Research Article

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Design and In-Vitro evaluation of immediate release tablets of a dibenzothiazepine derivative quetiapine fumerate: an anti-psychotic agent

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ABSTRACT

In the present intended research work, QUETIQPINE FUMERATE a dibenzothiazepine derivative was taken for formulating immediate release tablets, used in the treatment of schizophrenia and major depressive disorders. To prepare IR tablets microcrystalline cellulose and carboxy methyl cellulose was selected as major ingredients. Total ten trials were afforded to get optimization IR tablets. Pre-compression and post compression in-vitro evaluation parameters were found to be in average rage as bulk density- 0.23- 0.46, tap density 0.25-0.66, angle of repose 31.23-41.28 and compressibility index 27.58-38.23 and in case of post compression the values are hardness 3.4-5.7 kg/cm^{2,} thickness 0.4-6.6 mm, diameter 0.9-1.0, weight variation of 340mg variation was in the range of 334-345mg. and friability was found to be 0.26-0.75. Drug release of optimized trial T-10 after one month accelerated stability studies was forum to be 100 percent within 60 minutes. An attempt was made for determination of release rate kinetics and the prepared in-house IR tablets were showing the following order of release. KORESMEYER PEPPAS PLOT with R^2 value of 0.987>, HIGUCHIS PLOT with R^2 0.976 = ZERO ORDER R^2 0.976 >, FIRST ORDER R^2 0.855. The release of drug form QUETIAPINE FUMERATE immediate release tablets was found to be following KORESMEYER PEPPAS plot of kinetics release.

Keywords: QUETIQPINE FUMERATE, IR, Schizophrenia.

INTRODUCTION

A solid dosage form which contains medicinal substances with or without appropriate diluents and it may differ in shape, size and weight and is classed depending on the preparation method, as compressed tablet [1].

According to Indian pharmacopoeia, pharmaceutical tablets are firm, horizontal or arched dishes, unit dosage forms, formulated by squeezing a drug or mixture of drugs, with or without excipients.

Tablet is defined as the solid unit dosage form of medicine which may or may not consist suitable excipients and is prepared by any of the two methods, molding or by compression. It comprises of a blend of active ingredients and excipients, mostly in powder form, compressed from a powder into a solid dose. The excipients can be listed as binders, diluents or granulating agents, Glidant and lubricants to make sure proper tab letting; disintegrants to enhance tablet disintegration in the digestive tract; sweeteners or flavors to improve taste; and pigments to make the tablets visually appealing or helps in visual identification of an unknown tablet. A polymer coating is usually spread to allow ease in swallowing of the tablet, to restrict the deliverance rate of the active ingredient, and to provide more defiance to the

environment by expanding its stability or to improve its appearance. [2]

Tablets are just one of the many forms that an oral medicament can be taken such as syrups, elixirs, suspensions, and emulsions. Therapeutically tablets were initially made in the shape of a disk of any color their components bent on, but now days it is made in many shapes and colors to help in differentiating between medicines. Sizes of tablets to be swallowed can be discriminated from a few mm to about a cm^2.

History of tablets [3]

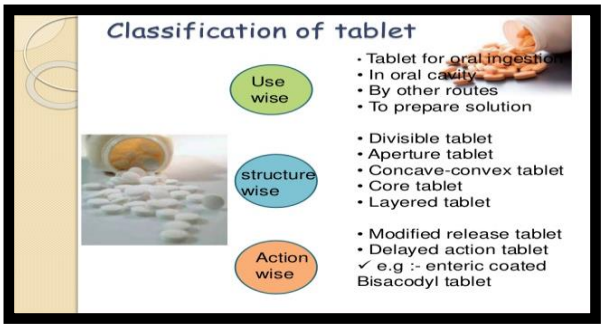
The origin of the initial dosage forms is adrift in the history. We can safely assume that earlier man took parts of plants including leaves, stems, roots and berries internally for a range of symptoms.

A line-up of plant and animal products would also have been applied externally to aid the treatment of wounds. The steam of volatile herbs would have been breathing upon, and later combinations would have been used, no doubt introduced into a selection of fats, oils and honey. As time passed they would have been adjusted by singing, crushing or dissolving. [3]

In ancient Greece, such medicine were known as katapotia ("a remark gulped"), and the Roman researcher Pliny, who lived from 23-79 AD , first gave a name to what we now call pills calling them pilula. [2]

Pills were a useful dosage form for medicines that had an irksome taste. Solid ingredients were powdered and then made into a rigid mass, which was then formed into roughly spherical pills. A variety of equipment was developed to facilitate this, and pill-making became an essential part of the pharmacist's art. Capsules and tablets became the dominant forms [3].

Classification of tablets



Different types of tablets

Tablets ingested orally

a. Compressed tablets, e.g paracetamol tablets
b. Multiple compressed tablets
c. Delayed release tablets, e.g. enteric coated bisacodyl tablets.
d. Sugar coated tablets e.g. multivitamin tablets.
e. Film coated tablets, e.g. metronidazole tablets
f. Chewable tablets, e.g. Antacid tablets

Tablets used in oral cavity

- Buccal tablet, e.g. vitamin c tablet
- Sublingual tablet, e.g. Vicks menthol tablet
- Torches or lozenges
- Dental cone

Tablets taken by other routes

- Implantation tablets
- Suppositories or inserts, e.g. Clotrimazole tablets

Tablets used to prepare solutions

- Effervescent tablets
- Dispensing tablets
- Hypodermic tablets
- Tablet triturates e.g Enzyme tablets [4].

Tablets are basically uncoated or coated. Uncoated tablets are chewable tablets, effervescent tablet, lozenge tablet, soluble tablet, and sublingual tablet. Coated tablets are enteric covered tablet, film covered tablet, embed, sugar

covered tablet, and adjusted discharge tablet. Broken portion of a covered tablet show a middle which is enclosed by a continuous covering of an alternate surface. The reasons for covering a tablet are.

a. For the conservation of the active drug from air, moisture, light,
b. Mask the displeasing taste and odor and,
c. Improve the appearance.

