FORMULATION AND IN-VITRO EVALUATION OF EXTENDED RELEASE TABLETS QUETIAPINE FUMERATE: USING A BIO-DEGRADABLE POLYMER

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ABSTRACT

In the present investigation Quetiapine fumerate, an anti-psychotic agent which acts as inhibiting dopamine and serotonin receptor blockade in central nervous system was selected for preparation of extended release tablet using Methocel E-50, and Microcrystalline cellulose as major ingredients apart from lactose and other hydrophobic agents. To attain the objectives of the work total six trials. Bulk density was found to be in the range from 0.41 to 0.44. Tapped density is form range 0.58-0.68, angle of repose form 34.15-39.35 and compressibility index was found to be from 27.58 to 38.23. Similarly post compression evaluation parameters values are Hardness from 8 to 9.1 kg/cm2, thickness was found to be 0.4 to 0.6 mm, weight variation rage from 498mg t0 502 mg and friability was found to be in from 0.5 to 1.06 %. Based on the drug release, post and pre-compression evaluation parameters trial T-6 was optimized and taken for one month accelerated stability studies at 60oC and 80%RH. After one month stability studies there was slight changes in the values of post compression evaluation parameters and the values are as hardness 9.5 kg/cm2, thickness 0.6mm, weight variation ±502, diameter 1.2 and friability was found to be 0.74 %. Drug release was found to be in the order as Koresmeyer Peppas model 0.995> Zero order-0.976>first order-0.971>Higuchis model-0.965. Based on the R2 values, release rate of the drug Quetiapine fumerate from the extended release tablets was in Koresmeyer Peppas model release.

***Key Words*:** Quetiapine fumerate, Methocel E-50, Koresmeyer Peppas model

No: of Tables: 8 **No: of Figures : 13** **No: of References:19**

INTRODUCTION

A tablet is generally defined as hard element form of dosing which is made of a constituent or constituents using suitable excipients and equipped moreover by moulding or firm compression. It contains a fusion of reactive substances and excipients, frequently in fine particle form, hard-pressed or compressed from fine particles to rock solid dose. (Wikipedia, 2017).HISTORY OF TABLETS: (The Los Angeles Times, 2002). George Griffenhagen, who was a retired pharmacist with a fondness for history who stayed in Vienna, Va. (Griffenhagen has completed rather a study of the pill question. He has also written regarding pill history.) Pills, he said, dated back to approximately 1500 BC-- and they were most probably invented so as to measure the quantity of a therapeutic substance that can be given to a patient. Previously about 4,000 years ago formulas would normally be for fluid measures. For example, a tolerable curative formula decorated on an Assyrian soil pill advices the consumer to crush a variety of seeds, plant resins and leaves together after that liquefy them in cocktail. The initial tablet denotation arises in early Egyptian period, Griffenhagen said. One well-known collection of file is crammed with therapeutic cures, with tablets completed from honey or grease or bread dough. Plant extracts, or erstwhile active ingredients, would be assorted with these substances after that small balls, or tablets would be shaped with the fingers. (Early on formulas of tablets incorporated myrrh, saffron, tree resins, cinnamon and a list of erstwhile botanicals. Then the word pill was not used. In early Greece, the circular balls or different shapes would be known as katapotia (which means "a thing which is to be swallowed"). A Roman scholar named Pliny, lived from 23-79 AD, was the one who penned the word "pilula."

Extended Release Drug Delivery System

Sustained release tablets are usually consumed on a daily basis jus once or twice, contrasted to the counterpart usual forms which has to be ingested multiple times a day to attain the similar beneficial result. The benefit of giving a solitary quantity of a drug which is released over a long duration is to keep a steady blood level of a medicine that frequently interprets a enhanced patient conformity, and also better efficacy for its intended use of the drug. (Gupta and Robinson, 1992).To recognize drug delivery systems the terms used are extended release prolonged release modified release, sustained release, or depot formulations and in a single dose they are calculated to attain effective beneficial results over an extended time period. (Jantzen and Robinson, 1995)The enhanced specific distribution of the drug, reduced changes in the peak trough concentration, frequency of the administration being reduced greater bioavailability all are reasons which render these dosage forms

greatly desirable. (Altaf, Friend, Masrx and Cosrx 2003).

To prepare ER dosage forms one has to keep the following points in mind: (Gwen and Joseph, 1996).;It is sustained on its own. If the active compound has a long half-life.; Whether the pharmacological action of the active element is inversely proportional to blood levels.; Whether an active transport is concerned in the liberation of the drug.; A large sum of the drug would be required if the active component has a short half-life.

The marketing of new drug involves many difficulties and are pretty expensive, greater attention on development of sustained or controlled liberating drug delivery systems is being given by the pharmaceutical industry. (Salsa, Veiga and Pina, 1997). For the reason of sustained release Matrix arrangement is broadly being used. Prolong or controlled liberation of the drug in the dissolved or dispersed phase is resolute by the release system. In reality, a matrix is said to be as a well-mixed compound of one or extra drugs along with gelling agent that could be a hydrophilic polymers. Maintaining the beneficial drug level in plasma for long time period is the ultimate goal of the extended release dosage forms.

Advantages of Tablets: (U K Essays, 2015).

Dosage forms are precise, constant dose and huge accuracy and slightest unpredictability; Mainly steady regarding to physiochemical and microbiological properties; Very ease to handle, use, carry and looks very much elegant and attractive ;Cheap, ease in swallowing manufacture doses not involves multiple steps ;These kinds of dosage forms provide a shield against light, temperature and atmospheric pressure.; Long-lasting constancy to medicaments; Low production cost ;Accurate amount can be administered in minute doses; Sugar coating camouflages the unpleasant taste; Whenever a fraction of the dose is required it can be easily broken into halves and quarters; Less space is required for storage and the packing is cheap too.

