scale from 0 to 5 where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and strong bitterness.

Preparation of Quetiapine Fumarate Orally Fast Disintegrating Tablets by Super disintegration addition method

The composition for the preparation of Quetiapine Fumarate orally fast disintegrating tablets batches was shown in **Table 1**. DPC equivalent to 25 mg other than lubricant were accurately weighed. Passed through 60-mesh sieve and mixed in poly bag for 5-10 min. The obtained blend was lubricated with Magnesium stearate and Talc for another five min and the resultant mixture was directly compressed into tablets. Tablets were compressed using 8 mm round flat punches using 16- station rotary tableting machine (Cadmach, Ahmedabad, India).

Micromeritic properties of powder blend of tablets before compression

The prepared tablet blends are evaluated for different tests like angle of repose, apparent bulk density, tapped density, percent compressibility and Hausner ratio,

Evaluation of Tasted masked Quetiapine Fumarate Fast Disintegrating Tablets[18-21]

Weight variation

Average weight of 20 tablets is calculated using an electronic balance. Individual weight of each tablet is calculated and compared with the average weight. The Mean±SD and RSD were noted. The tablets meet USP specifications if no more than 2 tablets outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Tablet Thickness

Randomly 10 tablets should be taken and thickness was measured for each tablet by placing it between two anvils and rotating the sliding knob until the tablet was tightly fitted and the reading was noted. The tablet thickness should be controlled within a ±5% variation of a standard value.

Hardness and Friability

Tablet hardness has been defined as "the force required to break a tablet in a diametric compression test". To perform this test, the tablet is placed between two anvils, force is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded. Hardness is thus sometimes called as "tablet crushing strength". Several devices that commonly serve the purpose of determining the tablet hardness are the Monsanto tester, the Strong-cobb tester, the Pfizer tester, the Erweka tester and the Schleuniger tester. Hardness of tablet was determined by using a Monsanto tablet hardness tester (Cadmach Machinery Co, Ahmedabad, India). Friability of ten tablets from each formulation was determined using the Roche friabilator (Campbell Electronics, Mumbai, India). This device subjects a no of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and re-weighed.

Content uniformity

Six tablets from each formulation were taken randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100mL volumetric flask, containing 0.1 N HCL and mixed thoroughly for few minutes and the volume was made up to 100mL with 0.1 N HCL. The solution was filtered through whatman filter paper and suitably diluted with the same medium and the drug content was estimated from the standard plot by measuring the absorbance at 290 nm using UV-Visible spectrophotometer.

***In vitro* disintegration time**

In vitro disintegration time of FDTs was determined by following the procedure described in earlier reports (Gohel et al., 2004). Briefly 10 mL of pH 6.8 phosphate buffer at room temperature was taken in a petri dish of 10cm in diameter. The tablet was then carefully placed in the centre of petridish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in triplicates.

Wetting Time and Water Absorption Ratio

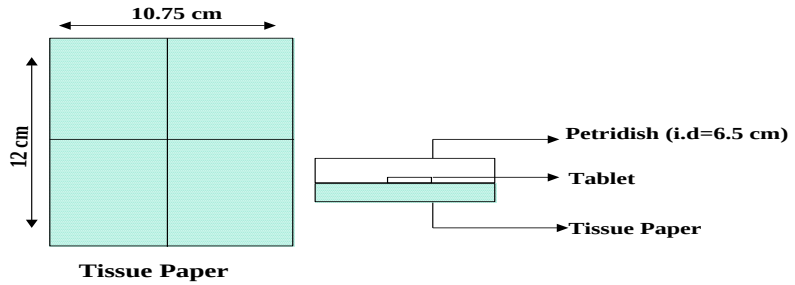
The wetting time of the tablets was measured using a simple procedure**.** Five circular tissue papers of 10-cm diameter were placed in a Petri dish with a 10-cm diameter. Ten milliliters of water containing a water-soluble dye was added to the petri dish. A tablet was carefully placed on the surface of tissue paper in the petri dish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out (n=6) and the mean value was calculated.

The weight of the tablet before keeping in the petri dish was noted (W_b). The wetted tablet from the petri dish was taken and reweighed (W_a). The Water absorption ratio, R, was determined according to the following equation:

$$R = 100 (Wa - W_b) / W_b$$

Where W_b and W_a are the weight before and after water absorption respectively.