Chewable tablets

The tablet which are expected to be softened and bitten up between the teeth previously ingestion. Chewable are mostly available as antacids and vitamin tablets .It is prescribed to children's and elderly patients who have problem in swallowing.

Effervescent tablet

Effervescent tablets consist of carbonate or hydrogen carbonate and acid substances that react instantaneously in the presence of water to deliver carbon dioxide. Tablets can be made effervescent by adding tartaric acid, sodium bicarbonate and citric acid to the active drug.

Lozenge tablet

The tablets which are meant to create uninterrupted action on the mucous membrane of the throat. Disintegrating agent is absent and the quality of the binding agent is enhanced so as to build slow dissolution. Suitable (sugar), flavoring and coloring agents must be added in this formulation. Gum is also added to provide strength and cohesiveness to the lozenge a facilitating slow release of the active drug.

Soluble tablet

They are the tablet which dissolves entirely in liquid to give a solution of specific concentration.

Sublingual tablet

The drug that gets absorbed along the mucosal tissue of the oral cavity and gets inactivated in the gastrointestinal tract is given in this preparation. These tablets are to be put under the tongue for slow release of drug.

Enteric coated tablet

Drugs that get inactivated by the gastric squeeze or may make disturbance the stomach, these elements can be overwhelmed by covering the tablet with cellulose acetic acid derivation phthalate. It is a polymer which is insoluble in gastric substance yet is quickly dissolvable in intestinal substance. Hence there is a postponement in the breaking down of the drug until it reaches the small intestine.

Film coated tablet

This tablet is envelope in a thin coating of polymeric substance which shields the drug from environmental conditions and covers the unpleasant taste and the odor of the drug.

Implant

A small tablet that is formulated for placing beneath the skin by giving a small surgical cleave into the skin which is mend after placing the tablet. This tablet must be sterile one.

Sugar coated tablet

The tablet consists of active ingredient of objectionable taste is covered by a sugar coating to make it more acceptable.

Modified release tablet

Modified-release tablets consist of special additives or is prepared in order to modify the rate of release of the drug into the gastrointestinal tract. It expands the action of drug and decreases the prevalence of administration of drug [5]

Advantages of tablets

- Unit measurements shape with exact, stable dosage and incredible accuracy and slightest inconstancy.
- Tablets are the most stable dosage form.
- Easy to handle,
- Shoddy, simple to regulate and arrangement does not require extra preparing strides.
- Give assurance of medicaments from environmental conditions like air, dampness and light, and so forth.
- Provides extended stability to medicaments.
- Low production cost when compared to other solid dosage forms and large scale production is possible.

- Administration of small dose of drug in accurate amount.
- Objectionable taste can be masked by sugar coating.
- Packing and production is cheap and does not require more space for storage [6]

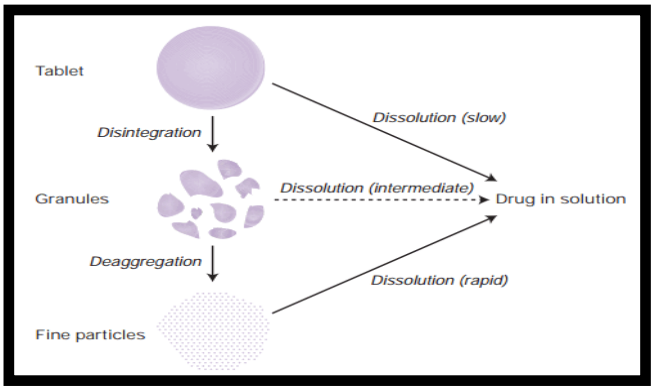
Disadvantages of tablets

- Medications which are shapeless and low thickness character are hard to pack into tablet.
- Drugs with higher absorption rate are not suitable for compressed tablets.
- Medications with low or poor water dissolvability, moderate disintegration, high absorbance in GI tract might be hard to define.
- Sensitive to oxygen drugs may require special coating.
- Cost of production may be increased because of coating and encapsulation to remove bitter and unpleasant taste.
- Some tablet may cause difficulty in bioavailability.
- Difficult to formulate liquid in tablet and swallowing is difficult especially for children and ill [6]

Immediate release tablets

The aim for most drug delivery systems is quick dissolution of drug after administration; such products are called immediate release systems. The aim with these is to target drug to the site of action or into the bloodstream as fast as possible. The product is outlined to give the fastest dissolution rate possible, with the expectation that this will give the fastest absorption and effect. As discussed, rapid dissolution can be attain by increasing surface area A of drug particles (reducing particle size) and by using appropriate excipients to intensify solubility of drug in diffusion layer.

The given figure elucidate the drug release and dissolution process of an oral tablet. Immediate-release tablets are intended to undergo rapid break-down to smaller granules and following dissociation to fine particles. A bigger surface territory is uncovered to the disintegration medium, coming about separation to fine particles. Excipients that encourage breaking down (disintegrants) and deaggregation (surfactants) are generally included quick discharge strong measurement shapes.



The procedure used in dissolution of a active ingredient from a tablet in the presence of fluids. Although dissolution takes place from the complete tablet, fine particles and granules, the large surface area of the granules and even larger surface area of the fine particles give dissolution rates.

When an immediate-release product is administered, the drug quantity in blood increases quickly, peaks right after administration, and then reduces. If the peak concentrations is too high, the drug may show undesirable side effects. If the reduction in blood concentration is also rapid, the product will have to be dosed frequently to maintain therapeutic blood levels. Such a large change in blood concentration may not be appropriate for some drugs, or may require dosing frequencies that are impractical [7].