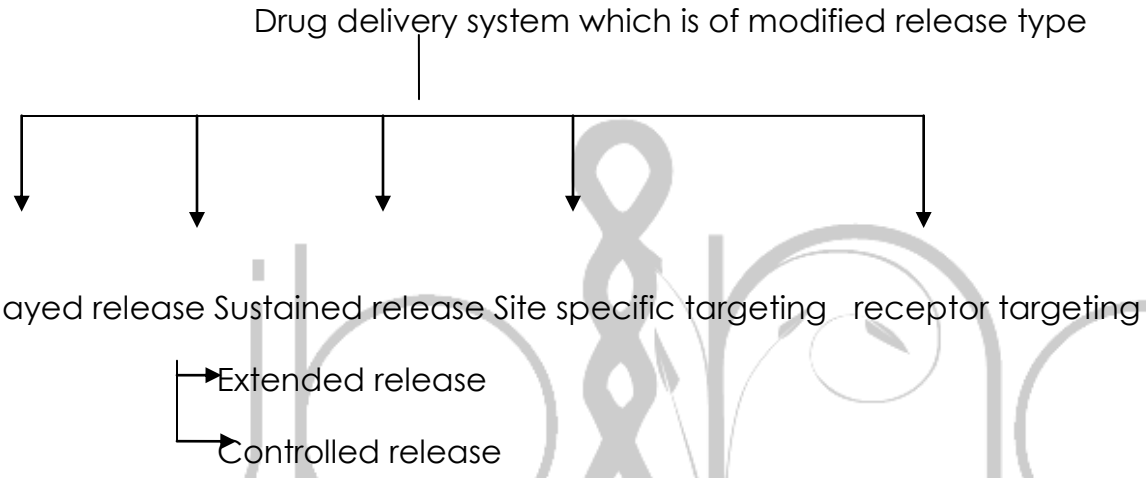
Disadvantages of Tablets: (U K Essays, 2015).

Unstructured and drugs whose density is less face a difficulty of being compacted into tablets; Drugs that absorb moisture cannot be compressed into tablets.; Formulation of those drugs becomes difficult which have great assimilation in the digestive tract, low solubility of water and slow dissolution.; Receptive to oxygen special covering is required for such drugs.; To remove the unpalatable taste and smell it requires extra coating and encapsulation which increases the cost ;Liquids cannot be made up into tablets and most of the children and ill patients refuse to have tablets.

Present Trends of Tablets: (Hayashi et al., 2005).

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self medication, pain avoidance, versatility, leading to high levels of patient compliance. Tablets and capsules are the most powerful dosage forms. But one important drawback of such dosage forms is 'Dysphasia' or difficulty in swallowing. This is seen to afflict nearly 35%of the general population. This disorder is also associated with a number of conditions like: Parkinsonism; Motion sickness; Unconsciousness; Elderly patients; Children; Mentally disabled people; Unavailability of water

Classification of Modified Release Drug Delivery System



History of Extended Release Delivery System: (Hayashi et al., 2005). In Israel, Lipowsk patented the ER tablets in the year 1938. He covered small tablets that gave form to covering the particles. In the late 1940's and 1950's oral controlled and sustained release tablets were developed this gave way to the introduction of marine anti-foulants and fertilizers in the year 1970s. Liberation is frequently affected by disintegration, dissolution, or degradation of excipients in which the active compound is made.

MERITS OF ERDDS: (Venkatraman, Davar and Chester, 2000) and (Banker and Rhodes, 1995).

Extended-release products offer several potential benefits:

Sustained blood levels

The pharmacodynamic and pharmacokinetic characters of the drug determine the size and incidence of dosing. Fluctuation of the blood concentration is less when the rate of assimilation is slow. Less frequently higher

doses can be given in such cases. Therapeutic concentrations over long-standing periods may be maintained by the use of extended release products for drugs which have a shorter half-life.

Attenuation of adverse effects

With the use predictable dosage forms, soaring peak blood concentrations might be achieved soon after ingestion with probable unhelpful effects associated to the briefly high concentration. One such example is high blood pressure in patients having immediate-release nifedipine products. Use of an extended-release product keeps away the high early blood concentrations that give rise to the unexpected decrease in blood pressure and other major haemodynamic differences as in reflex tachycardia.

Improved patient compliance

Short half-lives drugs frequently have is to be used at regular intervals to preserve blood concentrations in the beneficial limits. A contrary association might be between the occurrence of patient compliance and dosing. A lessening in the number of every day doses obtainable by extended-release products has the possibility to perk up fulfilment. Though, this benefit most likely only occurs when conventional formulations have to be given three or more times in a day.

Other possible profits are as follows:

The extended release formulations lessen dosing rate of drugs.; Therapeutic concentrations are maintained by the extended release formulations.; Slow drug absorption reduces the toxicity.; Shuns the high blood concentration by the use of these formulations;Have the high probability of the patient acceptance and convenience by the use of extended release formulations;Localised and systemic repercussions are minimized.; Protection of the drug from hydrolysis or other destructive variations in GIT increases the stability ;Treatment efficacy is improved.; With chronic dosing drug accumulation is minimised ;Bioavailability of a number of drugs is improved ;Development in the capability to offer unique effects. For example, Morning relief of arthritis through bed time dosing.

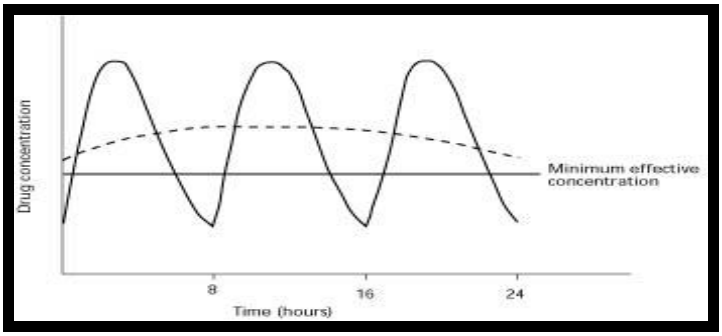


Figure no 1: Graphical representation of drug plasma concentration vs. time profile

Disadvantages of Extended release Dosage Forms: (Venkatraman, Davar and Chester, 2000) and (Banker and Rhodes, 1995).Extended release formulation has a superior drug load and hence any failure in the discharge characteristics leads to serious repercussion The big size of extended release products may roots problems in intake or transportation through gut. The discharge rates are pretentious by different factors as in food and the speed of transport through the gut. Few variations in the liberation rate from a dose to another dose however they have been reduced by contemporary preparations.

Cost of preparation is high now and then the intended tissue will be surfaced to constant sum of drug over long periods of time resulting in drug tolerance

Rationale of Extended Release Delivery: (Banker and Rhodes, 1995). Pharmacokinetics parameters are the chief purpose to be looked at to make an API as an ER dosage form. A suitable formulation can produce the ADME outline of a drug a great deal more constructive. The variation of the ADME could be capable of having a profound impact on various aspects of the medicinal use of the drug from patient acceptance and ease to its very effectiveness, tolerance and wellbeing parameters.

