Available Online at www.jddt.in

ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 2 (22) 2014, 07-11

REVIEW ARTICLE

Design of oral sustain release drug delivery of quetiapine fumarate

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Received 21 September 2014; Accepted 29 September 2014

ABSTRACT

Oral administration of drugs has been the most common and preferred route for delivery of most effective agents. It occurs the prior route of administration investigated in the discovery and development of new drug candidates and formulations. The popularity of oral route is attributed to accurate dosing, ease of administration, cost effective manufacturing method, patient acceptances and generally improved shelf life of the product. In recent years, considerable attention has been focused on development of sustained release drug delivery systems. The rationale for the development of sustain release drug delivery system of a drug is to enhance its therapeutic advantages, reducing its side effects while improving the management of the diseased condition.[15]

Quetiapine fumarate is a dibenzothiazepine derivative, & a recent antipsychotic drug with an atypical neuropharmacological profile. It has the highest serotonin dopamine binding ratio, being the serotonin type 2. ($5HT_2$) receptor blocking effect about twice as strong as the dopamine D2-receptor blocking effect, thereby leaving more active neurotransmitter in the synapse. It is widely prescribed for the treatment of schizophrenia & bipolar disorder.

Quetiapine fumarate is a BCS class II (poorly soluble, highly permeable) drug. It has a plasma half life of 6±1h. & a bioavailability of 83% in 1.5 h. For such drug hydrophilic matrix systems are more suitable.[25]

INTRODUCTION:

A sustained release system includes any delivery system that achieves slow release of the drug over an extended period of time. The primary objective of this system is to ensure safety and to improve efficacy of the drugs as well as patient convince. This is acquirement by best control of plasma drug levels and less frequent dosing. Pharmacokinetic theory suggests that the ultimate method for reducing the plasma maximum concentration (C_{max}) to plasma minimum concentration (C_{min}) ratio is to have zero- order absorption. Once steady state is achieved under these conditions, drug concentration in plasma is constant as long as absorption persists.[12,19, 20]

REQUIREMENTS OF ANTIPSYCHOTIC DRUGS EFFECTS:

Recently, sustained release drug delivery system has become the standards in the modern pharmaceutical design and intensive search has been undertaken in achieving much better drug safety, reliability and product effectiveness. Quetiapine fumarate is a prescription antipsychotic drug used in the treatment of bipolar disorder and schizophrenia. Quetiapine fumarate is a BCS class II (high permeable, less soluble) drugs, a good candidate which make it, to be prepared in sustain release dosage form. It has a plasma half life of 6±1 hours. [15]

Quetiapine fumarate is the drug of choice by many psychiatrics today as it is very much effective and shows very minimal side effects as compared to the other antipsychotics in market. The dose of the conventional tablet is 3 & 2 times in a day depending on the pharmacological condition of the patient. Due to its short half life 6-7hrs the drug has to be administered twice a day, thus having a repeted dosing. This is a difficult job for the patients, the patient taking this medication are mainly schizophrenic or suffering from bipolar disorder thus showing the mood disturbance. The development of once regular dosage form will ensure the patient convenient, removing the frequent changes in blood plasma levels and maintenance of the therapeutic concentration in plasma.[18,25] For the sustain release formulations there are various approaches used such as reserve devices, controlled osmotically, ion exchange resin etc. the most famous among these systems are the matrix devices.

In this study, easily available and most readily available polymer HPMC and its different grades were used to prepare the matrix tablets.[17]

Objective:

The objective of the study was:

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- To design and develop once daily formulation of Quetiapine fumarate using hydrophilic matrix system.
- To study the effect of various viscosity grades of HPMC and their combinations on the release profile.

To study the effect of commonly used excipients on release pattern of drug. [5]

Designing of Sustained Release System:

Technologies for designing of controlled release oral dosage forms can be classified according to two characteristics i.e. delivery mechanism and structure of the system. The "Delivery Mechanism" refers to physical and chemical principles involved i.e. dissolution, diffusion, erosion, ion exchange and osmosis. An ideal structure of a controlled release oral dosage form is that which allows the mechanism to yield the desired drug delivery rate. Depending upon the manner of drug release from the oral sustained release systems, these are classified as,

a. Continuous release systems
b. Delayed transit and continuous release system
c. Delayed release system

a. Continuous release systems:

These systems release the drug for a prolonged period of time along the entire length of gastro-intestinal tract with normal transit of the dosage form. It includes dissolution-controlled release, diffusion-controlled release, ion exchange, pH dependent and osmotic pressure controlled system.[1,2]

b. Delayed release systems:

The design of such system involves release of drug only at a specific site in the gastro intestinal tract. The two types of delayed release systems are intestinal release system and colonic release systems. [14]

Intestinal release system: A drug can be enteric coated for intestinal release for several reasons such as to prevent, disturbance of gastric pH prevent gastric irritation.