History of immediate release tablets

Immediate-release tablets were the scientific decendant emerging from the research mainly meant for preparing fast dissolving buccal tablets aimed at systemic absorption of the drug. If the drug has prospective for buccal absorption fast dissolving tablets can grant improved bioavailability, by passing the GIT and first-pass metabolism. However, if the drug does not have enough buccal absorption, and is swallowed, the patient still can benefit from faster liberation, disintegration and dissolution of the drug, leading to rapid onset of action. Moreover, as the dosage dissolves in the oral cavity into a liquid form it helps the swallowing process [8]

Most conventional immediate release oral drug manufacture, such as tablet and capsules, are made to release the active ingredient quickly after oral consumption. In the planning of standard medication items for the most part stamp in generally moment sedate ingestion and beginning of going with pharmacodynamics impacts. On account of conventional oral items containing prodrugs, The pharmacodynamic activity might be ease back because of changing to the dynamic medication by hepatic or intestinal digestion or by concoction hydrolysis. On the other hand, regular oral items containing inadequately dissolvable (lipophilic medications), tranquilize ingestion might be continuous because of moderate disintegration in or particular retention crosswise over GI , additionally bringing about a deferred beginning time [9].

Types of immediate release tablets

Dosage forms intended for carriage to the intraoral cavity can be classed in terms of their dissolution or disintegration kinetics as either:-

1. Quick dissolving (QD)
2. Slow dissolving (SD)
3. Non dissolving (ND).

Quick dissolving delivery systems (QD)

They experience disintegration or dissolution in the saliva normally within few seconds to a minute delivering the drug and inactive ingredients into the oral cavity. The huge amount of the drug will eventually be gulped with the saliva and taken along the GIT where the drug is eventually absorbed.

Advantages

- Ease of swallowing
- Administration without water.
- Quick onset of action. Therapeutic class of drugs for QD consist of non-opoid analgesics, anti-migarine, cough and cold, GI, cardiovascular and CNS related drugs.

Slow dissolving delivery systems (SD)

They disperse in the oral cavity within 1 to 10 minutes and consist of the following products: chewable tablets, sublingual tablets, lollipops, mucoadhesive tablets and buccal tablets.

Non dissolving delivery systems (ND)

They don't break down totally when set in the mouth and can convey for controlled medication conveyance from 10 min to a few hours and up to a day or more. Cases of ND incorporate the accompanying measurements shapes: biting gums, buccal and gingival patches, periodontal filaments and medication conveyance gadgets [10].

Advantages and disadvantages of immediate release tablets

Advantages

1. Enhanced soundness bioavailability.
2. Diminished breaking down and disintegration times for prompt discharge oral dose frames.
3. Fit for controlled, supported discharge actives.
4. High medication stacking is conceivable.
5. Fit to give favorable circumstances of fluid medicine as strong arrangement.
6. Customizable and agreeable to existing preparing and bundling hardware.
7. Financially savvy
8. Enhances the consistence included comfort.
9. The quick/quick break up dose frames have the additional points of interest of accommodation and precise dosing when contrasted with fluids.
10. Simplicity of gulping is conceivable.
11. Bilayer tablet is feasible for ensuing arrival of two medications in organization together and isolate two inconsistent substance.

Disadvantages

1. Repeated dosing is important for tranquilize with short half-life.

2. Medication discharge at once may create high plasma focus which may deliver poisonous quality.

Unsuitable drug characteristic for immediate release tablets

- Drugs with shorter biological half-life.
- Drugs that exhibit low bioavailability.
- Drugs which exhibit rapid clearance and elimination half life are also not desirable candidate for immediate release tablet [11]

Drugs compatible for immediate release tablets-

Salbutamol Sulphate

The immediate release tablet of salbutamol sulphate along 6% w/w polyplasdone XL as the super disintegrants an replacement to and superior than the traditional tablet dosage forms, and the rapid dissolving concept in case of salbutamol sulphate could be of a great importance in relieving acute asthmatic attack.

Aceclofenac

Aceclofenac tablets can be formulated by direct compression using superdisintegrants. Ac disol was found to be best among the two super disintegrants, with anti inflammatory and analgesic effect.

Promethazine Theoclate

Immediate release tablets of promethazine theoclate were formulated by direct compression method after introducing super disintegrants Ac-Di-Sol,sodium starch glycolate and crospovidone in different concentrations. With Anti histaminic and Anti muscarinic activity.

Valsartan

Immediate release tablets of valsartan were formulated using various super disintegrants by direct compression method. Crospovidone is most acceptable. Valsartan is an angiotensin II receptor antagonist and is mostly used in the controlling of hypertension in order to minimize cardiovascular mortality and in management of other heart failure defects [11].

Biopharmaceutical classification system-

The biopharmaceutical order framework (BCS) is another thought in the field of pharmaceutical science and innovation. The present development had additionally enabled us to extend the solvency and porous-ness demonstrative of the medication atom in the underlying extension organizes so the important essential changes can be made to the particle with a specific end goal to overhaul the pharmacokinetic parameters. Thus BCS has also got a place in many direction documents of administrative importance.

The BCS was first designed in 1995, by Amidon et al. and since then it has become a standard in the adjustment of bioequivalence of oral drug products. The BCS plays a managing instrument for plan researcher, for proposing a way to deal with enhance the viability of medication improvement by suitable choice of measurement shape and bioequivalence tests, to recommend a class of prompt discharge (IR) strong dose frames, for which bioequivalence might be assessed in light of in-vitro disintegration tests, and to lay the impact of ex\cipient(s) on tranquilize penetrability [12].

BCS Classes

According to the Biopharmaceutical Classification System (BCS) drug substances are classed into four types depending upon their solubility and permeability:

Class I – High permeability, High solubility.

These compounds are rapidly absorbed and their absorption rate is usually greater than excretion.