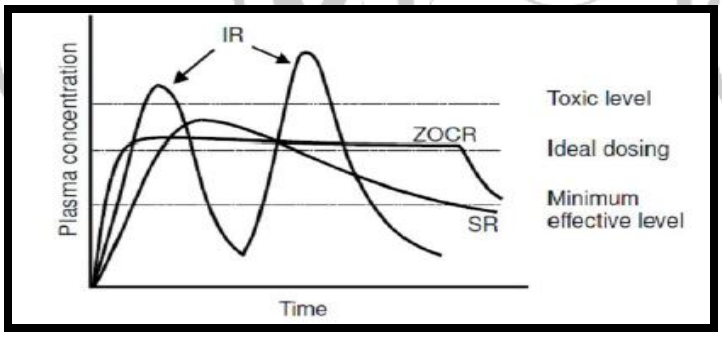


Figure no. 2: Plasma Concentrations Verses Time

Fig 2: Indicates feature illustration of plasma concentrations of a conventional immediate release dosage form (IR), a sustain release dosage form (SR) and a zero order controlled release (ZOCR) dosage form

FEATURES AFFECTING EXTENDED RELEASE FORMULATION: (Ratnaparkhi and Gupta, 2013).

Physicochemical Properties of Drug

a) Solubility in liquids:

Usually drugs that are feeble acids or weak bases, since the unchanged form of

a drug mostly infuses across lipid membranes, drugs solubility decreases by changing to an unaffected form. Drugs with less solubility in water will it hard to fit into extended release mechanism. The least limit on solubility for this product is said to be 0.1 gm/ml.

b) Partition coefficient

Partition coefficient is the portion of drug in an oil phase to that of an adjoining aqueous phase. As biological membrane has high affinity to lipids it makes the drugs to pass within it easily, hence partition co-efficient of medicine has a say over the bioavailability of drug very much. Drug having less partition coefficient values lesser than the most favorable activity are objectionable for oral ERDDS, as it will have very less lipid solubility and the drug will be at a particular place at the very first aqueous phase if it comes in contact e.g. Barbituric acid. Drug with high partition co-efficient value much more than the adequate activity are uncalled for oral ERDDS as high lipid permeable drug shall not partition out of the lipid membrane once it moves in the membrane. The value of partition co-efficient at which favorable activity is seen is about 1000:1 in 1-octanol/water system.

c) Drug pKa and Ionization at Physiological pH

Only non-ionized drugs are very well immersed and penetration of such ionized drug is insignificant, as the rate of assimilation of such ionized drug is three fold times lesser than of the unionized drug. Where ionization is pH responsive the pKa series for acidic drug is around 3.0 to 7.5 and whose ionization is pH responsive pKa range for basic drug is around 7.0 to 11.0 and it is perfect for adequate positive absorption. Drug should be non-ionized at the place to a degree 0.1 – 5.0%. For oral ERDDS drugs present highly in ionized form are poor candidates. e.g.:- Hexamethonium.

d) Drug stability

Enzymatic degradation and hydrolysis can be undergone in both acid/base when drugs are administered orally. Degradation in the solid form for the drugs will continue at a reduced rate. In the stomach if the drugs are unstable, formulation systems that delay delivery to the whole GI tract are useful. Compounds that are uneven in the digestive tract may show less bioavailability when taken in extended release dosage form. This is because a better sum of drug is received in the digestive tract and undergoes more degradation.

e) Molecular size and diffusivity

Greater the molecular size the poorer the candidate for oral ER since the capacity of the drug to disperse polymeric membrane is a purpose of its diffusivity (or diffusion co-efficient). Diffusivity mainly relies on size shape of the hollowness of the membrane. For transitional molecular

mass drug, the diffusion co-efficient is 100 - 400 Daltons; and polymer limit is 10 to 6 and 10 to 9 cm2/sec. If drugs have molecular weight greater than 500 Daltons, the diffusion coefficient in a lot of polymers is less i.e. lesser than 10-12 cm2/sec. Proteins and peptides are the examples of drugs that are hard to manage release rate of medicament from dosage form

f) Protein binding

The therapeutic activity of drug relies on unbound drug concentration than the total concentration and roughly all drugs attach to plasma or tissue proteins. A noteworthy function in the therapeutic effect is played by protein binding despite whatever type of dosage form it may be as extensive binding to plasma increase biological half life therefore ERDDS is not necessary for such a drug.

g) Dose size: In general, a single dose which contains drug about 500mg-1.0g is considered maximal for a conservative dosage form. Same criteria also hold for extended release dosage form. Compounds which having large dosing size that can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety which involves administration of large quantity of a drug with a narrow therapeutic range.

Biological Properties of Drug

a) Absorption

The way a drug is absorbed effects the extended release systems highly. The purpose of preparing an extended release system is to have a control over it. It is necessary that the rate of liberation is lesser than the speed of absorption. If we presume the transit time of the majority drugs and devices in the absorptive areas of GI tract is about 8-12 hours, the greatest half-life for permeation should be just about 3-4 hours. Or else the device will go by absorptive regions sooner than the drug release is done. As a result the compounds with lesser absorption rate constants are meagre candidates for extended release systems. A number of probable reasons for a low degree of absorption are reduced water solubility, metabolism or its site of absorption, small partition co-efficient and acid hydrolysis.

b) Distribution

The division of drugs in tissues can be vital factor in the general drug elimination kinetics. As it not only lessens the concentration of distributing drug but it also can be rate preventive in its stability with blood and extra vascular tissue, as a result noticeable volume of distribution takes up varied values based on time route of drug disposition. Drugs with great apparent volume of circulation, that control the speed of excretion of the drug, are unfortunate aspirant for oral ERDDS e.g. Chloroquine. One must have information on disposition of the drug for design of extended release products

c) Metabolism

Drug, that are broadly broken down are not appropriate for ERDDS. A drug competent of suggesting metabolism, resisting metabolism or which are metabolized at the place of assimilation or first-pass effect is underprivileged contenders for ER delivery, given that it could be tricky to uphold constant blood level e.g. Levodopa, Nitroglycerine. Drugs that are broken down prior assimilation, either in lumen or the tissues of the intestine, show less bioavailability from the extended releasing systems. On the whole intestinal walls are flooded with enzymes. As drug is liberated at a slow rate to this region very fewer drugs is accessible in the enzyme system. Therefore the systems must be devised because drug remains in those surroundings to permit more total exchange of the drug to its metabolite.

d) Biological half-life

The chief goal of an oral ER invention is to uphold therapeutic blood levels over a prolonged time. To apply this, drug should enter in the circulation around with the similar rate at which it is removed. The removal rate is explained by half-life (t1/2). Beneficial compounds with short half-lives are admirable entrants for prolonged release formulations since this can lessen dosing occurrence. A drug with biological half-life amid 2-8 hours is suitable for oral ERDDS. As if biological half-life < 2hours the system will need very large rate and greater dose and biological half-life > 8hours preparations of such drug into oral ER drug delivery system is not required.

e) Margin of safety

Greater the worth of therapeutic index, greater chances of the drug being safe. Drugs with less beneficial index are frequently poor entrants for preparations of oral ERDDS as to industrial restriction of manage over release rates.

f) Plasma Concentration Response Relationship

In general biological retort of drug relies on plasma drug concentration than dose. However pharmacological activity of some drugs is self-governing of plasma concentrations, that are poor entrants for oral ERDDS e.g. Proserpine.

g) Transfer of Drug relies on concentration

Transfer of drug from one section to other and if it follows zero kinetic process subsequently such drugs are weak contenders for oral ER delivery system, it must follow first order kinetics.

