VER
Vascular & Endovascular Review

A Novel Controlled-Release Formulation of Quetiapine for Extended Antipsychotic Action

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ABSTRACT

In the current study, several grades of HPMC and ethyl cellulose were used as the retarding polymers to create controlled release tablets of quetiapine fumarate. All the formulations were created utilizing the direct compression method on an eight-station rotary tablet punching machine with a 12mm punch. All the formulations combined demonstrated good flow characteristics in terms of angle of repose, bulk density, and tapped density. The created tablets had good post-compression properties, and they met all the I.P.-required quality control evaluation criteria. F2 is regarded as an optimal formulation because it had the highest percentage of drug release of all the formulations (97.3 percent in 8 hours).As the polymer content increased, the formulations incorporating HPMC K100M displayed greater retardation. Guar gum compositions failed to generate the desired rug release pattern.

KEYWORDS: Quetiapinefumarate, HPMC K15M,HPMC K100M,Guar gum,Controlledreleasetablets.

How to Cite: Dr. N. Deepa[1]*, Dr. Christian Gnanaraj Johnson[2], Dr. Darvin[3], Dr. T. K. Gopal[4], (2025) A Novel Controlled-Release Formulation of Quetiapine for Extended Antipsychotic Action, Vascular and Endovascular Review, Vol.8, No.9s, 286-298.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper sitein the body to achieve promptly and then maintain the desired drug concentration. That is, thedrug delivery system should deliver a drug at a rate dictated by the needs of the body over aspecifiedperiod oftreatment.

1.1.1. Oraldrug delivery:

This is the most widely utilized route of administration among all the routes that have beenexplored for systemic delivery of drugs via pharmaceutical products of different dosage forms.The oral route is considered the most natural, uncomplicated, convenient, and safe due to its ease ofadministration,patient acceptance,andcost-effectivemanufacturingprocess.Oral drug delivery is the most desirable andpreferredmethod of administering therapeuticagents for their systemic effects. In addition, oral medication is generally considered thefirst avenue investigated in the discovery and development of new drug entities, and pharmaceuticalformulations,mainlybecauseof patientacceptanceand conveniencein administration.The oral route of drug administration has wide acceptance up to 50-60% of total dosage forms.Soliddosageformsarepopularbecauseofeaseofadministration,accuratedosage,self-medication, pain avoidance, and most importantly patient compliance. The most popular soliddosage forms are tablets and capsules. But the important drawback of these dosage forms is thedifficultyto swallow.The oral dosage form is the most popular route for drug therapy. Over 80% of the drugs formulatedto produce systemic effects in the United States are produced in oral dosage forms. Compared toother oral dosage forms, tablets are the manufacturer's dosage form of choice because of theirrelativelylow cost of manufactureand package.The term modified-release drug product is used to describe products that alter the timing and/orthe rate of release of the drug substance. A modified-release dosage form is defined "as one forwhich the drug-release characteristics of time course and/or location are chosen to accomplishtherapeuticallyorconvenienceobjectivesnotofferedbyconventionaldosageformssuchassolutions,ointments, or promptlydissolvingdosageforms as presentlyrecognized".1-3

Controlledreleasedrugdeliverysystem:

The US FDA defines a sustained release dosage form is one that allows a reduction in dosingfrequencyfromthatnecessitatedbyaconventionaldosageform,suchassolutionoranimmediatereleasedosageform.4

DrugCandidatesforControlled ReleaseProducts

To be a successful sustained release product the drug must be released from the dosage form at apredetermined rate, dissolve in gastrointestinal fluids, maintain gastrointestinal residence time,andbeabsorbed ataratethat willreplacetheamount ofdrugbeingmetabolized and excreted.5-6

CharacteristicsofControlledreleaseproducts.
Theyexhibit neitherveryslownor veryfast ratesofabsorption and excretion.Theyareuniformlyabsorbed fromthegastrointestinaltract.Theyareadministeredinrelativelysmalldosages.Theypossessa goodmarginofsafety.Theyareused in thetreatment ofchronicratherthanacuteconditions.6-8

AdvantagesofControlledreleasedosageformsoverconventionaldosageforms:
Less fluctuationindrugbloodlevels.Reductionin dosingfrequency, Enhancedconvenience,andcompliance, Reductioninadversesideeffects, and Reductioninoverallhealthcarecost.

