Research Article

J. innov. appl. pharm. Sci, 6(1) 2021, 01-07

Journal of Innovations in Applied Pharmaceutical Science
(JIAPS)

Content avvlable on: www.saap.org.in ISSN:2455-5177

Formulation and evaluation of taste masking sachets containing quetiapine fumarate

A.Abhilash *[1], T.Malyadri[2] , Ch.Saibabu[3]

[1] Department of Pharmaceutics, M.L. College of Pharmacy, S. Konda-523101

[2] Assistant professor, Department of Pharmaceutics, M.L. College of Pharmacy, S. Konda-523101

[3] Head, Department of Pharmaceutics, M.L. College of Pharmacy, S. Konda-523101

Article History

Receiced: 05-01-2021
Revised: 28-03-2021
Accepted: 31-03-2021

Keywords: Quetiapine fumarate, FTIR, PEG 6000, & Poloxamer.

Abstract

Quetiapine fumarate is a tetracyclic piperazino-azepine antidepressant agent. It is given with a dose of 15-45mg orally once a day. The absorption of this drug is rapid and complete. Due to first pass metabolism in the liver and metabolism in the gut wall, absolute bioavailability is about 50%. Peak blood concentrations are attained within about 2 hours after an oral dose. This leads to lower bioavailability of Quetiapine fumarate also having bitter taste. So to improve its bioavailability and to mask the taste solid dispersion technique was used using different carriers like PEG 6000, & Poloxamer. Results of prepared taste masking sachets by solid dispersion technique of Quetiapine fumarate by Fusion method & kneading method were discussed which includes solubility, drug content uniformity, and *in vitro* dissolution studies. Characterization in solid state was done by FT-IR studies. Finally by comparing all the formulations i.e., F1-F12 containing Quetiapine fumarate, Poloxamer and PEG 6000 in different ratios, *Invitro* drug release of Quetiapine fumarate with PEG 6000 in 1:3 by Fusion method shows 98.62% drug release at the end of 60mins. By comparing the release kinetics studies of best formulation of Quetiapine fumarate with zero order and first order we can say that the best formulation follows Zero order release kinetics studies.

*Corresponding Author
A.Abhilash
Department of Pharmaceutics, M.L. College of Pharmacy, S. Konda-523101

Production and Hosted by
www.saap.org.in

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 . it id chemically called as (2E)-but-2-enedioic acid; bis(2-[2-(4-{2-thia-9-azatricyclo[9.4.0.0{3,8}]pentadeca-1(15),3,5,7,9,11,13-heptaen-10-yl}piperazin-1-yl)ethoxy]ethan-1-ol

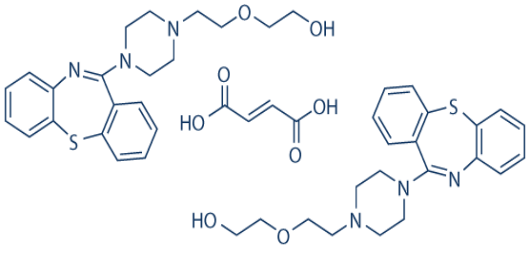

Fig 01: Chemical structure of Quetiapine Fumarate

Materials

Quetiapine fumarate from BMR Chemicals, Hyderabad ,

Poloxamer, PEG 6000, Methanol S.D Fine Chemicals

Methodology

Preformulation studies [4-11]

The following preformulation studies were carried out for Quetiapine fumarate

a) Solubility studies

b) Drug– excipient

compatibility studies

a) Solubility studies

Solubility of Quetiapine fumarate was carried out in different buffers. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 hrs at 25°C under constant vibration. Filtered samples (1ml) were diluted appropriately with suitable buffer and solubility of Quetiapine fumarate was determined spectrophotometrically at 207 nm.

b) Drug–polymer compatibility studies

In the preparation of tablet formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Quetiapine fumarate, and the selected polymers. The pure drug and drug with excipient were scanned separately.