APPROACHES TO ACHIEVE ERDDS: (Vyas and Khar, 2012).

The purpose of formulating ER dosage form is to build up consistent preparations that have all the benefits of instant liberation of dosage form without any dose dumping. Many ways are employed in the formulation of ER products. In general, extended formulations can be divided into

different categories based on the mechanism of drug release.

A) Diffusion Controlled Release

B) Dissolution Controlled Release

C) Ion Exchange Resins Controlled Release

D) pH independent formulations

E) Altered density formulations

POLYMERS USED IN MATRIX TABLETS: (Hadi and Lokeswara, 2012).

Hydrogels:Polyhydroxyethylemethylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene-oxide (PEO), Polyacrylamide (PA). Soluble polymers: Polyethyleneglycol (PEG), Polyvinylalcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methylcellulose (HPMC).

Biodegradable polymers: Polylacticacid (PLA), Polyglycolicacid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters Non-biodegradablepolymers: Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyetherurethane (PEU), Polyvinyl chloride(PVC), Cellulose acetate(CA), Ethyl cellulose(EC)

Mucoadhesive polymers: Polycarbophil, Sodium carboxymethylcellulose, Polyacrylic acid, Tragacanth, Methylcellulose, Xanthamgum, Guargum, Karayagum.

KINETICS OF DRUG RELEASE: (Pundir and Badola, 2013).

Zero order kinetics:

From the pharmaceutical dosage the drug dissolution does not disaggregate, drug liberation in slow manner represented by,

Wo-Wt =K0t Where,

Wo =Initial sum of drug concentration in solution.

Wt = quantity of drug release dissolved in time t.

K0t = Zero order rate constant.

When the information was plotted as cumulative % drug release verses time, the data follows zero order kinetics if the plot is linear with slope as K0. This model represents an ideal release profile in bid to attain the prolonged pharmacological action.

First order kinetics:

Release of drug expressing in this model:

Log Qt=Log Qo+K1t/2.303

Qt=quantity of drug release in time t.

Q0=Initial quantity of drug in solution.

K1t =First order release rate constant.

Information when plotted as log cumulative % drug left over verses time gave a straight line showing that the release pursue first order kinetics. By multiplying slope values the constant K can be obtained

Korsmeyer Peppas model:

In 1983 Korsmeyer-peppas made an easy, semi-empiric model, the chief drug liberation method follows diffusion, relating exponentially the drug liberation to the elapsed time (t).

At/A= ktn

Where,

k = Constant.

n =Release.

t = Time

At and A∞= Absolute cumulative quantity of drug liberated at time (t)

This is used when more than one kind of liberation event could be involved or when the liberation method is uncommon

Higuchi model: From the matrix device the liberation of the drug is by diffusion has been described by Higuchi's Diffusion equation:

ft = Q = √Dδ/τ (2C- δCs)Cst

Where,

Q is quantity of drug given out in time t.

D is Diffusion coefficient of the drug in the matrix

Cs is Solubility of the drug in the matrix.

δ is Porosity of matrix.

τ is Tortuosity.

t is Time (h).

The equation may be simplified then equation becomes;

ft = Q = KH Xt1/2

Where,

KH = Higuchi dissolution constant.

When data was plotted in accordance to this equation, i.e. cumulative drug released verses square root of time, it gives a straight line, showing the drug was liberated by diffusion means.

MATERIALS and METHODS:

API QUITEPINE FUMERATE was procured from ASPEN pharmaceuticals limited as a gift sample.

Methocel E 50 was procured SD fine chemicals, Micro-crystalline cellulose, lactose and other excipients were procured as gift samples from gland Pharma limited, Hyderabad.

ANALYTICAL METHOD DEVELOPMENT

Preparation of 6.8 phosphate buffer

6.8 gms of KH2PO4 and 0.94 gms of NaOH are dissolved thoroughly in 1000ml of

distilled water to obtain 6.8 pH phosphate buffer.

Determination of λmax of Quetiapine fumarate using 6.8 phosphate buffer:

Procedure:

Working standard: 5mg of Quetiapine fumarate was taken and dispersed in 100ml of 6.8 phosphate buffer gives 50µg/ml concentrated stock solution.

Dilutions: From the working standard solution 1ml was diluted to 100ml with 6.8 phosphate buffer giving 5µg/ml concentrated solutions.

The similar step is repeated for 2ml stock solution with 8 ml of 6.8 phosphate buffer and make volume to 10 ml which in turn is 0.2 ml i.e 10µg/ml.

The same is repeated taking 3ml, 4ml, 5ml, 6ml till 8ml with the corresponding concentrations which are 15µmg/ml, 20µg/ml , 25µg/ml, 30µg/ml, 35 µg/ml, 40 µg/ml.

Solutions undergo are scanned at 200-400nm wavelength, resultant scan spectrum is noted.

The resultant wavelength giving peak absorbance is known as λmax

Standard caliberation curve of Quetiapine fumarate in 6.8 phosphate buffer

Procedure: 5mg of Quetiapine fumarate was weighed and dissolved to a volume of 100ml with 6.8 phosphate buffer i.e. 50µg/ml stock solution.

Dilutions: From the working standard solution 1ml was diluted to 10ml with 6.8 phosphate buffer, 5 µg/ml concentrated solution.