Class II – High permeability, Low solubility.

The bioavailability of these products is restricted by their solvation rate. A link between the in vivo bioavailability and the in vitro salvation can be found.

Class III – Low permeability, High solubility.

The absorption is finite by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class-I

Criteria can be applied.

Class IV – Low permeability, Low solubility

These compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected [13].

METHODS OF TABLET PREPARATION

Granulation

Granulation may be defined as a size expansion process which transforms small particles into physically secure and larger mass. The purpose of granulation is to refine powder flow and handling, reduce dustiness, and avert segregation of the constituents.

Granulation method can be mainly classified into two types

(i) Wet granulation and (ii) Dry granulation

(i) Wet granulation

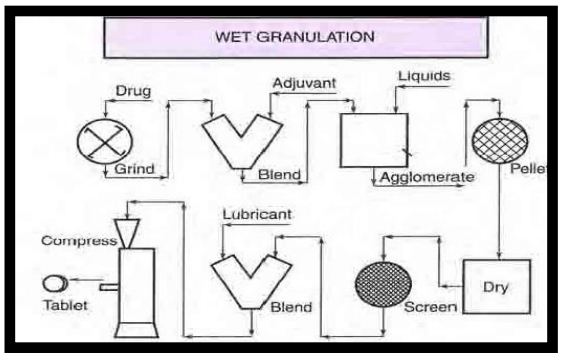
Wet granulation is a commonly used operation in the pharmaceutical industry. Wet granulation is often carried out utilizing a high-shear mixer. The shear granulation process is a quick technique which is susceptible for over-wetting. Thus, the liquid quantity is critical and the optimal quantity is afflicted by the properties of the raw materials. Power consumption of the impeller generator and the impeller are band have been enforced to direct the rheological assets of the wet aggregate during collection and, thereby, have been used to find out the end-point of water addition. Anyways, these methods are afflicted by the equipment valuables.

Important steps involved in wet granulation-

1. Mixing of drug(s) and excipients.
2. Formulation of binder solution.
3. Blending of binder solution with powder mixture to form damp mass.
4. Course shielding of wet mass using a appropriate sieve (6-12 screens).
5. Drying of damp granules.
6. Screening of arid granules through a relevant sieve (14-20 screen).
7. Mixing of screened granules with disintegrant, Glidant, and lubricant.

Special wet granulation techniques

High shear mixture granulation
Fluid bed granulation
Extrusion-spheronization
Spray drying



Dry granulation

In dry granulation system the powder blend is squeezed without the utilization of warmth and dissolvable. The two essential methods are to shape a smaller of material by pressure and after that to process the minimal to get granules.

Two methods are used for dry granulation.

The most widely used method is slugging, where the powder is precompressed and the resulting tablets or slugs are milled to yield granules.

Steps in dry granulation

1. Milling of drugs and excipients.
2. Mixing of milled powders.
3. Compression into large, hard tablets to make slug.
4. Screening of slugs.
5. Mixing with lubricant and disintegrating agent.
6. Tablet compression.

TWO MAIN DRY GRANULATION PROCESSES

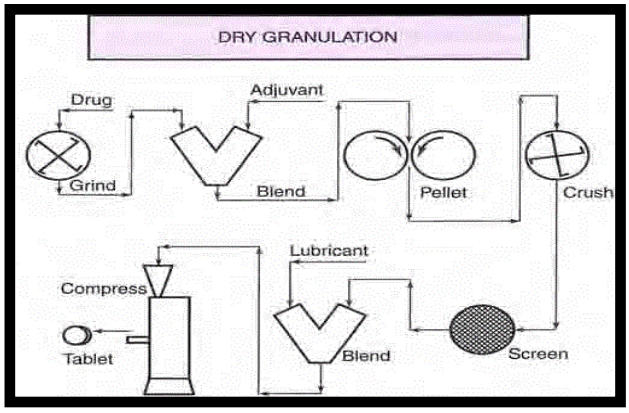
Slugging process

Granulation by slugging is the way toward packing dry powder of tablet detailing with tablet press having the dust cavity sufficiently expansive in measurement to fill rapidly. The precision or state of slug is not very critical. Just adequate strain to smaller the powder into uniform slugs ought to be utilized. When slugs are created they are diminished to fitting granule estimate for definite pressure by screening and processing.

Roller compaction

The compaction of powder by methods for weight roll can likewise be proficient by a machine called chilosonator. Not at all like tablet machine, the Chilosonator turns out a compacted mass in a relentless ceaseless stream. The powder is bolstered down between the rollers from the container to encourage the powder into the compaction zone.

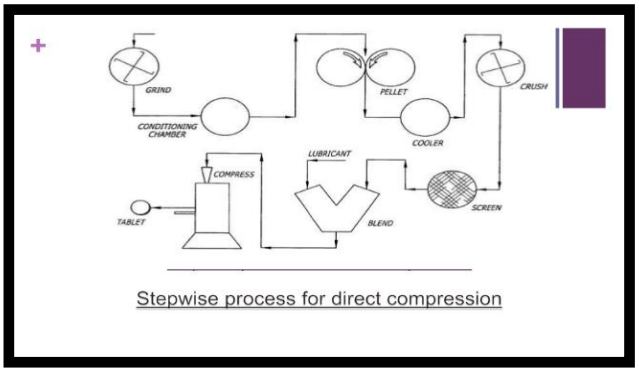
Like slugs, the totals are screened or processed for creation into granules.



Direct compression

The expression "coordinate pressure" is characterized as the procedure by which tablets are packed specifically from powder blend of API and reasonable excipients. No pre-treatment of the powder mix by wet or dry granulation technique is required.

Among the methods used to plan tablets, coordinate pressure is the most progressive innovation. It includes just mixing and pressure, consequently offering advantage especially as far as quick creation, s it requires less unit operations, less hardware, diminished number of work force and extensively less processing time alongside expanded item soundness [14].