FT-IR studies

Sample/KBr ratio

The concentration of the sample in KBr should be in the range of 0.2% to 1%. The pellet is much thicker than a liquid film, hence a lower concentration in the sample is required (Beer's Law). Too high a concentration usually causes difficulties obtaining clear pellets. The IR beam is absorbed completely, or scattered from the sample which results in very noisy spectra.

Experimental Methods

Determination of UV spectrum

10mg of Quetiapine fumarate was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8pH phosphate buffer to give stock solution containing 1000µg/ml. From the stock solution 1ml was pipette out and transferred into 10ml volumetric flask and make upto the mark with 6.8pH phosphate buffer for making 100µg/ml concentration. From the stock solution 1ml was pipette out and transferred into 10ml volumetric flask and make upto the mark with 6.8pH phosphate buffer for making 10µg/ml concentration. This solution was analysed in UV spectrum against blank.

Preparation of Standard Calibration Curve of Quetiapine fumarate in 6.8pH phosphate buffer

10mg of Quetiapine fumarate was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8pH phosphate buffer to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with 6.8pH phosphate buffer to get 2 to 12µg/ml of Quetiapine fumarate. The absorbance of the solution was measured against 6.8pH phosphate buffer as blank at 207 nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Formulation of Quetiapine fumarate Taste Masking Sachets

By Fusion method

SDs was prepared by fusion method (FM). carrier was melted at 60°. Quetiapine fumarate was added to the molten polymer, which was then mixed well and cooled to room temperature to obtain the solid mass. The solidified masses were crushed, pulverised and passed through mesh #40. The resulting SDs was stored in desiccators

By Kneading method

Drug and carriers were weighed accurately in various ratios and transferred to china dish sufficient quantity of methanol:water (1:1) was added and the thick slurry was needed for 1hr and then dried at 45^0 C until dryness. The dried mass was pulverized and sieved through sieve number #120. The resulting solid dispersions were stored for 24 hrs in desiccators to congeal. The mass obtained was crushed, pulverized. Finally, dispersions were stored in air tight containers till further use.

Table 01: Formulation of Quetiapine fumarate with poloxamer by Kneading method

Formulation code	Drug: polymer	Drug : polymer ratio
F1	Quetiapine fumarate: poloxamer	1:1
F2		1:2
F3		1:3

Table 02: Formulation of Quetiapine fumarate with poloxamer by Fusion method

Formulation code	Drug: polymer	Drug : polymer ratio
F4	Quetiapine fumarate: poloxamer	1:1
F5		1:2
F6		1:3

Table 03: Formulation of Quetiapine fumarate with PEG 6000 by kneading method

Formulation code	Drug: polymer	Drug : polymer ratio
F7	Quetiapine fumarate: PEG 6000	1:1
F8		1:2
F9		1:3

Table 04: Formulation of Quetiapine fumarate with PEG 6000 by fusion method

Formulation code	Drug: polymer	Drug : polymer ratio
F10	Quetiapine fumarate: PEG 6000	1:1
F11		1:2
F12		1:3

Evaluation Studies [12-14]

Prepared polymer drug conjugates were evaluated by

1. Estimation of drug content
2. *In- vitro* dissolution studies
3. Evaluation of taste of complexes

Drug Content

A quantity, which was equivalent to 15 mg of drug, was accurately weighed and transferred to 100 ml volumetric flask. Then the volume was made up with, 6.8pH phosphate buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving 15 mg of standard drug in 6.8pH phosphate buffer. For both the sample and standard solutions absorbance was measured at 257 nm for Quetiapine fumarate in UV-Visible spectrophotometer.

***In Vitro* Dissolution Studies**

The quantity of solid dispersion equivalent to 15 mg of Quetiapine fumarate was filled in a capsule and kept in dissolution medium. The dissolution study of solid dispersions were conducted using dissolution testing USP apparatus I (basket method) in 900 ml of 6.8pH phosphate buffer at 37±0.5ºC and at a speed of 50 RPM. Aliquot of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 257 nm against suitable blank using UV-visible spectrophotometer (T60 PG Instruments).