From dilution 1, take 0.2, 0.4, 0.6, 0.8 and 1 ml and was dilute up to mark in 10ml flask to obtain 2, 4, 6, 8 and 10 µg/ml concentrated solutions. This solutions absorbance was noted at λmax=298µm

PREFORMULATION PARAMETERS:

The following preformulation studies were carried out for Quetiapine fumerate

Drug- polymer(s) compatibility studies by Fourier-transform infrared

Spectroscopy

FTIR studies were carried out to check for any interactions and compatibility between

the API and polymer

Organoleptic studies- The API was examined for colour odour and taste

Bulk density-

It's the relation of the total mass of powder to the bulk volume of powder. It is

calculated by placing the already weighed powder in measuring cylinder, then the starting weight was noted. This starting volume is called as the bulk volume.

This is written as g/ml and thereby denoted by the formula

$$\mathbf{D_b} = M/\mathbf{V_b}$$

Where

M - Quantity of the powder

Vb - bulk volume of the powder.

Tapped density-

Thereafter performing the procedure that was given with the quantities of bulk density, the cylinder that has the model is subsequently tapped by utilizing a suitable mechanical tapped density tester which provides 100 drops/minute, then this was redone the there is a difference between continuing measurement of less than 2% and then the tap volume is calculated to the closest graduated unit. The tapped density is denoted by g/ml and is calculated using formula

$$\mathbf{D_t} = M/\mathbf{V_t}$$

Where

M - Mass of powder

Vt - tapped quantity of powder.

Angle of repose-

It is the maximum angle that is possible between the exterior of the heap of powder to the horizontal plane. The fine particles combination is then permitted to go by through the channel that is attached to a support at a definite height. The angle of repose is then checked by measuring the height and also the radius of the pile of powder that is formed. Precaution is taken to guarantee that the powder particle slip and role over each other through the sides of the funnel.

It is given by –

Tan Θ= h/r

$$\Theta = \mathbf{tan^{-1}}\ h/r.$$

Where Θ - angle of repose

h- Height in cm and r – radius in cm

Compressibility index-This shows powder flow properties. This is expressed in % and is given by

$$\frac{\mathbf{D_t - D_b}}{\mathbf{D_t}} * \mathbf{100}$$

Where

Dt - tapped density

Db - bulk density

Partition coefficient-

Partition coefficient is the fractional concentration of solute in two insoluble or slightly soluble liquids, in two solids, when it is in evenness across the crossing point stuck between them.100 ml of N- octanol (oily phase), 100 ml of Distilled H20 (aqueous phase) are taken in a beaker and are mixed properly. Then to it 100 mg of Quetiapine Fumarate (drug) is added and mixed thoroughly.

Then the mixture is poured in a separating funnel and shaken vigorously to separate the oily and aqueous phase, shake well for about 15-20 minutes till the two phases gets separated.

Then slowly take the oily an aqueous phase in different beakers or flasks and let the drug get separated using filter paper.

Now that the phases are separated, take the absorbance using UV spectrophotometer.

Partition Coefficient is given by the following formula:

Po/w = Organic phase/ Aqueous phase x 100

FORMULATION DEVELOPMENT

Collect all the ingredients according to their weights in a self sealing cover separately.

Sieve all the pregranulation excipients from #80 in one container.

Check for (for sieved powder)

Bulk density

Tapped density

Angle of repose

Compressibility index

Particle size distribution

Prepare 5% binder solution by taking 5gms of starch in 10ml of water or suitable solvent

Take 5gms of starch.

Place in 50 ml beaker containing 10 ml water.

Place it in beaker under mechanical stirrer and mix thoroughly till the starch gets completely dissolved.

Collect medium or small size mortar and pestle (wash, clean, dry completely). No traces of water should be present.

Place sieved powder in mortar

Add binder solution slowly (10 drops)

Triturate with pestle

Sieve the dough mass or wet mass through #20 and keep for drying at room temperature for 5 hours or at 60°c for 20 minutes in hot air oven.

Now mix post granulation excipients with the dried granules in a polybag.

Take all the granules (pre and post) for blending with colour in a blender or in another polybag.

Take the final blend for

Content uniformity/ blend uniformity

Bulk density

Tap density

Angle of repose

Compressibility index

Particle size distribution.

11. Final blend taken to compress the tablets.

FORMULATION OF QUETIATIPINE FUMARATE

Table no 1: Ingredients and their concentrations used in preparations of ER Tablets

Ingredients	T-1	T-2	T-3	T-4	T-5	T-6
Quetiapine fumerate	25	25	25	25	25	25
Methocel E50	200	225	250	275	300	350
Lactose	200	175	150	125	74	-
MCC	54	54	54	54	80	104
10%Starch Solution	q.s.	q.s.	q.s.	q.s	q.s	q.s
Magnesium stearate	10	10	10	10	10	10
Talc	11	11	11	11	11	11
TOTAL WEIGHT-MG	500	500	500	500	500	500

Figure no 3: In-House prepared tablets

POST-FORMULATION PARAMETERS

Thickness Test-

In this, the thickness that is in millimeters (mm) was measured independently for 10 already, pre weighed tablets by the usage of Vernier Caliperse. Then the standard thickness with the customary deviation were reported.

Hardness Test -

In this the tablet hardness is measured by utilizing a Monsanto hardness tester. The crushing power of these selected 10 tablets, whose weight and thickness were known was recorded in kg/cm2 and also the customary hardness with the characteristic change was reported.

Friability Test-

Twenty (20) tablets were chosen from each trial and weighed. Every grouping of tablets was turned around at 100 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then re dusted and weighed once again to know the difference in weight. The friability was checked as per weight difference from the starting tablets.

Weight variation-

To examine the weight variation, 20 tablets each with formulation are then weighed by the usage of an electronic digital balance. Then the expected mass of each of the tablet are then calculated and then the percentage variation in the weight was then calculated.

Content uniformity-

Ten tablets with already known weight of each group was taken then powdered with a mortar, then their weight corresponding to one constant tablet is then taken, then it is poured into a 250mL volumetric flask and then 6.8 phosphate buffer was introduced. Then the current volume is filled up to a point with 6.8 phosphate buffer. The solution is then filtered and then the filtrate was adequately dissolved, which then the absorbance is checked against the blank

at 298 nm. The standard of the drug content having the drug powder is then determined.

Disintegration Time-

In-vitro disintegration time is determined by using with the aid of disintegration test apparatus. For this, a tablet is laid in all of the six tubes of the apparatus and one disc is attached to each tube. The time that takes for the whole breakdown of the given tablet with null seen weight left in the apparatus is calculated.

In-Vitro Drug Release Studies

The dissolution test was undertaken with the aid of 900 ml of 6.8 phosphate buffer, at 37 ± 0.5°C and 50 rpm. A sample, with the measurement of 5mL of the given solution is taken from the dissolution apparatus; every hour for the next 8 hours, then the samples was replaced with a fresh dissolution solution. The samples were then watered down to a fitting concentration with 6.8 phosphate buffer. Absorbance of the given solutions is then measured at 298 nm by the usage of an UV- spectrophotometer.