Stepwise process for direct compression

MATERIALS AND METHODS

Active pharmaceutical ingredient Quetiapine fumerate was acquired as a gift sample form aspen pharmaceutical limited, remaining inactive ingredients were purchased locally form SD fine limited, Hyderabad.

Preformulation Studies

Physico chemical properties of API

Methodology

Preformulation Studies

It is one of the significant requirements in expansion of some drug transport system. Preformulation studies are done on the drug, which involved explanation, solubility, pH, and compatibility studies.

Organoleptic Characters

The organoleptic characters and appearance was noted using vivid terms.

Melting point determination

The MP of the drug sample was determined by capillary method using melting point apparatus The Reported and observed Melting point is 171-174°c

Determination of solubility

The solubility of Quetiapine Fumerate Hcl was determined by totalling surplus amount of drug in the solvent and balanced solubility was determined by taking the supernatant and analyzing it spectro photo metrically with water, 0.1N HCL, Methanol, 6.8pH buffer, chloroform and Alcohol by using the below formula:

% solubility = sample absorbance/ standard absorbance *dilution factor*100

Analytical Method Development of Quetiapine Fumerate HCL

Preparation of 0.1 N HCL

8.5 ml of concentrated HCl was taken and dilute with distilled water up 1000ml.

Determination of λ_{max} of Quetiapine Fumerate HCL using 0.1 N HCL

Procedure

Working standard

5mg of Quetiapine Fumerate was taken and dispersed in 100 milli litre of
0.1N HCl gives 50µg/ml concentrated stock solution.

Dilutions

From the working standard solution 1ml was diluted to 100ml with 0.1N HCL 5µg/ml concentrated solutions.

The similar steps are repeated for 2ml stock solution with 8 ml of HCL 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 scanned at 200-400nm wavelength resultant scan spectrum is noted. The resultant wavelength requiring peak absorbance is known as λ_{max}

Construction of standard curve of Quetiapine fumerate 0.1N HCl

Procedure

5mg of Quetiapine Fumerate was weigh up and dissolved and then invented to a volume of 100ml with 0.1N HCL 50µg/ml stock solution.

Dilutions

From the working standard solution 1ml was diluted to 10ml with 0.1NHcl 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 λ_{max}=289µm

Table no 4: Concentration for calibration curve

CONCENTRATION	ABSORBANCE
10µg/ml	0.228
20 µg/ml	0.293
30 µg/ml	0.438
40 µg/ml	0.575
50 µg/ml	0.676

Y=0.014x+0.088
R2= 0.937

Angle of Repose (Θ)

It is the maximum angle between the lower surface of a stack of powder and the flat plane. It is measured using the funnel method. Precisely weighed Microsphere mixture is in use in the funnel. Stature of cone was accustomed in a way the angle of the funnel just touched the topmost of the powder mixture. Microsphere mixture was permitted to flow over the funnel easily on to the lower surface. Diameter of the powder was measured and Θ was calculated using the following formula:

Θ = tan-1 (h/r)

Where:

P = Angle of repose

h = height r = radius

The viewpoint of rest has remained used to portray the flow properties. It is characteristic linked to inter particulate resistance or resistance to association amongst particles.

Table no 5: Flow possessions and conforming angles of repose

Flow Property	Angle of Repose
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate,	46–55
Very poor	56–65
Very, very poor	>66

DENSITY

Bulk Density: (BD)

It is the proportion of entire bulk of powder to the bulk size of powder, The complete amount of Microspheres in each individual trial are taken carefully and measured using a measuring cylinder. Firstly the trial 1 is measured then T2, T3, T4…..respectively.

The BD is given:

Bulk density = heaviness of powder / Bulk volume.

$$\mathbf{Pp} = \frac{M}{V_0}$$

M = quantity of the powder

V_0 = unpackaged volume of the powder.

Tapped Density

Is the proportion of complete bulk of powder to the tapped size of powder. The entire amount of Microspheres in each individual trial are taken carefully and measured using a measuring cylinder. Then the microspheres are tapped first at100times then the vales are notes. Next after 100 taps more 100 taps are done i.e200 and volume of the microspheres is noted. Firstly the Trial 1 is measured then T2, T3, T4….. respectively.

The TD is given by following formula:

Tapped density = Weigh up of powder / Tapped volume

Dt = (M) / (**V_f**.**

M = quantity of the powder

V_f = tapped size of the powder.

Determination of 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) and taken in a beaker and are mixed properly. Then to it 100 mg of Quetiapine Fumerate HCl (drug) is added and mixed thoroughly.

Then the mixture is use 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:

$P_{o/w}$ = Organic phase/ Aqueous phase x 100

Formulation of Quetiapine Fumerate immediate release tablets

Table no: Formulation of immediate release tablets

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Quetiapine fumerate	10	10	10	10	10	10	10	10	10	10
2	Lactose	100	75	50	25	25	25	25	25	25	25
3	Microcrystalline cellulose	100	100	125	125	125	125	150	175	200	225
4	Carboxy Methyl cellulose	100	100	100	125	125	100	75	50	25	0
5	Starch	25	50	50	50	75	75	75	75	75	75
6	Talc	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50
7	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
8	Total weight	340	340	340	340	340	340	340	340	340	340

Method of preparation of IR tablets

Immediate Release tablets of Quetiapine fumerate was prepared by Direct Compression method according to the formula given in the Table no -3. All the components were separated. The active ingredient and microcrystalline cellulose was blended be minute section of both each time and mixing it to get a consistent mixture. Then the contents were balanced and blended in analytical order. The resulting drug-excipients mixture was compressed at 10 mm sizes horizontal round strike to get tablet using tablet punching machine. The tablet press position was kept invariable across all formulations.