Measurement of wetting time of a tablet was shown in **Figure.**



Simple method for the measurement of wetting time of a tablet

In vivo disintegration time

The In Vivo disintegration time and was performed on 6 healthy human volunteers from whom informed consent was first taken. All the volunteers were asked to rinse their mouth distilled water prior to the test. One tablet was placed on the tongue and the stop watch started immediately. Volunteers were allowed to move the tablet in the mouth and cause gentle tumbling action on the tablet without chewing it. Swallowing of saliva was prohibited during the test and the mouth was rinsed water after each measurement.

In Vitro Dissolution Studies [22]

The *in vitro* dissolution study of taste masked Quetiapine Fumarate FDTs were performed using USP type II (paddle) apparatus. The dissolution medium consists of 900mL of 0.1N HCL thermostated at 37±0.5°C and stirred continuously at 50 rpm through out the experiment. An aliquot of 5mL was collected at predetermined time intervals (5, 10, 20, 30, 45, 60 min) and replaced with fresh dissolution medium. The samples were filtered, by passing through 0.45 µm membrane filter and analyzed spectrophotometrically at 290 nm. Dissolution rate was studied for all designed formulations.

Fourier Transform Infrared Spectroscopy (FTIR)

The chemical interaction between the drug and polymer was evaluated by subjecting drug, polymer, DPC to FTIR studies. FTIR spectra were obtained on Shimadzu FTIR (Shimadzu Corp., India). Samples were prepared in KBr disks, the scanning range was 4000 and 400 cm^{-1}.

RESULTS AND DISCUSSION

Taste evaluation

Taste evaluation was performed on six healthy human volunteers and the results were reported in the **Table 2.** The pure drug was felt bitter immediately after it was kept on the tongue and the sense was even carried up to 5 min. However the bitterness of the drug was reduced or even masked after complexation with eudragit EPO in different ratios (1:0.5, 1: 1, 1:2, 1:3). In case of 1: 0.5 ratio it was felt slightly bitter after 1 min and it is apparent from the results that the increasing concentrations of the polymer have completely have completely masked the bitter taste of the drug. Since the drug is not in the native form and entrapped within the polymeric matrix, and there by reduction in the solubility of the drug in the saliva could have led to the masking of the bitter taste. Even though the Quetiapine Fumarate taste was masked with drug polymer complex (1:0.5, 1: 1, 1:2, 1:3) ratios, we have selected 1:1 for further studies, since higher amounts of polymer may retard the dissolution performance of the final fast disintegrating tablets of Quetiapine Fumarate. Erythritol (1%w/w) was included in all the formulations to improve the palatability.

The formulation batches were prepared by using superdisintegrants (CP, CCS and SSG), at different concentrations. Micromeritic properties such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio were evaluated for the blend of all formulations shown in **Table 3**. The angle of repose was found to be in between 26.3° to 37.5°, this indicates passable flowability. All these batches contain spray dried mannitol as diluent. The compressibility index and hausner's ratio were within the limits.

All the formulations were evaluated for weight variation, hardness, thickness, friability, disintegration time (DT), wetting time (WT), water absorption ratio (R), content uniformity were shown in **(Table 4).**

All the Quetiapine Fumarate FDT formulation batches were passed the weight variation test. The hardness was constantly maintained between 2-3 kg/ cm^2 for all the batches. Friability was found to be less than 0.90% which is in acceptable limits indicating that these formulations have sufficient mechanical strength.

The disintegration time (DT) was decreased with increasing the concentration of the superdisintegrant shown in **Fig 1**. The formulation batches prepared with super disintegrants crospovidone (CP) exhibited lower DT compared to the batches prepared with CCS and SSG. This may be due to rapid wicking and swelling properties of the CP. The concentration dependent disintegration was observed. Content of Quetiapine Fumarate from all the formulation batches was found to be in the range of 97% to 104%. And water absorption ratio(R) in between 57 to 89.

The *in vitro* drug release profile from formulation batches prepared with CCS was shown in **Fig 2**. Formulations A1 – A3 showed 67.46 %, 71.95 % and 74.74 % drug release after 30 min, A1 and A2 showed 96.989 % and 99.44 % drug release in 60 min respectively. Whereas A3 formulation the initial drug release at 10 min is 45.5 and at 55 min all most 99.99 % drug is released. From the above observations, it is concluded that by increasing the concentration of CCS, the drug releases at faster rate. A3 formulation showed better drug release.