Disadvantages:Lossofflexibilityinadjustingthedrugdoseandordosageregimenandriskofsuddenandtotaldrugreleaseordose dumpingduetoa failureoftechnology.Sustained release products contain a higher drug load and thus any loss of integrity of thereleasecharacteristics ofthe dosageform has potentialproblems.They should be never crushed or chewed, as the slow-release characteristics may be lost, andtoxicity may result. This is particularly important in patients unable to follow whole tablets, aproblemcommonlyaffectingtheelderly.Thelargesizeofthe
Sustainedreleaseproductmaycausedifficultiesiningestionortransittothegut.9-11

ControlledReleaseTechnologyforOralDosageForm.
Fororallyadministereddosageforms,Sustainedreleaseactionisachievedbyaffectingtherateat which drugsare released from the dosage form and or by slowing the transit time of the dosageformthrough thegastrointestinal tract.The rate of drug release from solid dosage forms may be modified by the technologies which ingeneralarebased onModifying drug dissolution by controlling access of biological fluids to the drug using barrier coatings.Controllingdrugdiffusion rates from dosageforms.Chemicalreactionorinteractionbetweenthedrugsubstanceoritspharmaceuticalbarrierandsite-specificbiological fluids.

MonolithicMatrix System:In pharmaceutical CRDDS, matrix-basedsystems are the most usedtype of releasecontrolling methodology owing to their simplemanufacturing process.The preparation of atablet with the matrix involves the direct compression of the blends of drug, release retardant andother additives,inwhich the drug isuniformly distribute throughoutthe matrixcore ofthereleaseretardant. Alternatively, drug-releaseRetardant blends may be granulated to make the mixsuitable forthe preparation of tablets bywetgranulation or beads.12-14
Basedonthechemicalnatureoftherelease retardant(s),thematrixsystemsareclassifiedasgivenin Table1.

TableNo1.1:ClassificationofMatrixSystems.15-18

Typeof the MatrixSystem	**Mechanism**
Hydrophilic	Unlimitedswellingdeliverybydiffusion,Limitedswelling-controlled delivery eg.: Hydroxyethyl cellulose,Hydroxypropyl methylcellulose.
Inert	Inertinnature Controlleddeliverybydiffusioneg.:Ethyl cellulose
Lipidic	Deliverybydiffusion& erosion eg.:Carnaubawax.
Biodegradable	Nonlipidicnature Controlled deliverybysurfaceerosion
ResinMatrices	Drugreleasefrom drug-resincomplex eg.:Ion exchangeresins

Mechanismof DrugReleasefromMatrixTablets
As shown in Figure 1, in erodible matrices, polymer erosion from the surfaceof the matrix determines the drug release; whilst in hydrophilic matrices, formation of the gellayer and its dynamics as a function of time determines the drug release. Gel layer thickness,which determines the diffusion path length of the drug, corresponds to the distance between thediffusion and erosion fronts. As the swelling process proceeds, the gel layer gradually becomesthicker,resultinginprogressivelyslowerdrug-releaserates;however,duetocontinuoushydration,polymerdisentanglementoccursfromthesurfaceofthematrix,resultinginagradually decreasingdepletion zoneand an increased dissolution rate.19-21

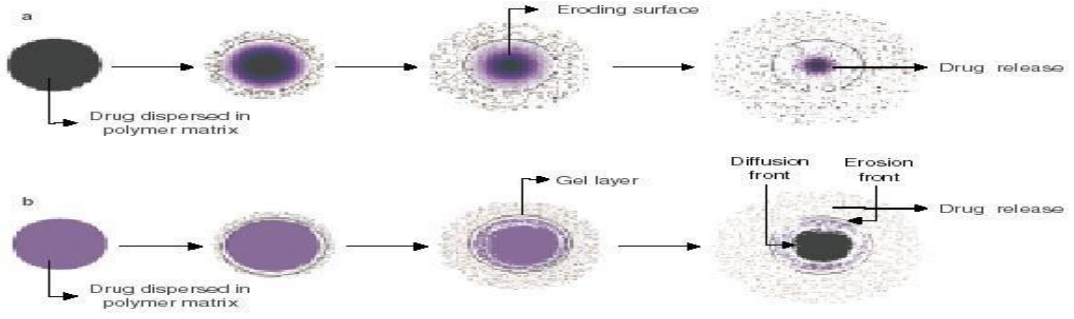


Fig.1.1. Schematic drug release from matrix diffusion controlled-release drug delivery systemswith the drug homogenously dispersed in: (a) an erodible polymer matrix; and (b) a hydrophilic,sellablepolymer matrix.