Determination of release rate kinetics

If you want to describe the DS release kinetics from individual pill formulations, the corresponding dissolution facts were equipped in diverse kinetic dissolution fashions:

Order, first order, and Higuchi respectively.

$Qt = Q0 + K0_t$

Where, Qt is the amount of drug launched at time t; Q0 the quantity of drug in the solution at t = zero, (normally, Q0 = zero) and K0 the zero order launch regular.

$\log Qt = \log Q\alpha + (K1 /2.303)\ t$

Qα being the total amount of drug within the matrix and K1 the primary order kinetic consistent.

$Qt = KH.\ t\ ½$

Wherein, KH is the Higuchi rate constant.

Further, to higher characterize the mechanism of drug release from matrices, dissolution information had been analyzed the use of the equation proposed by means of Koresmeyer and Peppas.

$Q\ (t\text{-}l)\ /Q\alpha = KK\ (t\text{-}l)\ n$

Where, Qt corresponds to the quantity of drug released in time t, l is the lag time (l = 2 hours), Qα is the full quantity of drug that ought to be launched at countless time, KK a constant comprising the structural and geometric

characteristics of the tablet, and n is the discharge exponent indicating the kind of drug release mechanism. To the determination of the exponent n, the points in the launch curves where Q (t-l)/Qα>zero.6, had been simplest used. If n approaches to 0.five, the release mechanism can be Fickian. If n tactics to one, the discharge mechanism can be zero order and then again if zero.5<n<1, non-Fickian (anomalous) transport could be received. Anomalous (non-Fickian) shipping generally refers back to the drug launch by way of the summation of each diffusion and erosion of the polymeric matrix. The standards employed to choose the ‘‘fine version’’ changed into the one with the very best coefficient of dedication (r2).

Stability Studies

According to ICH guide lines, the prepared in-house oral disintegrating tablets were subjected to one month stability studies at specified temperature and humidity conditions.

1. 25^0C/60% RH analyzed every month for length of 1 month.
2. 30^0C/seventy five% RH analyzed each month for duration of 1 month.
3. 40^0C/75% RH analyzed each month for duration of 1 month.

RESULTS AND DISCUSSION

Results of methodology are described accordingly.

Preformulation studies of API

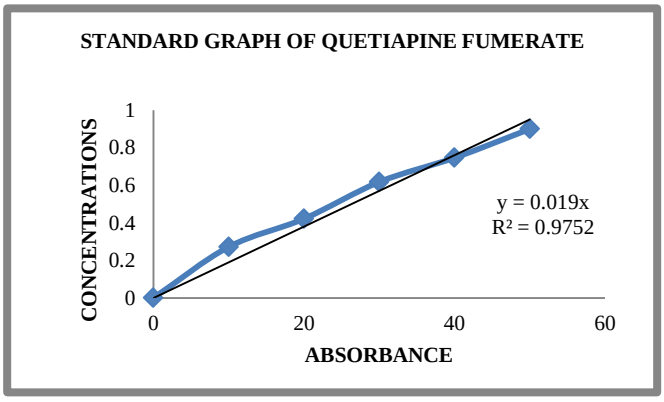
API CHARACTERIZATION:

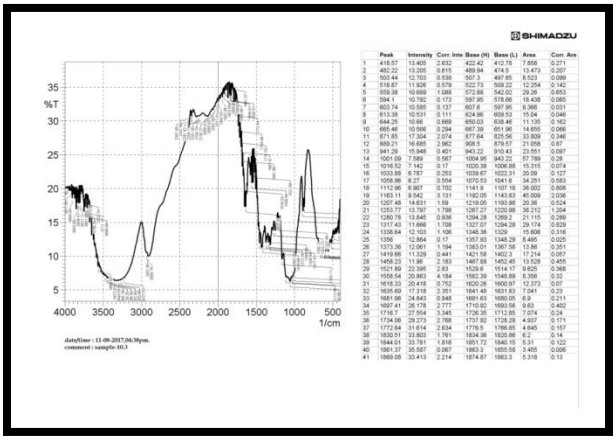
Table no 07: Physical Properties of API

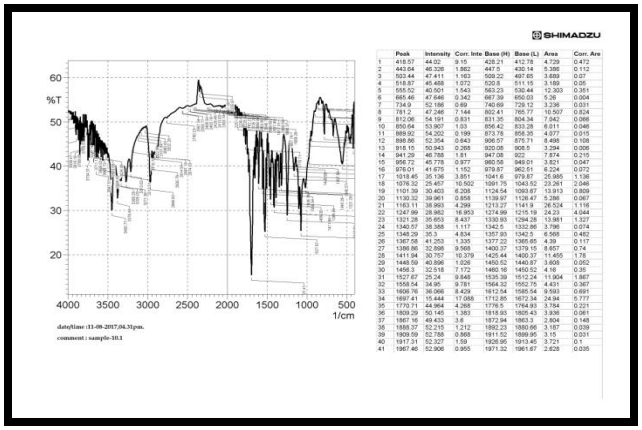
S.NO	API CHARACTERISATION	RESULTS
1	Physical Appearance	White powder
2	Melting point	168^{o}C
3	Solubility	0.1N HCL, Methanol, water
4	Bulk density	0.27GM/ML
5	Tapped Density	0.45GM/ML
6	Carr’s index	14.29
7	Hausner’s Ratio	1.35

The value of API compressibility index is 14. 29%, 15-25%, less than 15% indicates poor flow ability, optimum flow ability and high flow ability respectively.