Evaluation of taste of complexes

The sample of drug complex underwent sensory evaluation by a panel of five members with respect to the bitter taste; the evaluation was performed by classifying the bitter taste into the following five classes.

Class 5: Very strong bitter taste

Class 4: Strong bitter taste

Class 3: Moderately bitter taste

Class 2: Slightly bitter taste

Class 1: No bitter taste

The pure drug was used as a standard control, with a mean bitter taste of 5.0. Written consent was obtained from the members of the panel and it was explained that the procedure involved testing the taste of complexes. Each of the members was given the control, *i.e.*, the pure drug. They were asked to compare the bitterness of each of the ratios of the complex with that of the control, indicating the level of bitterness perceived by them. The members of the panel were asked to gargle and wait for 20 minutes before another sample was given to them for tasting. The mean bitterness value of each of the ratios was calculated based upon the level of bitterness sensed by each individual member of the panel.

Kinetics of Drug Release [15-18]

The mechanism of drug release for the Quetiapine fumarate solid dispersions was determined using zero order and first order.

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.

Results & Discussion

Preformulation Studies

Solubility

Solubility of Quetiapine fumarate was carried out at 25ºC using 0.1 N HCL, 6.8 phosphate buffer, 7.4pH buffer, methanol and ethanol.

Table 05: Solubility studies of Quetiapine fumarate

Medium	Solubility (mg/ml)
Methanol	2.762
Ethanol	1.124
0.1N HCL	0.667
6.8pH buffer	0.891
7.4pH buffer	0.684

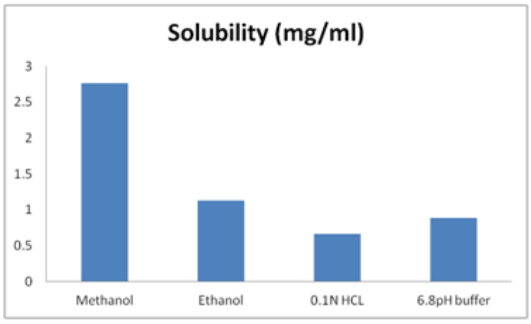

Fig 02 : Solubility studies of Quetiapine fumarate

From the above conducted solubility studies in various buffers we can say that 6.8pH phosphate buffer has more solubility when compared to other buffer solutions & methanol as greater solubility when comparted to organic solvents.

Analytical method development by U.V. Spectroscopy

UV Scan Spectrum of Quetiapine fumarate

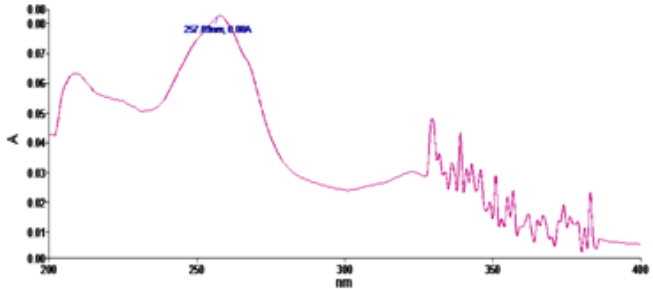

Fig 03: UV Scan Spectrum of Quetiapine fumarate.

Calibration curve data of Quetiapine fumarate In 6.8pH phosphate buffer

Table 06: Calibration curve data of Quetiapine fumarate In 6.8pH phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.172
4	0.336
6	0.496
8	0.675
10	0.823
12	0.964