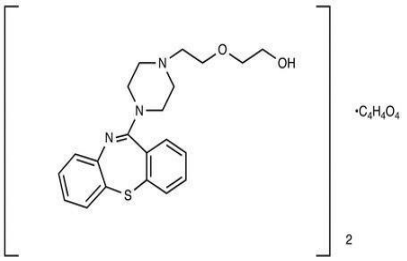
DRUGPROFILE22-26

Drug :Quetiapinefumarate

Solubility : moderatelysolubleinwater3.29mg/mlSolubleinDMSO(36mg/ml),water(<1mg/ml), and ethanol(<1 mg/ml)

Physical state: SolidMeltingpoint:174-176°C(lit.)CASNO :111974-72-2

Structure:



Molecularformula:2(C21H25N3O2S) •C4H4O4

Molecularweight: Average:383.507Monoisotopic:383.166747749

Bioavailability :100%.

Half-life :6hours

Protein binding :83%

Dose : 25-400mg

Category:AntipsychoticAgents

METHODOLOGY

DeterminationOFUVAbsorptionmaxima:

Quitiapine fumarate solution was prepared in 0.1 N HCL and diluted suitably. TheUVspectrumofthesolutionwastakenonLabIndia3200UV/VisdoublebeamSpectrophotometer. The Solution exhibited UV maxima at 298 nm. The procedure wasrepeatedwith pH 6.8 phosphate buffer.

PreparationofStandardCalibrationCurveof Quitiapinefumarate:

100 mg ofQuitiapine fumarate was accurately weighed and dissolved in littleamount of Methanol andmake up the final volume up to 100 ml with 0.1 N HCl (pH1.2) to prepare stock solution. The 10 ml of stock solution was further diluted with 0.1 NHCl (pH 1.2) in 100ml to get 100µg/ml (working standard). Then 0.2,0.4,0.6.0.8, and 1 mlof working standard was taken in 10 ml standard volumetric flask and made up thevolume with 0.1N HCl to prepare 2µg,4µg,6µg,8µg, and 10µg drug per ml solution. Thenthe absorbance was measured in a UV spectrophotometer at 298 nm against 0.1 N HCl(pH 1.2) as blank. The absorbance so obtained was tabulated as in Table 2.1.1 Calibrationcurve was constructed and shown in Fig. 2.1.2 The procedure was repeated with pH 6.8phosphate bufferandabsorbance's weremeasuredat299nm.Theabsorbancesandstandard graph werementionedin Table 2.1.1 andfigure2.1.2 respectively.27,28

Tabletformulation:

FormulationofQuitiapinefumarateControlledreleaseTablet byDirect-Compression:

CompositionofpreliminarytrialsforQuitiapinefumarateControlledreleaseTabletbydirectcompressionisshownintable6.1.Alltheingredientswereweighed. required quantity of drug and excipient mixed thoroughly in a polybag. The blend iscompressed using rotary tablet machine-8 station with 12mm flat punch, B tooling. Eachtabletcontains100mgof Quetiapine fumarateandotherpharmaceutical ingredients.

2.1.1FormulationofQuetiapinefumarateControlledreleasetablets

INGREDIENT	F1	F2	F3	F4	F5	F6
Quitiapine fumerate	100	100	100	100	100	100
HPMCK15M	50	150	-	-	-	-
HPMC K100M	-	-	50	100	-	-
GUARGUM	-	-	-	-	50	200
Talc	5	5	5	5	5	5
Mg.Stearate	5	5	5	5	5	5

MCCpH102	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
TOTAL	500	500	500	500	500	500

Allingredientsare expressedin mgonly

Evaluationparameters:
Precompressionparameters:
BulkDensity(Db):
Itistheratiooftotalmassofpowdertothebulkvolumeofpowder.Itwasmeasuredbypouringtheweightpowder(passedthroughstandardsieve#20)intoameasuringcylinderandinitial weight was noted. This initial volume is called the bulk volume. From this the bulk densityis calculated according to the formula mentioned below. It is expressed in g/ml and is given by,
Db= M/ Vb
Where,Misthe massof powder
Vbisthebulkvolumeofthepowder.
TappedDensity(Dt):

It is theratio oftotal mass of the powder to the tapped volume of the powder. Volumewas measured by tapping the powder for 750 times and the tapped volume was noted if thedifference between these two volumes is less than 2%. If it is more than 2%, tapping is continuedfor1250timesandtappedvolumewasnoted.Tappingwascontinueduntilthedifferencebetween successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/mlandis given by,
Dt= M/Vt

Where,
Mis themass ofpowder
Vtisthetappedvolumeofthepowder.