The *in vitro* drug release profile from formulation batches prepared with SSG was shown in **Fig 3**. Formulations B1 – B3 showed 71.01 %, 73.64 % and 79.94 % drug release after 30 min, B1 and B2 showed 99.78 % and 99.26 % drug release in 60 min and 50 min respectively. Where as B3 formulation the initial drug release at 10 min is 48.13 and at 45 min all most 99.51 % drug is released. From the above observations, it is concluded that by increasing the concentration of SSG, the drug releases at faster rate. B3 formulation showed better drug release.

The *in vitro* drug release profile from formulation batches prepared with CP was shown in **Fig 4.** Formulations C1 – C3 showed 75.28 %, 81.22 % and 90.42 % drug release after 30 min, C1 and C2 showed 99.11 % and 99.72 % drug release in 50 min and 45 min respectively. Whereas C3 formulation the initial drug release at 10 min is 51.96 and at 35 min 98.72 % drug is released. From the above observations, it is concluded that by increasing the concentration of CP, the drug releases at faster rate. B3 formulation showed better drug release.

The *in vitro* drug release profile from formulation batches prepared with three superdisintegrants was shown in **Fig 5**. Formulation A3 showed 99.99 % percent release after 55 min, B3 and C3 showed 99.51 % and 98.72% drug release in release in 45 min and 35 min respectively. From the above observations, it is concluded that Crospovidone shows better drug release profile compared with other superdisintegrants. So Crospovidone was selected as best formulation.

In the present study the IR spectra for pure drug and its formulations with various polymers and other excipients is taken to establish the physical characterization of drug and its formulations **(Fig 6).** FTIR analysis was used to study the possible chemical interaction between the drug and polymer. The pure drug which is an dibenzothiazepine derivatives showed a characteristic peak at 3317.5 cm^{-1} this is due to N-H stretching and peaks at 1598.99 $cm^{-1}$and 1571.99 cm^{-1} indicative of the N-H deformation. The peak at 1336.67 cm^{-1} is due to the C-O stretching and peaks at 1458.18 cm^{-1} and 1413.82 cm^{-1} are indicative of C=C stretching of aromatic nucleus. Eudragit E100 which is an methacrylic acid ester showed important peaks at 1732.08 cm^{-1} indicative of C=O stretch of the ester group. The peaks at 2954.95 cm^{-1} indicative of C-H stretch in the alkane and 2769.78 cm^{-1} and 2821.86 cm^{-1} can be assigned to the dimethyl amino group.

The FTIR spectra of Drug Polymer Complex (DPC) displayed all the characteristic peaks of both drug and polymer. The N-H and C-O stretch band of drug and C=O stretch and C-H stretch in dimethyl amino group and C-H stretch in alkane of the polymer bands were detected in the same position. Consequently the FTIR of DPC and physical mixture seemed to be summation of drug and eudragit E100. The physical mixture showed additional characteristic peak at 3385.07 cm^{-1} indicative of free O-H stretch. This peak may be due to presence of Mannitol SD (polyols). Overall there was no alteration in the characteristic peaks of drug and polymer in the DPC suggesting that there was no interaction between the drug and polymer.

TABLE 1: TABLET COMPOSITIONS FOR QUETIAPINE FUMARATE ORALLY FAST DISINTEGRATING TABLETS.

Formulation/ ingredient(mg)	A1 5%	A2 10%	A3 15%	B1 5%	B2 10%	B3 15%	C3 5%	C2 10%	C3 15%
DPC	50	50	50	50	50	50	50	50	50
CCS	7.5	15	22.5						
SSG				7.5	15	22.5			
CP							7.5	15	22.5
Erythritol	2	2	2	2	2	2	2	2	2
Orange Flavour	2	2	2	2	2	2	2	2	2
Mg. Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Mannitol SD	82.5	75	67.5	82.5	75	67.5	82.5	75	67.5
Total Weight	150	150	150	150	150	150	150	150	150

TABLE 2: COMPARATIVE TASTE EVALUATION.