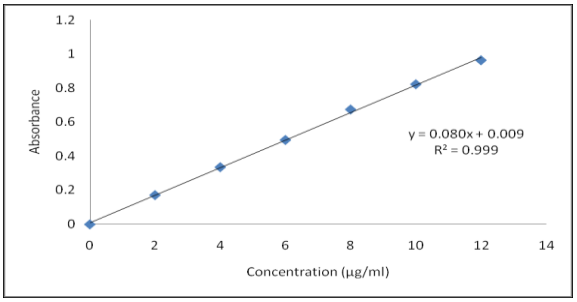

Fig 04: Calibration curve of Quetiapine fumarate in 6.8pH phosphate buffer

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

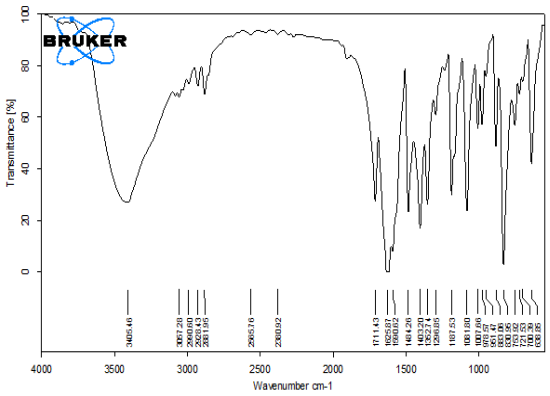

Fig 05: IR spectrum of Quetiapine fumarate Optimised Formulation

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Quetiapine fumarate) and optimized formulation (Quetiapine fumarate: excipients) which indicates there are no physical changes.

Evaluation Stuides

Table 07: Evaluation Stuides of Quetiapine fumarate Taste masking sachets

Formulation Code	Precentage Drug content	Practical Yield (%)
F1	92.63	98.30
F2	95.65	96.50
F3	97.43	97.60
F4	96.42	95.50
F5	95.63	98.30
F6	95.32	99.90
F7	97.05	95.33
F8	96.04	97.00
F9	92.56	96.50
F10	97.63	98.80
F11	97.06	99.10
F12	99.42	97.40

The entrapment efficiency of formulations F1-F12 were found to be in the range of 92-99%.

The percentage yield of formulations F1-F12 were found to be in the range of 95-99%.

***Invitro* Drug Release Studies of Quetiapine fumarate Taste Masking Sachets**

Table 08: *Invitro* drug release studies for formulations (F1-F3)

Time (Min)	Percentage drug release		
	F1	F2	F3
0	0	0	0
5	29.63	35.65	37.65
10	37.65	41.71	43.05
15	42.96	46.08	47.94
20	46.34	50.24	51.78
30	52.84	56.53	58.28
45	60.59	64.95	67.38
60	69.17	73.25	76.89

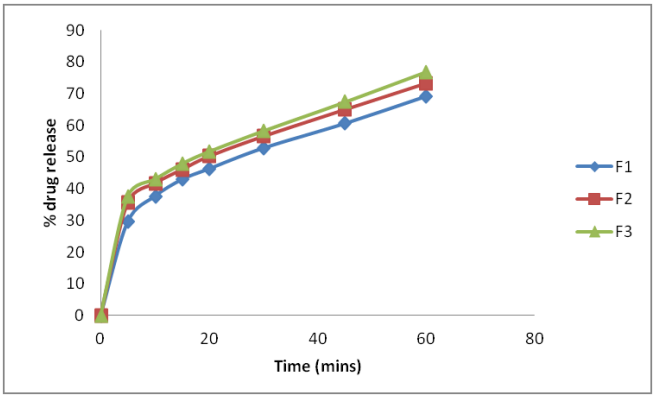

Figure 06: *Invitro* drug release profile for F1-F3

Invitro drug release of Quetiapine fumarate taste masking sachets with poloxamer in various ratios by kneading method were observed which shows at the end of 60 mins, the formulation F1 releases 69.17%, formulation F2 releases 73.25%, F3 releases 76.89%.

Table 09: *Invitro* drug release studies for formulations (F4-F6).