1. AngleofRepose(Ɵ):
The friction forces in a loose powder can be measured by the angle of repose (q). It is anindicative of the flow properties of the powder. It is defined as maximum angle possible betweenthesurfaceof thepileofpowder and thehorizontal plane
tan(Ɵ)= h/ r
Ɵ= tan-1(h / r)
Where,
Ɵistheangleofrepose.his theheight in cm
risthe radiusin cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definiteheight (h). The angle of repose was then calculated by measuring the height and radius of theheap of powder formed. Care was taken to see that the powder particles slip and roll over eachother through the sides of the funnel. Relationship between angle of repose and powder flowproperty.
Angleof ReposeasanIndicationofPowder FlowProperties
Shown in table no 2.1.2:

Sr.No.	Angleof Repose (^{0})	Typeof Flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	VeryPoor

Carr'sindex(or)%compressibility:

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Itindicatespowderflowproperties.Itisexpressedinpercentageandis given by,
Where,
Dtisthetappeddensityofthepowderand Db isthebulk densityofthe powder.
Relationshipbetween% compressibilityandflowability
Shown in table no 2.1.3

Srno.	%Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	FairPassable
4	23-35	Poor
5	33-38	VeryPoor
6	<40	VeryVeryPoor

Hausnersratio:Hausnersratioisanindirectindexofeaseofpowderflow.Itiscalculatedbythefollowingformula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where,Dtisthetappeddensity,Dbisthebulkdensity.
LowerHausner ratio(<1.25)indicatesbetterflow propertiesthanhigherones(>1.25).

Postcompressionparameters:
Weightvariation:
20tablets wereselectedrandomlyfrom thelot andweighted individuallytocheckforweightvariation.Weightvariation specificationasperI.P.isshownin table No.2.1.4
WeightVariationSpecification asperIP

AverageWeightofTablets	%Deviation
80mgorless	±10
Morethan 80 mgbut less than 250 mg	±7.5
250 mgor more	±5

Hardness:
Hardnessortabletcrushingstrength(fc),theforcerequiredtobreakatabletinadiametric compression was measured using Monsanto tablet hardness tester. It is expressed inkg/cm2.
Thickness:
Three tablets were selected randomly from each batch and thickness was measured byusingVernier Caliper.

Friability(F):
Friability of the tablet determined using Roche friabilator. This device subjects the tabletto the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm anddropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets wasplaced in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using asoftmuslin cloth and reweighed. Thefriability(F)is given bythe formula.29-31

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

In-Vitrodrugrelease:
Invitrodissolutionstudieswerecarriedoutbyusing900mlof0.1NHClinUSPdissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolutionmedium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphatebufferwasaddedtothedissolutionmedium(900ml)andthedissolutionwascarriedoutforabout6hours.Thesampleswerewith drawnatregulartimeintervalsof30min,1hour,2hr,3,5,5,6,7&8 hoursrespectively.32, 33

Assay:
10 tablets were weighedand triturated.The tablet triturate equivalent to10 mg of thedrug was weighed accurately, dissolved in pH 1.2 buffer, and diluted to 100 ml with the same.Further dilutions were done suitably to get a concentration of 10 µg/ ml with simulated gastricfluid pH 1.2. Absorbance was read at 210 nm against the reagent blank, and the concentrations ofQuitiapinefumaratein µg/ ml was determined byusingthe regression equation.11-15
Y=0.007x + 0.001

Drugcontentinmg/tablet=conc.µg/ml*dilutionfactor
% Drugcontent=drugcontentinmg*100/labelclaim.

RESULTS & DISCUSSION

Standard Calibration curveofQuitiapinefumarate:

Table 2.1.5: Concentration and absorbance obtained for calibration curve ofQuitiapine fumaratein0.1 N hydrochloricacid buffer (pH1.2)

S.No.	Concentration (µg/ml)	Absorbance* (at298 nm)
1	2	0.193
2	4	0.34
3	6	0.461
4	8	0.579
5	10	0.709
CorrelationCoefficient=0.9985 y=0.0636x+0.0751		

ItwasfoundthattheestimationofQuitiapinefumaratebyUVspectrophotometricmethod at λmax 298 nm in 0.1N Hydrochloric acid had good reproducibility and this method wasusedinthestudy.Thecorrelationcoefficientforthestandardcurvewasfoundtobecloserto1,at the concentration range, 2-10µg/ml. The regression equation generated was y = 0.0636x +0.0751.