Form of Quetiapine Fumarate	10 sec	30 sec	1 min	2 min	5 min
Pure drug	3	3	3	3	2
DPC (1:0.5)	0.5	1	1	1	0
DPC (1:1)	0	0	0.5	0.5	0
DPC (1:2)	0	0	0.5	0	0
DPC (1:3)	0	0	0.5	0	0

TABLE 3: MICROMERITIC PROPERTIES OF THE FORMULATION BATCHES

Formulation code	Angle of Repose (°)	Bulk Density (gm/cm^3)	Tapped Density(gm/ cm^3)	Percent Index (I)	Compressibility	Hausner's Ratio
A1	31.8	0.5	0.64		21.87	1.28
A2	35.1	0.5	0.6		16.66	1.2
A3	33.4	0.5	0.65		23.07	1.3
B1	28	0.5	0.62		19.35	1.24
B2	26.7	0.5	0.57		12.28	1.14
B3	27.4	0.48	0.58		17.24	1.20
C1	27.3	0.5	0.6		16.66	1.2
C2	26.5	0.49	0.6		18.33	1.22
C3	26.1	0.52	0.62		16.12	1.19

TABLE 4: EVALUATION TESTS FOR PREPARED TASTE MASKED QUETIAPINE FUMARATE FDT

Formulation code	Weight in (mg)**	Thickness (mm)*	Hardness (kg/cm^2)	Friability (%)
A1	149 ± 1.83	2.5 ± 0.09	2-3	0.53
A2	150 ± 0.99	2.3 ± 0.03	2-3	0.62
A3	148 ± 2.06	2.6 ± 0.11	2-3	0.85
B1	149 ± 1.16	2.4 ± 0.05	2-3	0.56
B2	148 ± 2.35	2.5 ± 0.12	2-3	0.72
B3	147 ± 4.31	2.4 ± 0.08	2-3	0.74
C1	149 ± 2.56	2.5 ± 0.04	2-3	0.52
C2	149 ± 1.86	2.6 ± 0.07	2-3	0.53
C3	150 ± 0.65	2.7 ± 0.12	2-3	0.62

**** All values represent mean ± standard deviation (SD) n=20**
***All values represent mean ± standard deviation (SD) n=6**

TABLE 5: EVALUATION TESTS FOR PREPARED TASTE MASKED QUETIAPINE FUMARATE FDT

Formulation code	Disintegration time (sec)*	Wetting time (sec)*	Water absorption ratio (R)*	Content
A1	175 ± 4.1	86.00 ± 4.16	68.66 ± 8.1	100.59 ± 1.84
A2	136 ± 4.3	102.00 ± 2.51	80.15 ± 19.4	100.52 ± 1.90
A3	098 ± 3.0	80.00 ± 2.51	78.00 ± 2.0	99.75 ± 1.38
B1	169 ± 4.3	112.00 ± 9.29	70.30 ± 3.2	98.44 ± 1.03
B2	097 ± 6.6	110.00 ± 9.71	73.00 ± 1.0	100.05 ± 2.77
B3	084 ± 4.0	82.00 ± 3.0	73.00 ± 4.5	98.43 ± 1.19
C1	142 ± 4.0	70.00 ± 2.0	73.96 ± 1.7	100.58 ± 2.53
C2	085 ± 4.7	64.00 ± 3.0	83.00 ± 1.73	99.65 ± 2.30
C3	067 ± 3.0	52.00 ± 2.5	89.30 ± 7.0	98.70 ± 3.8

***All values represent mean ± standard deviation (SD) n=3**

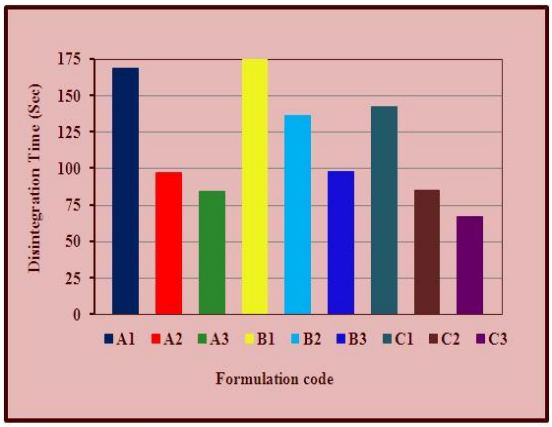


Fig 1: Disintegration time v/s Formulation (A1 – A3, B1 – B3 and C1 – C3).