Time (Min)	Percentage drug release		
	F4	F5	F6
0	0	0	0
5	36.59	42.74	53.15
10	45.86	51.78	61.92
15	51.95	57.89	66.85
20	57.05	62.67	70.75
30	65.85	70.76	77.84
45	74.56	79.84	86.75
60	83.35	89.94	95.68

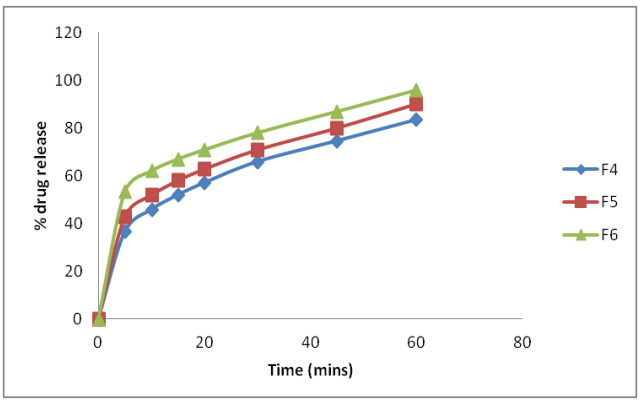

Figure 07: *Invitro* drug release profile for F4-F6

Invitro drug release of Quetiapine fumarate taste masking sachets with poloxamer in various ratios by Fusion method were observed which shows at the end of 60 mins the formulation F4 releases 83.35%, formulation F5 releases 89.94%, formulation F6 releases 95.68% .

Table 10: *Invitro* drug release studies formulations for F7-F9

Time (Min)	Percentage drug release		
	F7	F8	F9
0	0	0	0
5	37.89	41.86	48.69
10	43.92	47.78	55.68
15	48.62	51.69	59.87
20	52.86	56.05	64.13
30	60.64	64.03	71.44
45	71.05	74.19	80.65
60	80.59	84.08	89.62

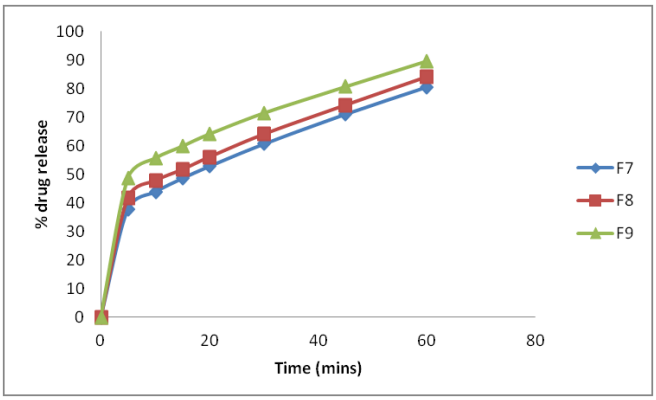

Fig 08: *Invitro* drug release profile of F7-F9

Invitro drug release of Quetiapine fumarate with PEG 6000 in various ratios by kneading method were observed which shows at the end of 60 mins the formulation F7 releases 80.59%, formulation F8 releases 84.08%, formulation F9 releases 89.62%.

Table 11: *Invitro* drug release studies formulations for F10-F12

Time (Min)	Percentage drug release		
	F10	F11	F12
0	0	0	0
5	46.65	50.86	56.25
10	53.65	58.92	62.84
15	58.98	63.86	67.72
20	63.85	68.59	72.09
30	71.19	76.19	79.75
45	80.56	85.63	88.62
60	90.42	95.56	98.62

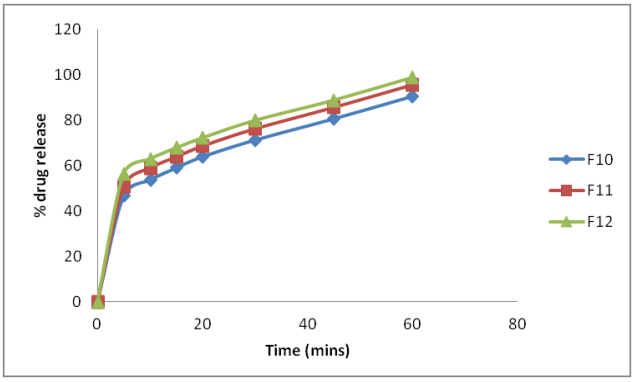

Fig 09: *Invitro* drug release profile of F10-F12

Invitro drug release of Quetiapine fumarate with PEG 6000 in various ratios by Fusion method were observed which shows at the end of 60 mins the formulation F10 releases 90.42, formulation F11 releases 95.56, formulation F12 releases 98.62%. Finally by comparing all the formulations F1-F12 formulation F12 containing Quetiapine fumarate: PEG 6000(1:3) by Fusion method shows better results at the end of 60 min with drug release of 98.62%, hence it was selected as the best formulation among all the formulations.