Swelling index or water uptake studies-

Polymer matrices that represent the swellable matrix drug delivery systems are known to be porous in nature. And when these matrices come to contact with water, GI fluid then the polymer takes in the water and gets swollen or hydrated. The quick development of a sticky gel layer on hydration shows that the swelling is connected with the polymer chain relaxation with the volume expansion. The liquid goes through the polymer matrix at a steady velocity, the speed of diffusion of the given liquid with that of huge molecular repose of the polymer are more or less of the exact scale or, perhaps, the time of diffusion of the given liquid is much greater than that of reduction of the given polymer segment. This mechanism allows giving the idea about the water intake study of the different types of polymer. This given phenomenon is attributed, that the swelling is increased due to water intake, which then gradually decreases due to the erosion.

The swelling measurement was carried out separately in order to accumulate that on the basis of the weight increase over time. This swelling is due to the fact of the presence of a hydrophilic polymer, which tends to get wet and then permits water intake, which causes an increase in its weight.

In the drugs, the swelling properties were checked by putting the tablet matrices in the dissolution test apparatus. (900 ml of 0.1 N HCL at 0 37± 0.5oC) Then these tablets were removed occasionally from the dissolution medium. After draining the tablets free from water by the usage of a blotting paper, they were then checked for increase in weight. The swelling characteristics are then expressed in the terms of percentage water uptake (WU %).

This shows the association amid swelling index and also time

$$\text{Water uptake} = \frac{\text{wt.of swollen tablet} - \text{initial wt of tablet}}{\text{initial wt of tablet}} \times 100$$

Swelling studies-

The swelling studies are carried out to calculate the molecular parameters of swollen polymers. Swelling studies is therefore known by the usage of a Dissolution apparatus, optical microscopy and many various sophisticated techniques that embrace H1NMR imaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc

Swelling ratio = size of swollen tablet – size of initial tablet

Accelerated stability studies-

According to ICH guidelines the prepared in-house Quetiapine Fumerate tablets were taken for one month stability study at 60°C and 60% RH based on the in-vitro evaluation parameters.

RESULTS AND DISCUSSION:

Analytical Method:

Standard graph of Quetiapine fumerate was taken in 6.8 phosphate buffer at 298 nm

Table no. 2: observations of standard graph of Quetiapine fumerate

S.No	Concentration in µg	Absorbance
1	10	0.272
2	20	0.422
3	30	0.618
4	40	0.747
5	50	0.9

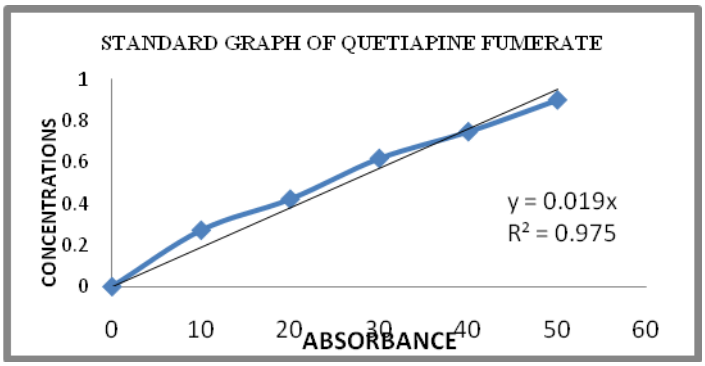


Figure No 4: Standard Graph of Quetiapine Fumerate

FTIR STUDIES

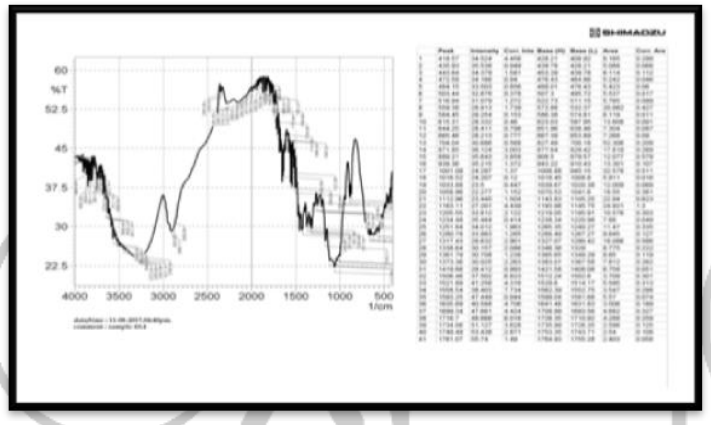


Fig no. 5: FTIR spectra of Quetiapine fumerate

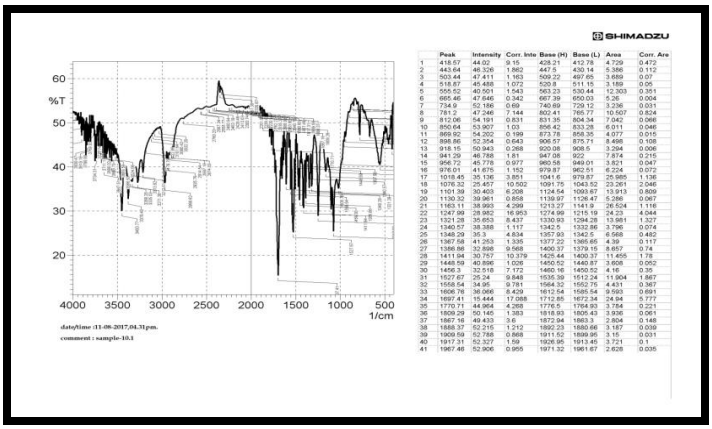


Fig no 6: FTIR spectra of Methocel E 50

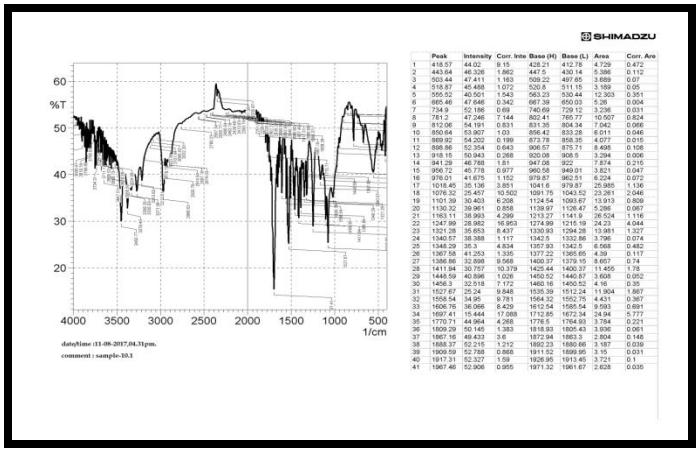


Fig no. 7: FTIR spectra of trial 06

Organoleptic properties: Crystalline solid, white to off white in color and bitter in taste.