Standard graph of quetiapine fumarate was taken in 0.1N HCL phosphate buffer at 298 nm







Blend characterization-physical properties of trial T1 to T10 are as:

Table no: physical characterization of powder blend from trial T-1 to T-10

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	Compressibility index
Trial -1	0.23	0.25	31.23	30.18
Trial -2	0.34	0.45	32.34	37.31
Trial -3	0.35	0.64	35.23	27.58
Trial -4	0.42	0.74	35.27	31.66
Trial -5	0.46	0.38	31.32	38.23
Trial -6	0.39	0.37	41.28	35.93
Trail -7	041	0.65	32.38	37.31
Trial -8	0.38	0.66	37.38	29.03
Trial -9	0.41	0.65	35.43	36.76
Trial -10	0.39	0.59	35.65	34.37

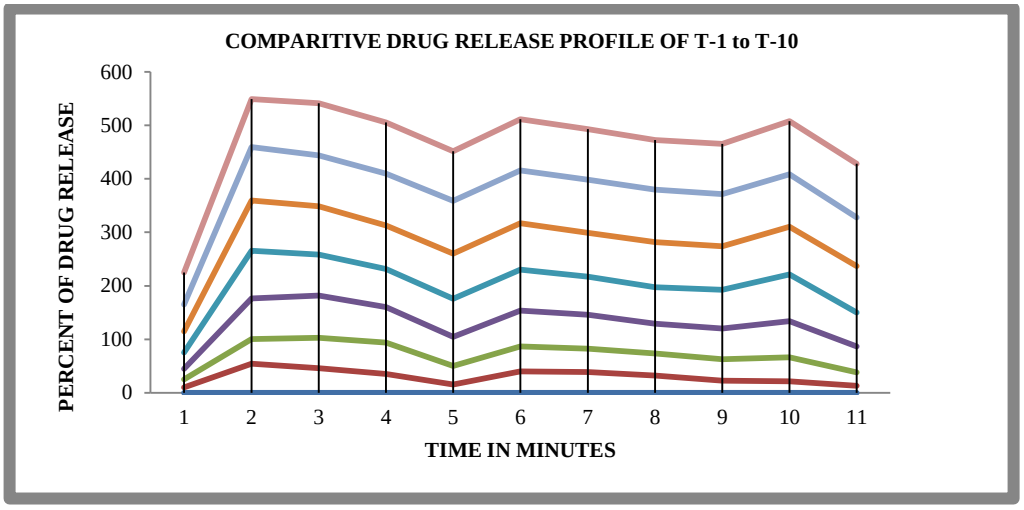
Table no: post evaluation parameters from trial T-1 to T-10

Formulation	Hardness (kg/cm^2)	Thickness (mm)	Diameter (mm)	Weight variation (mg)-340	Friability
Trial -1	3.4	0.4	0.9	338	0.06
Trial -2	4.3	0.5	0.9	341	0.35
Trial -3	4.7	0.6	1.0	340	0.26
Trial -4	5.3	0.4	0.9	344	0.49
Trial -5	4.8	0.4	0.9	339	0.50
Trial -6	5.3	0.4	0.9	345	0.75
Trail -7	5.7	0.4	0.9	342	0.52
Trial -8	4.6	0.4	0.9	336	0.52
Trial -9	4.8	0.4	0.9	338	0.40
Trial -10	5.3	0.4	0.9	334	0.62

Drug release studies

PERCENT OF DRUG RELEASE FROM ALL TRIALS										
TIME	**T-1**	**T-2**	**T-3**	**T-4**	**T-5**	**T-6**	**T-7**	**T-8**	**T-9**	**T-10**
0	0	0	0	0	0	0	0	0	0	0
10	54.45	45.86	35.34	15.39	40.23	38.84	32.34	22.34	21.29	12.93
15	45.89	56.83	58.35	34.93	46.22	43.84	41.39	40.27	45.27	25.34
20	76.24	78.93	66.38	54.34	67.34	63.37	55.38	57.83	67.28	48.29
30	88.94	76.93	71.34	71.34	76.22	71.34	68.37	72.3	87.47	63.72
40	94.22	89.94	81.23	83.98	87.27	81.93	84.24	81.38	88.94	86.43
50	99.93	95.38	97.34	99.24	98.82	99.34	98.39	97.37	98.47	91.39
60	89.49	97.39	95.38	92.45	95.25	94.23	92.74	94.27	99.03	100.01

GRAPHICAL REPRESENTATION



DETERMINATION OF RELEASE RATE KINETICS

Table no rate of release kinetics of optimized trial

ZERO ORDER		FIRST ORDER		HIGUCHIS PLOT		KORESMEYER PEPPAS PLOT	
Time	**% Drug Undissolved**	**Time**	**Log 100-Q**	**Sq. Time**	**Mean % Drug Dissolved**	**Log Time**	**Log Cumulative % Drug Dissolved**
0	100	0	2	0	0	0	0
10	89.72	10	1.99	3.16	10.28	1	1.01
15	75.71	15	1.99	3.87	24.29	1.18	1.39
20	60.61	20	1.99	4.47	39.39	1.30	1.60
30	43.62	30	1.99	5.48	56.38	1.48	1.75
40	21.62	40	1.99	6.32	78.38	1.60	1.89
50	16.52	50	1.99	7.07	83.48	1.70	1.92
60	1.63	60	2.00	7.75	98.37	1.78	1.99