Drug release kinetics studies for best formulation F12:

Zero order release kinetics studies

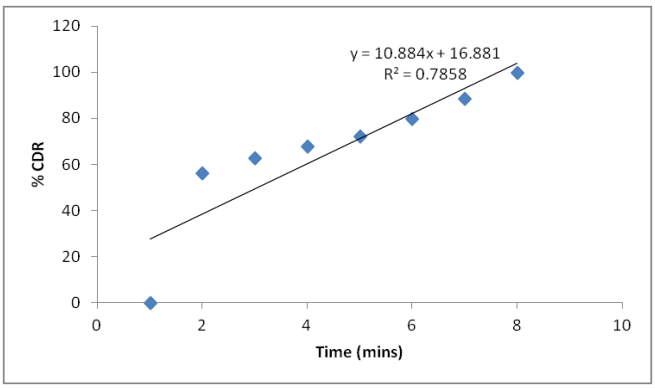

Fig 10: Zero order release profile for best formulation (F12).

First order release kinetics studies:

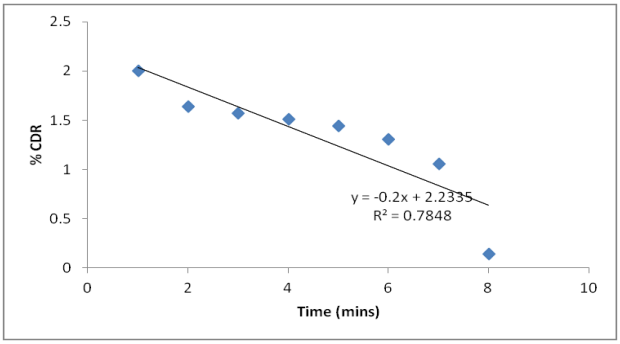

Fig 11: First order release profile for best formulation (F12)

By comparing the release kinetics studies of best formulation with zero order and first order we can say that the best formulation follows zero order release kinetics studies having R^2 value 0.785 were as first order release kinetics studies having R^2 value 0.784, hence we can say that the best formulation follows zero order release kinetics.

Taste evaluation of the complexes

Table 12: Taste evaluation of the complexes

Formulations	Mean bitterness value		
	Pure drug	poloxamer	PEG 6000
1:1	5	4	4
1:2		3	2
1:3		2	1

Summary

Quetiapine fumarate is a tetracyclic piperazino-azepine antidepressant agent. It is given with a dose of 15-45mg orally once a day. The absorption of this drug is rapid and complete. Due to first pass metabolism in the liver and metabolism in the gut wall, absolute bioavailability is about 50%. Peak blood concentrations are attained within about 2 hours after an oral dose. This leads to lower bioavailability of Quetiapine fumarate hydrochloride, and also having bitter taste. So to improve its bioavailability and to mask the taste solid dispersion technique was used using different carriers like PEG 6000, & Poloxamer. Solid dispersions of Quetiapine fumarate were prepared with polymers in different ratios of drug and carrier (1:1, 1:2, and 1:3) by solvent evaporation method& kneading method. Results of prepared solid dispersions of Quetiapine fumarate were discussed which includes solubility, drug content uniformity, and *in vitro* dissolution studies. Characterization in solid state was done by various analytical techniques such as FT-IR studies.

Finally by comparing all the formulations i.e., F1-F12 containing Quetiapine fumarate, PEG 6000 and Poloxamer in different ratios. The formulation F12 containing PEG

6000 (1:1) shows better results by solvent evaporation method at the end of 60 min with drug release of 98.62%, hence it was selected as the best formulation. By compairing the release kinetics studies of best formulation of Quetiapine fumarate with zero order and first order we can say that the best formulation follows zero order release kinetics studies having R^2 value 0.785 were as first order release kinetics studies having R^2 value 0.784.