Table no 3: physical characteristics of blend trial T1-T6

Trials	Bulk density	Tapped density	Angle of repose	Compressibility index
Trial - 1	0.44	0.62	35.21	29.032
Trial - 2	0.42	0.67	34.15	37.31
Trial - 3	0.42	0.58	33.28	27.58
Trial - 4	0.41	0.6	37.21	31.66
Trial - 5	0.42	0.68	38.25	38.23
Trial - 6	0.41	0.64	39.35	35.93

The powder characterization properties like bulk density, tablet density, angle of repose, compressibility index were established to be within the limits.

Post formulation studies In-vitro evaluation parameters.

Table no 4: Physical characteristics of trial T1-T6

Trials	Hardness	Thickness	Diameter	Weight variation	Friability
T-1	9	0.4	0.9	498	1.06
T-2	8.7	0.5	0.9	501	1.35
T-3	8.2	0.6	1	499	1.26
T-4	9.1	0.4	0.9	501	0.49
T-5	8	0.4	0.9	500	0.5
T-6	8.6	0.4	0.9	502	0.75

Hardness: Hardness the prepared tablets from T01 toT06 was established to be in between 8-9 kg/cm2, of which hardness of 8.6 kg/cm2 for trial 06 was optimized, based on friability and drug release studies

Thickness and diameter: the uniformity of the thickness and diameter was maintained in all the trials from T-01 to T-06 in between the narrow range of 0.4 to 0.6mm for thickness and 0.9 to 1.0 for diameter.

Weight variation: variation in the weights of prepared tablets of all the trials T-01 to T-06 was in the range between 498-502mg i.e. not more than 2% in weight variation.Friability: The percent of friability for the prepared tablets was established to be in the range of 0.49 – 1.35 % and the trial 06 with 0.75 % of friability were optimised.

In-Vitro drug release from trial T – 01 to T – 06

These were prepared with Methocel E50 the percent of drug release of three trials is given in the table below and the graphical illustration of drug discharge from T -01 to T-06 is given/represented individually and in comparison mode.

Table no 5: Drug release form T1-T6

T-1	T-2	T-3	T-4	T-5	T-6
0	0	0	0	0	0
34.29	43.28	35.12	30.87	25.48	15.38
40.18	58.29	57.29	48.92	39.29	27.19
63.28	76.28	65.28	59.29	54.29	41.74
76.92	89.27	76.92	81.47	68.29	52.84
94.38	94.28	87.82	94.29	78.27	68.49
97.83	97.83	89.93	95.28	87.38	76.3
99.02	101.93	92.82	97.37	92.18	81.39
97.38	99.39	94.29	101.72	96.48	89.37
97.87	96.12	98.28	94.28	99.16	94.84

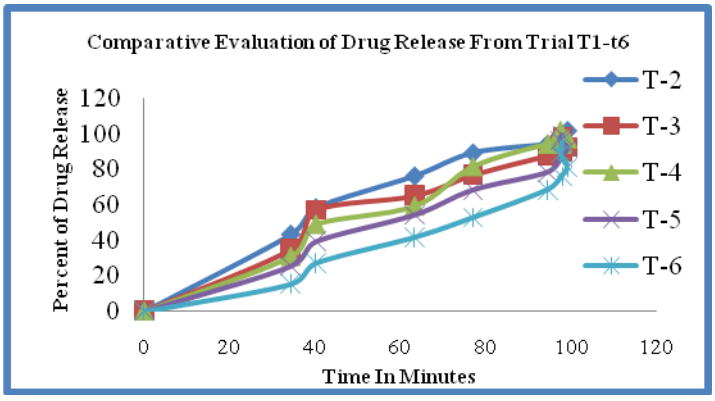


Figure no 8: comparative drug release profile from trial T1-T6

Accelerated Stability studies:

After one month accelerated stability studies the results are as below:

Table no 6: Physical characteristics of optimized trial T6

Trials	Hardness	Thickness	Diameter	Weight variation	Friability
T-6	9.5	0.6	1.2	501	0.74

Table no 7: In-vitro drug release of optimized trial T-6

Sampling interval (minutes)	Percentage drug release from OPTIMIZED TRIAL T-06
0	0
30	15.34
60	24.84
120	34.25
180	45.98
240	58.35
300	63.93
360	76.49
420	84.39
480	96.33

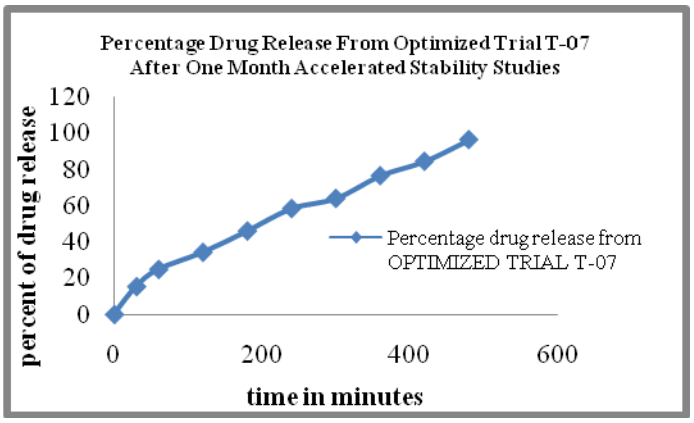


Figure no 9: Percent of drug release form optimized trial T-6

Determination of release rate kinetics:

Table no 8: release rate kinetic parameter and values

ZERO ORDER		FIRST ORDER		HIGUCHIS MODEL		KORESMEYER PEPPAS PLOT	
time	% drug undissolved	time	log 100-Q	sq. time	mean % drug dissolv	log time	log cumulative % drug dissolved
0	100	0	2	0	15.34	0	0
30	84.66	30	1.93	5.48	24.84	1.48	1.19
60	75.16	60	1.88	7.75	34.25	1.78	1.40
120	65.75	120	1.82	10.95	45.98	2.08	1.53
180	54.02	180	1.73	13.42	58.35	2.26	1.66
240	41.65	240	1.62	15.49	63.93	2.38	1.77
300	36.07	300	1.56	17.32	76.49	2.48	1.81
360	23.51	360	1.37	18.97	84.39	2.56	1.88
420	15.61	420	1.19	20.49	96.33	2.62	1.93