ZERO ORDER RATE KINETICS

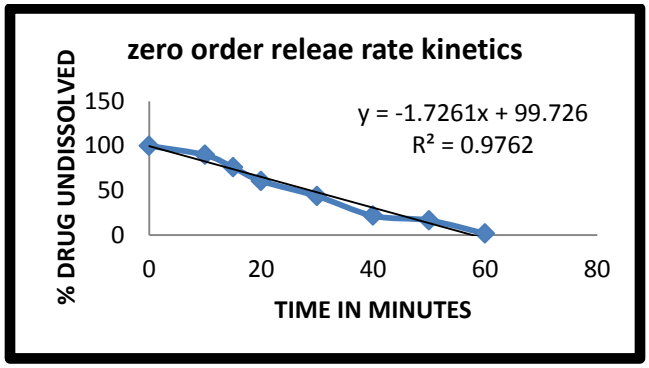


Figure no : Zero order release of trial T-10

FIRST ORDER RATE KINETICS

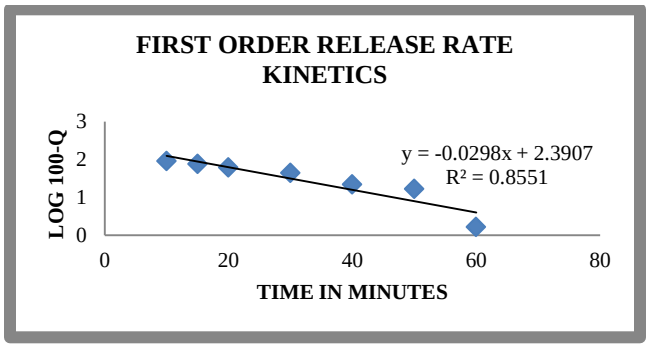


Figure No: First order release rate form trial T-10

HIGUCHIS PLOT

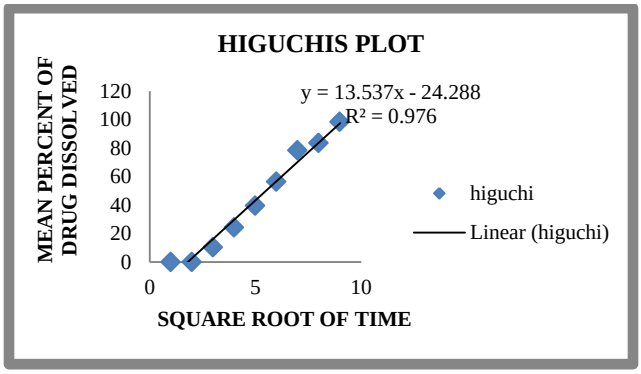


Figure No: Higuchis plot for release from trial T-10

KORESMEYER PEPPAS PLOT

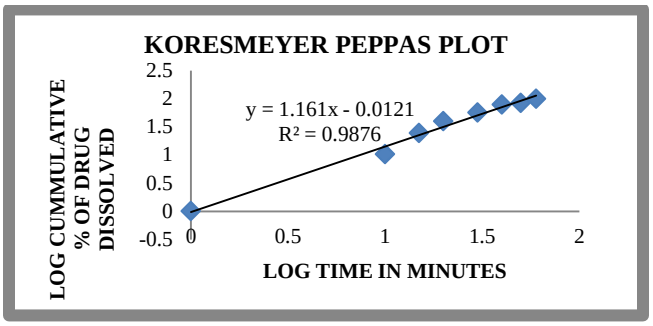


Figure no: Peppas Plot of drug release from trial T-10

ONE MONTH STABILITY STUDIES

Optimized formulation trial T-10, was taken for one month stability studies under accelerated stability conditions.

Table no: drug release from T-10 after one month stability accelerated conditions

TRIAL -10	one month stability data
TIME IN MINUTES	% DRUG RELEASE
0	0
10	10.29
15	18.47
20	37.28
30	52.87
40	78.29
50	91.39
60	100.01

GRAPHICAL REPRESENTAION OF ONE MONTH STABILITY STUDIES FORM T-10

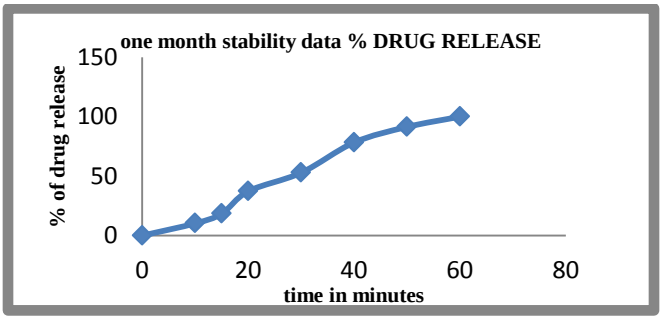


Figure No: Drug Release after One Month Form T-10

DISCUSSION

In the present research work, preparations of various trials were performed to meet the aim and objectives. FTIR studies were conducted for Pure QUETIQPINE FUMERATE, Carboxy Methyl Cellulose and Microcrystalline cellulose and the spectra obtained gives there is no much interaction between them.

Various excipients like microcrystalline cellulose, car boxy methyl cellulose were used as diluents and disinter grants to achieve optimized

formulation of QUETIAPINE FUMERATE IMMEDIATE RELEASE TABLETS.

From formulation trial T-1 to T10 combination of microcrystalline cellulose and carboxy methyl cellulose was taken in various rations.

The optimized trial T-10, was taken for one month accelerated studies and the drug release was obtained gave satisfactory results.

Release rate kinetics was also determined by interpreting the percent of drug release and time into various kinetic models.

The order of release was found to be in the following order.

KORESMEYER PEPPAS PLOT with R^2 value of 0.987>, HIGUCHIS PLOT with R^2 0.976 = ZERO ORDER R^2 0.976 >, FIRST ORDER R^2 0.855.

The release of drug form QUETIAPINE FUMERATE immediate release tablets was found to be following KORESMEYER PEPPAS plot of kinetics release.

Acknowledgement

We authors heart fully give thanks to our beloved Founder and promoter late Sri VIZARAT RASOOL KHAN and our chairman Mr. SHAH-ALAM RASOOL KHAN for providing good infrastructure and basic necessary requirements to fulfill the preset intended research work entitled

“DESIGN AND IN-VITRO EVALUAITON OF IMMEDIATE RELEASE TABLETS OF A DI-BENZOTHIAZEPINE DERIVATIVE QUETIAPINE FUMARATE: AN ANTIPSYCHOTIC AGENT”

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