Conclusion

PEG 6000, Poloxamer was used in the preparation of solid dispersions for taste masking by solvent evaporation & kneading method. By observing the dissolution studies Quetiapine fumarate with PEG 6000(1:3) by solvent evaporation method shows better drug release than the other formulations.

References

1. Seroquel XR Sustained-Release Tablets information http:// www.drugs.com/ mtm/ seroquel.htm.
2. Bauer M, Pretorius H, Constant E, Earley W, Szamosi J, Brecher M. Extended release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. J Clin Psychiatry. 2009;70:540-549.
3. El-Khalili N, Joyce M, Atkinson S, Buynak R, Datto C, Lindgren P, Eriksson H, Brecher M. Adjunctive extended release quetiapine fumarate (quetiapine XR) in patients with major depressive disorder and inadequate antidepressant response. Poster presented at: the 161st Annual Meeting of the American Psychiatric Association; May 3-8, 2008; Washington, DC
4. Brahmankar D. M., Jaiswal S.B., "Biopharmaceutics & Pharmaceutics"; First Edition, 1995, PP 335.
5. Watanabe Y., Ishikawa Y., Utoguchi N. and Matsumoto M., "Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter taste masked granules by the compression method", Chem. Pharm. Bull., 1999, 47, PP 1451- 1457.
6. Sk. Benajeer et al. New Simple UV Spectrophotometric Method for Determination of Mirtazapine in Bulk and pharmaceutical dosage forms. International Journal of Pharma Sciences and Research (IJPSR) Vol 3 No 10 Oct 2012.
7. Karaşen, N & Altinöz, S. (2001). Determination of mirtazapine in tablets by UV spectrophotometric and derivative spectrophotometric methods. Journal of pharmaceutical and biomedical analysis. 24. 11-7.
8. Yajima T., Fukushima Y., Itai S., Kawashima K. Method of evaluation of the bitterness of clarithromycin dry syrup. Chem. Pharm. Bull. 2002;50:147–152. doi: 10.1248/cpb.50.147.
9. Gabriels M., Plaizier-Vercammen J. Design of a dissolution system for the evaluation of the release rate characteristics of artemether and dihydroartemisinin form tablets. Int. J. Pharm. 2004;274:245–260.
10. Liu C., Desai K. G. H., Liu C., Park H. J. Enhancement of dissolution rate of rofecoxib using solid dispersions with urea. Drug. Dev. Res. 2004;63:181–189.
11. Gohel M., Patel M., Amin A., Agrawal R., Dave R., Bariya N. Formulation, design and optimisation of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS PharmSciTech. 2004;5.
12. Roy GM: Taste masking in oral pharmaceuticals. Pharm. Tech. 1994; 18: 84-99).
13. T.hayashida & M.Hatayama,"Carbohydrates as taste masking agents for oriental to drugs", in JP 05 17,372 to Yoshitomi Pharmaceutical IndustriesLtd. (1993).
14. Chauhan B, Shimpi S, Paradkar A. Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique. AAPS Pharm Sci Tech 6 (3) (2005) 405-412.
15. Higuchi T. Mechanism of sustained action medication. Theroetical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963; 51: 1145-9.
16. Peppas NA. Analysis of Fickian and non-fickian drug release from polymer. Pharm Acta Helv 1985; 60: 110-11.
17. Marabathuni VJ, Dinesh P, Ravikumar R, Yamini P, Kiran PS, Hussain SP, Rao CM. Chitosan based sustained release mucoadhesive buccal patches containing amlodipine besylate (AMB). Asian J Res Pharm Sci. 2017 Jun 28;7:97-104.
18. Marabathuni VJ, Bhavani M, Lavanya M, Padmaja K, Madhavi N, Babu P, Rao CM. Formulation and evaluation of mouth dissolving Tablets of carbamazepine. Asian Journal of Pharmacy and Technology. 2017;7(3):137-43.