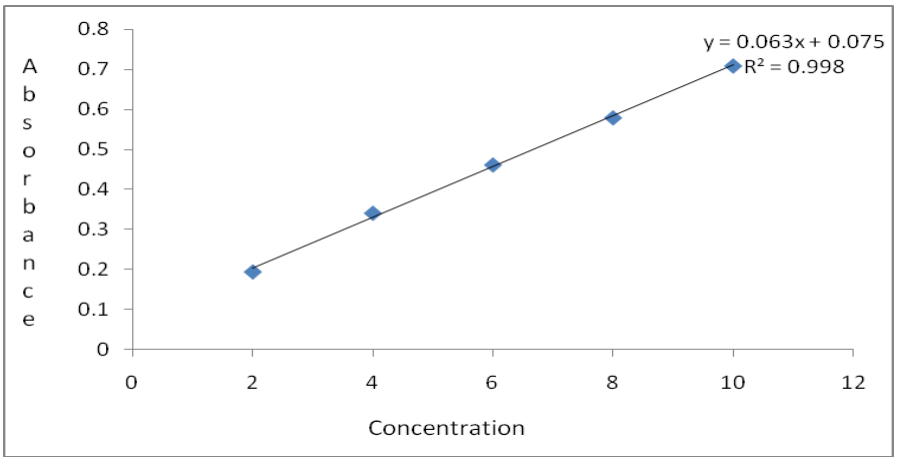


Fig 1.1.2:Standardgraphof Quitiapinefumaratein 0.1NHCl

Table 1.2.5: Concentration and absorbance obtained for calibration curve ofQuitiapine fumarateinpH 6.8 Phosphatebuffer.

S.No.	Concentration (µg/ml)	Absorbance* (at299nm)
1	2	0.193
2	4	0.331
3	6	0.446
4	8	0.553
5	10	0.677
CorrelationCoefficient=0.9982 y=0.0595x+0.083		

ItwasfoundthattheestimationofQuitiapinefumaratebyUVspectrophotometricmethod at λmax 299 nm in pH 6.8 Phosphate buffer. had good reproducibility and this method wasusedinthestudy.Thecorrelationcoefficientforthestandardcurvewasfoundtobecloserto1,at the concentration range, 2-10µg/ml. The regression equation generated was y = 0.0595x +0.083.

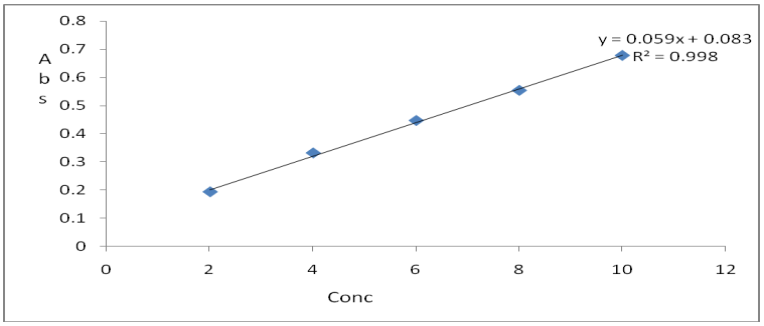


Fig1.1.3:StandardgraphofQuitiapinefumaratein pH6.8Phosphatebuffer

EvaluationParametersfor ControlledreleasetabletsofQuitiapinefumarate:
Pre-compressionparameters:
The data were shown in Table 7.3. The values for angle of repose were found in therange of 25°-30°. Bulk densities and tapped densities of various formulations were found to be inthe range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of theprepared blends falls in the range of 13.06% to 18.18%. The Hausner ratio n fall in range of 1.14to 1.22.From the result it was concluded that the powder blends had good flow properties, andthesecan beused for tablet manufacture.
Table1.2.6:Pre-compressionparameters

Table1.2.6:Pre-compressionparameters

Formulations	BulkDensity (gm/cm^2)	TapDensity (gm/cm^2)	Carr'sIndex (%)	Hausnerratio	AngleOf Repose(Ɵ)
F1	0.45	0.55	18.18	1.22	27.91
F2	0.50	0.58	13.79	1.16	29.34
F3	0.50	0.58	13.79	1.16	29.34
F4	0.47	0.55	14.54	1.17	28.23
F5	0.41	0.50	18	1.21	26.78
F6	0.41	0.54	18.11	1.22	26.71

PostcompressionParameters:
Weightvariationtest:
Tablets of each batch were subjected to weight variation test, difference in weight andpercent deviation was calculated for each tablet and was shown in the Table 1.2.7 The averageweightofthetabletisapproximatelyinrangeof495to505mg,sothepermissiblelimitis±5%(>220 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardnesstest:
Hardness of the three tablets of each batch was checked by using Pfizer hardness testerand the data were shown in Table 1.2.8 The results showed that the hardness of the tablets is inrangeof 4to 4.5 kg/cm2,which was withinIP limits.
Thickness:
Thickness of three tablets of each batch was checked by using Vernier Caliper and datashown in Table 1.2.9 The result showed that thickness of the tablet is raging from 5.00 to 6.14mm.