Graphical representation of drug release rate from optimized trial T-6:

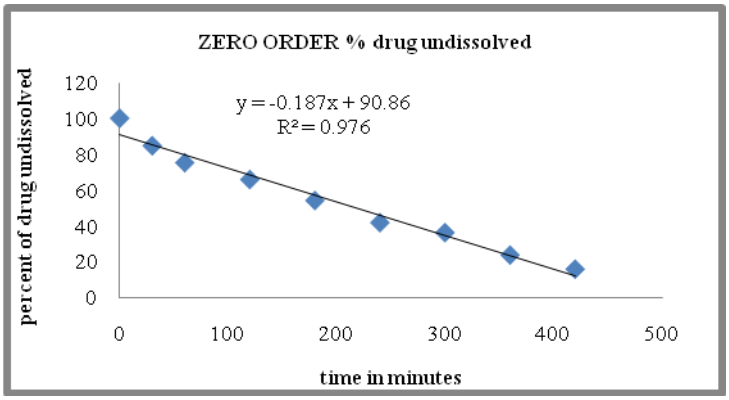


Figure no 10: Zero order Release kinetics from optimized trial T6

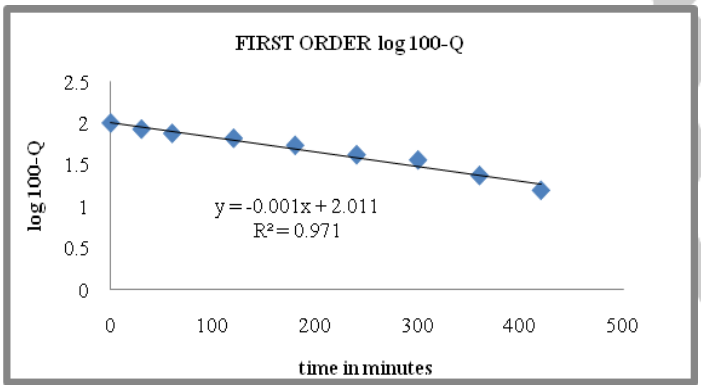


Figure no 11: First order Release kinetics from optimized trial T6

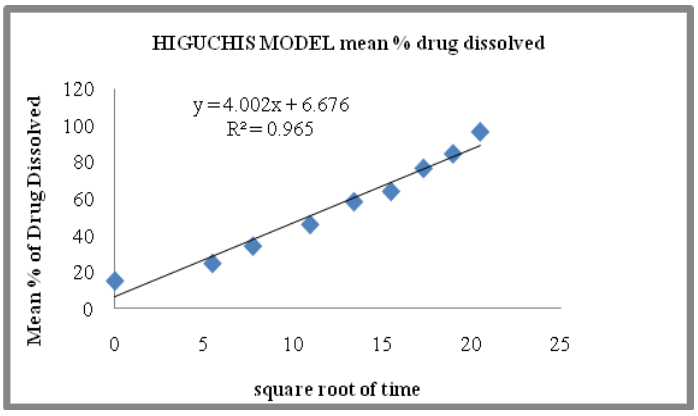


Figure no 12: Higuchis Model rate of drug release form optimized trial T6

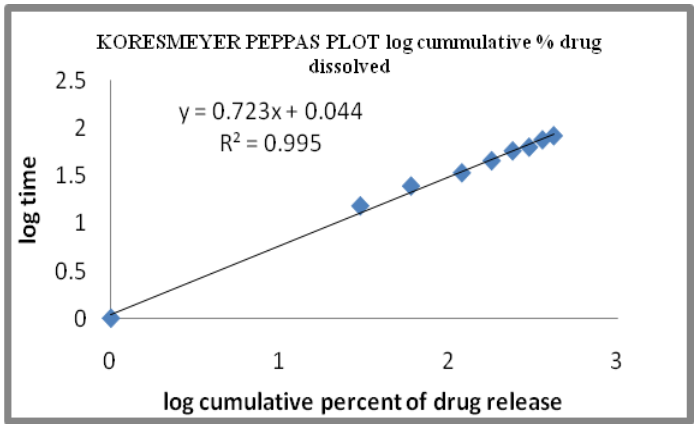


Figure no 13: Higuchis Model rate of drug release form optimized trial T6

Discussion:

Based on the review of literature and compatibility studies Methocel E-50 was selected as release retarding agent of extended release tablets of Quetiapine fumerate.The results of evaluated Preformulation parameters show good and satisfying results for all the six prepared trials and are given below:Physical characteristics of blend and prepared tablets are.Bulk density was found to be in the range from 0.41 to 0.44. Tapped density is form range 0.58-0.68, angle of repose form 34.15-39.35 and compressibility index was found to be from 27.58 to 38.23.Similarly post compression evaluation parameters values are Hardness from 8 to 9.1 kg/cm2, thickness was found to be 0.4 to 0.6 mm, weight variation rage from 498mg t0 502 mg and friability was found

to be in from 0.5 to 1.06 %.The in-vitro release form trial T1 to T6 was showing that the release of drug is time dependent and fluctuation in initial three trials and later was constant with the increase in the concentration of polymer Methocel E-50 up to trial T6.Based on the drug release, post and pre-compression evaluation parameters trial T-6 was optimized and taken for one month accelerated stability studies at 60oC and 80%RH.After one month stability studies there was slight changes in the values of post compression evaluation parameters and the values are as hardness 9.5 kg/cm2, thickness 0.6mm, weight variation ±502, diameter 1.2 and friability was found to be 0.74 %.The determination of release rate kinetics was calculated by fitting the dissolution values in to various kinetic models.Based on the R2 vales, rate of drug release was found to be in the order as Koresmeyer Peppas model 0.995> Zero order-0.976>first order-0.971>Higuchis model-0.965.Based on the R2 values, release rate of the drug Quetiapine fumerate from the extended release tablets was in Koresmeyer Peppas model release.

Conclusion:

In the present research work, preparation of Quetiapine fumerate was selected extended release tablet using Methocel E-50.To achieve the aim and objectives of the present work, an attempt was made to prepare total six trials, of which trial T6 was optimized based on the pre-compression and post compression evaluation parameters.Release rate of the drug form extended release tablets was also determined based on regression coefficient value and was found to be following Koresmeyer Peppas model of kinetics with R2 value of 0.995.

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