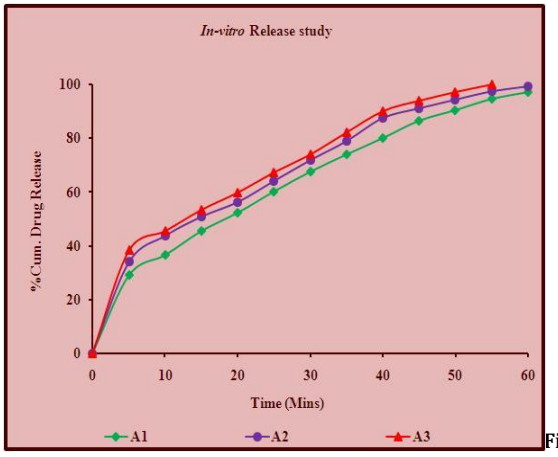


Fig 2: Release profile of formulation containing SSG (A1-3)

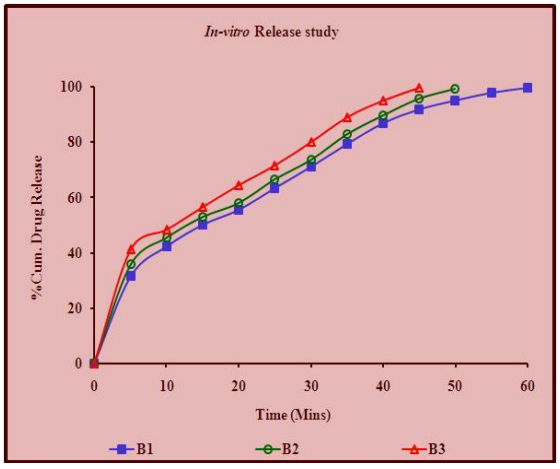


Fig 3: Release profile of formulation containing CCS (B1-B3).

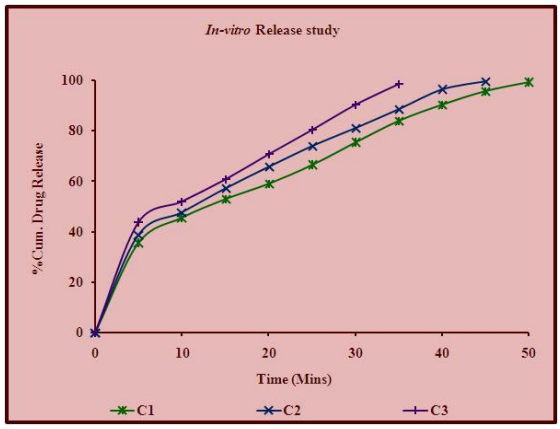


Fig 4: Release profile of formulation containing CP (C1-C3).

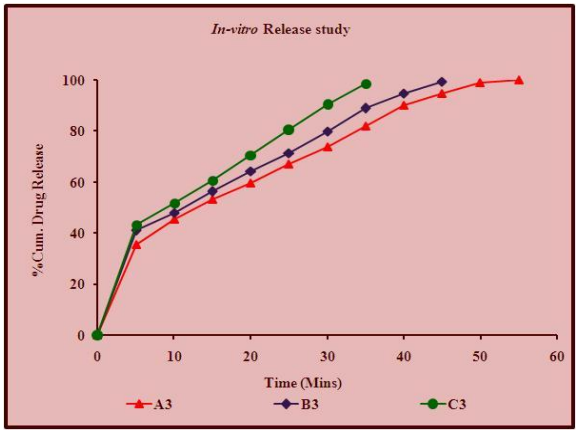


Fig 5: Release profile of best formulations containing CCS, SSG and CP (A3, B3, C3)

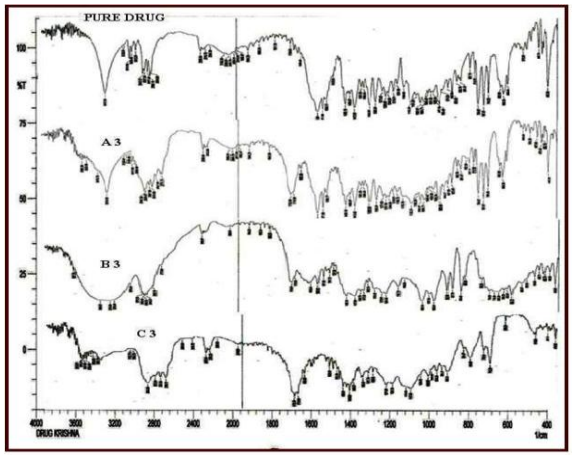


Fig 6: FTIR spectra of pure drug Quetiapine Fumarate and formulations A3, B3 and C3.

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