Friability:
Tablets of each batch were evaluated for percentage friability and the data were shown in theTable 1.3.0 The average friability of all the formulations lies in the range of 0.30 to 0.51% whichwas less than 1% as per official requirement of IP indicating a good mechanical resistance oftablets.

1.2.7.Post-Compressionparameters:

1.2.7.Post-Compressionparameters:

FD	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	494	4.5	5.5	0.43	97.23

F2	510	4.2	5.5	0.49	98.16
F3	502	4.3	5.5	0.49	98.16
F4	508	4.3	5.5	0.34	98.55
F5	506	4.4	5.5	0.34	99.25
F6	504	4.5	5.5	0.43	98.5

Assay: Assay studies were performed for the prepared formulations. From the assay studies itwasconcludedthatalltheformulationswereshowingthe%drugcontentvalueswithin97.23-99.25%.

InvitroDissolutionstudies:

Invitro dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolutionapparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium waswithdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was addedto the dissolution medium (900ml) and the dissolution was carried out for about 6 hours. Thesamples were withdrawn at regular time intervals of 30 min,1 hour,2 hr,3,5,5,6,7 & 8 hoursrespectively.Theresultsweredisplayed in table 1.2.8.

Table1.2.8: Invitrodissolutiondata

Time(Hrs)	F1	F2	F3	F4	F5	F6
0.5	25.5	16.4	15.4	10.4	49.5	18.9
1	46.7	26.7	29.4	16.5	78.8	28.3
2	76.5	34.6	38.5	28.6	96.9	36.4
3	98.4	42.4	55.4	39.5	96.1	49.5
4		55.4	68.4	48.5		69.3
5		67.4	87.1	59.4		78.1
6		85.4	98.3	69.2		89.7
7		91.5	82.3	74.5		97.5
8		97.3				

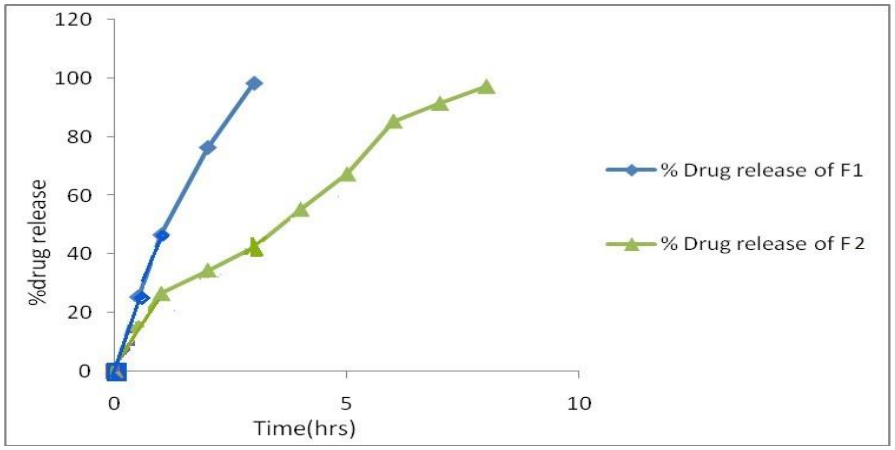


Fig1.1.4:DissolutionprofileofformulationspreparedwithHPMC K15Mpolym

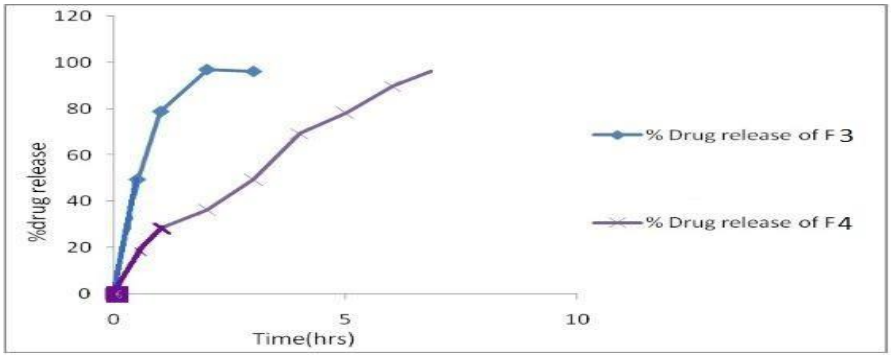


Fig1.1.5:Dissolutionprofileof formulationspreparedwith HPMC K100Mpolymer

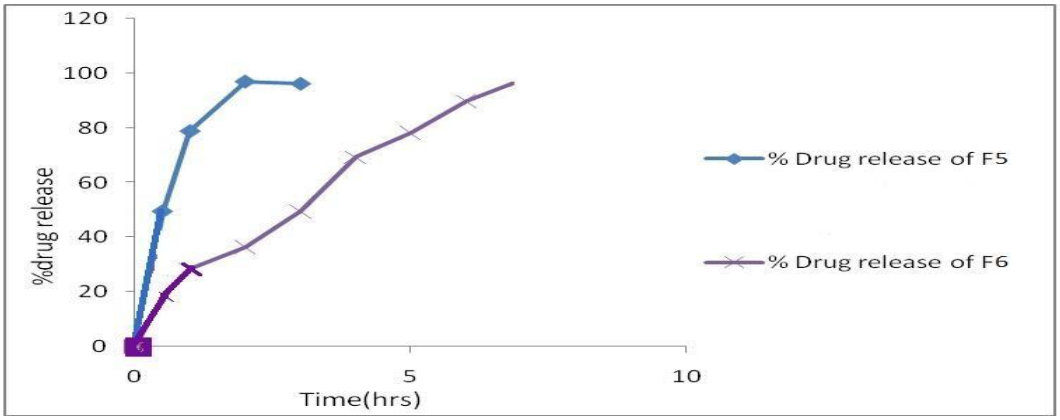


Fig1.1.6:DissolutionprofileofformulationspreparedwithGuar gum aspolymer

From the tabular column 7.5 it was evident that the formulations prepared with HPMCK15Masretardingpolymerinlowconcentrationsthepolymerwasunabletoproducetherequired retarding action to the tablets. As the concentration of polymer increases the retardingnature was also increased. HPMC K15 M in the concentration of 150 mg showed good % drugreleasei.e., 97.3 in 8 hours.

Whereas in case of formulations prepared with HPMC K100 M as retarding polymer, theformulations with 50 mg concentration of polymer showed complete drug release in6 hoursonly, whereas the concentration of polymer increases the retarding nature also increased. TheFormulation Containing HPMC K100M in 100 Mg Concentration Showed good retarding naturewithrequired drugreleasein 8 hours i.e., 82.3%.

Whereas in case formulations prepared with Guar gum as retarding polymer, as theconcentration of polymer increases the retarding nature was also increased. When compared withHPMC polymers it was failed to producedesireddrugreleasepattern.

From the above results it was evident that the formulation F2 is best formulation withdesireddrugreleasepattern extended up to 8 hours.

ApplicationofReleaseRateKineticstoDissolutionData:

Various models were tested for explaining the kinetics of drug release. To analyze themechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted intozero-order, first order,Higuchi,and Korsmeyer-Peppas releasemodel.

Table1.2.9:Releasekineticsdataforoptimisedformulation

CUMULATIVE (%)RELEASE Q	TIME(T)	ROOT(T)	LOG(%)RELEASE	LOG(T)	LOG(%)REMAIN	RELEASERATE(CUMULATIVE %RELEASE/t)	1/CUM%RELEASE	PEPPAS logQ/100	%DrugRemaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0 9.89	0	0			2.000				100	4.642	4.642	0.000
16.76	0.5	0.707	0.995	-0.301	1.955	19.780	0.1011	-1.005	90.11	4.642	4.483	0.158

22.53 27.43	1	1.000	1.224	0.000	1.920	16.760	0.0597	-0.776	83.24	4.642	4.366	0.275
33.66 37.11	2	1.414	1.353	0.301	1.889	11.265	0.0444	-0.647	77.47	4.642	4.263	0.379
44.67 53.87	3	1.732	1.438	0.477	1.861	9.143	0.0365	-0.562	72.57	4.642	4.171	0.470
61.3 69.1	4	2.000	1.527	0.602	1.822	8.415	0.0297	-0.473	66.34	4.642	4.048	0.593
78.2 84.22	5	2.236	1.569	0.699	1.799	7.422	0.0269	-0.431	62.89	4.642	3.977	0.665
90.33	6	2.449	1.650	0.778	1.743	7.445	0.0224	-0.350	55.33	4.642	3.811	0.831
	7	2.646	1.731	0.845	1.664	7.696	0.0186	-0.269	46.13	4.642	3.586	1.055
	8	2.828	1.787	0.903	1.588	7.663	0.0163	-0.213	38.7	4.642	3.382	1.259
	9	3.000	1.839	0.954	1.490	7.678	0.0145	-0.161	30.9	4.642	3.138	1.504
	10	3.162	1.893	1.000	1.338	7.820	0.0128	-0.107	21.8	4.642	2.794	1.848
	11	3.317	1.925	1.041	1.198	7.656	0.0119	-0.075	15.78	4.642	2.508	2.133
	12	3.464	1.956	1.079	0.985	7.528	0.0111	-0.044	9.67	4.642	2.130	2.511

Fig1.1.7:Zeroorderreleasekineticsgraph

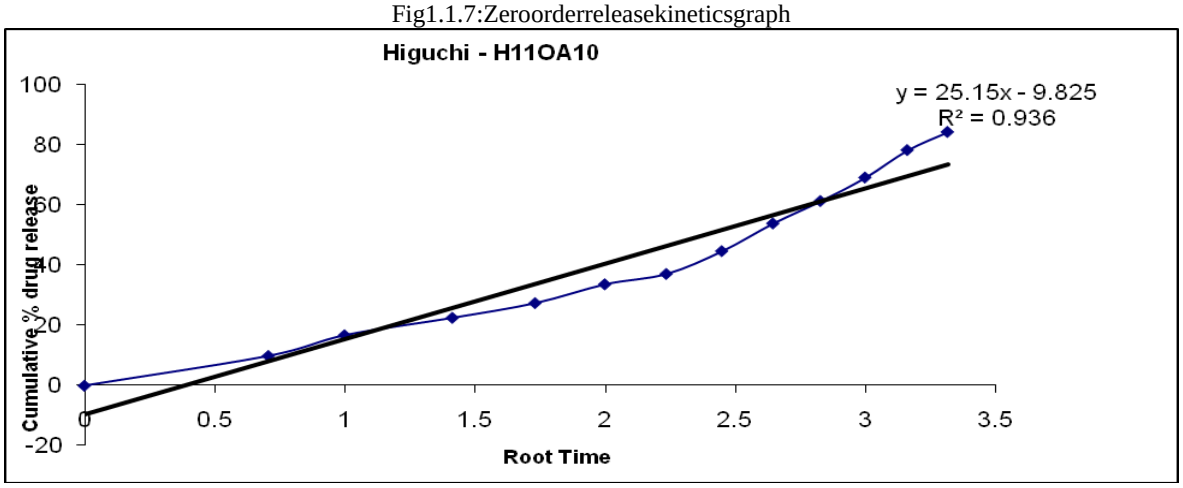


Fig1.1.8:Higuchireleasekineticsgraph

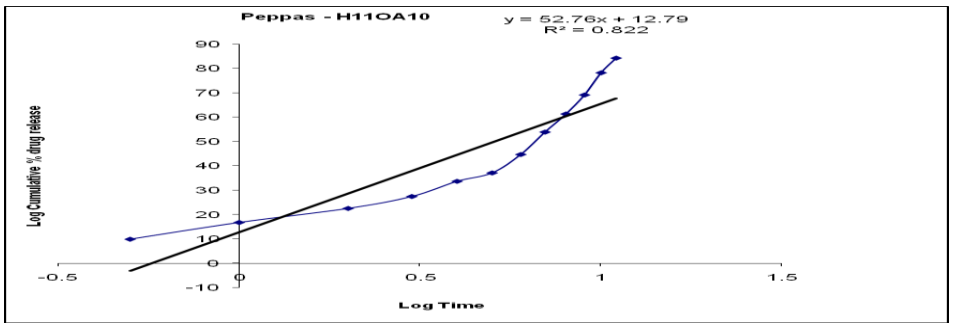


Fig1.1.9:Kars mayerpeppasgraph

Fig 1.2.0:Firstorderrelease kineticsgraph

From the above graphs it was evident that the formulation F2 was followed Zero orderreleasemechanism.

CONCLUSION

By using various grades of HPMC and ethyl cellulose as the retarding polymers, an effort has been made in the current study to create controlled release tablets of quetiapine fumarate. On an eight-station rotary tablet punching machine, a 12mm punch was used to prepare all the formulations utilizing the direct compression method. The combination of all the formulations displayed favorable flow characteristics in terms of angle of repose, bulk density, and tapped density. The produced tablets displayed favorable post-compression properties and passed all the quality control assessment criteria in accordance with I.P. limitations. The F2 formulation, which showed the highest percentage of drug release of 97.3 percent in 8 hours among all the formulations, is regarded as an optimal formulation.As the polymer content increased, the formulations incorporating HPMC K100M displayed greater retardation. Guar gum-based formulations failed to provide the anticipated medication release pattern.

Acknowledgement:
Authors are grateful thank to management of Swathi College of Pharmacy, Nellore, Andhra Pradesh.

Conflict of interest: NONE

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