Colonic release system: Drugs are poorly absorbed through colon but are delivered to such a site for local action as in the treatment of ulcerative colitis or inflammatory bowl diseases.[14]

VARIOUS CRITERIA FOR THE CHOICE OF DRUG FOR SUSTAINED RELEASE DOSAGE FORM:

A number of drug characteristics need to be considered in evaluating drug molecules for sustained release dosage form. Some of these characteristics are as follows-

I. Biopharmaceutical Characteristics of the drug:

Dose: The formulation of sustained release drug products may not be practical for drugs with large conventional dose (>500mg). Because, the size of the SR drug product would have to be quite large, too large for the patient to swallow easily.[23]

Aqueous solubility: The rate of dissolution is directly proportional to aqueous solubility. Therefore the aqueous solubility of a drug is the limiting factor in its dissolution.

Partition Coefficient*:* Drugs with extremely high partition coefficient readily penetrate the membranes, but are unable to proceed later. While drugs with highly water solubility so that. Minimum oil/water partition coefficient cant penetrate the membrane well.

Stability of drug*:* Drugs unstable in GIT (Gastro-intestinal) environment cannot be administered as oral sustained release formulation because of bioavailability problems.[22]

Mechanism and Site of absorption*:* Drugs absorbed by carrier-mediated transport process and those absorbed through a window are poor candidates for controlled release system e.g. several B vitamins

Molecular size and Diffusivity*:* The lower the MW (molecular weight), the rapidly and complete the absorption. In addition to biological membrane the molecule has to diffuse through a polymeric matrix in most of sustained release dosage forms. [27]

II. Pharmacokinetic Characteristics of the drug:

Absorption*:* For a drug to be administered as controlled release formulation, its absorption rate (Ka) must be efficient since the desired rate –limiting step is rate of drug release Kr. so that Ka>>Ka. A drug with slow absorption is a poor candidate for such dosage forms since continuous release will result in a pool of unabsorbed drug.[28]

Elimination Half Life: Minimum the $t_{1/2}$, more the amount of drug to be incorporated in the sustained release dosage form. Drugs with half life in the range of 2 to 8 hours make good candidates for such a system.

Rate of Metabolism*:* A drug, which is largely metabolized, is proper for controlled release system as long as the rate of metabolism is not too rapid. A drug capable of inducing or inhibiting metabolism is a poor candidate for such a product since steady-state blood level would be difficult to maintain.

Dosage form index*:* It is defined as the ratio of max steady state conc.($C_{ss.max}$) to min. steady state conc.(C_{ssmin}). Since the goal of sustained release formulation is to improve therapy by reducing the dosage form index while maintaining the plasma drug levels within the therapeutic range, ideally its value should be close to one as possible. [6,24]

III. Pharmacodynamic Characteristics of the Drug:

Plasma Concentration-Response Relationship*:* Drugs whose pharmacological activity is independent of its

concentration are poor candidates for sustained release systems.

Therapeutic index: The release rate of the drug with narrow therapeutic index should be such that the plasma concentration attended is within the therapeutically safe and effective range.

There are many advantages and disadvantages of sustain release formulations which can be listed as follows.[6]

Advantages:

- Decreasing in frequency of drug administration
- Decrease in fluctuation in steady state levels and therefore control of disease condition and reduced intensity of systemic side effects.
- Maximum use of drug abling reduction in total dose administration.
- Economical to the health care providers and patients.
- Reduction in drug toxicity.
- Product life cycle extension.
- Improved safety margin of high efficacy drugs due to better control of plasma levels.

Disadvantages:

- Delay in onset of drug action.
- Possibility of dose dumping due to food, physiological or formulation variables and thus increased risk of toxicity.
- Retrieval of drug is difficult in case of toxicity, poisoning and hypertension reactions.
- Higher cost of formulation.

POLYMER:

Table 1: Different classification of polymers which is used for matrix systems[9,21,29,30]

Hydrophilic	Cellulosic Non-Cellulosic: Gums and Polysaccharides Others	Methylcellulose, Hydroxyethylcellulose(HEC), Hydroxypropylcellulose(HPC), Hydroxypropylmethylcellulose(HPMC), Sodium carboxymethylcellulose(Na CMC) Locust bean gum, Xanthan gum, Guar gum, Pectin,Chitosan, Carrageenan, Cross-linked high amylase Starch,Sodium alginate. Polyethylene oxide, Homopolymers and co-polymers of Acrylic acids
Water insoluble and Hydrophobic		Ethyl cellulose, Hypromellose acetate succinate, cellulose acetate, Methycrylic acid co-polymers, Poly(vinyl acetate).
Fatty acids/alcohols and waxes.		Glyceryl behenate ,Bees' wax, Carnauba wax, , Paraffin waxes, Candelilla wax, Glyceryl monooleate, monosterate, palmitostearate, Hydrogenated vegetable oil Hydrogenated palm oil, Hydrogenated cottonseed oil, Hydrogenated soybean oil

Release mechanism from Hydrophilic matrices:

Swellable matrix tablets are activated by water, and drug release is controlled by the interaction between water, polymer and drug. The delivery kinetics depends upon the drug gradient in the gel layer. Therefore drug concentration and thickness of the gel layer governs the drug flux. Drug concentration in the gel depends on solubility drug and loading. Gel layer thickness (Area) depends on the relative concentrations of solvent penetration, chain disentanglement and mass transfer in the solvent.[5]

The mechanism of drug release from hydrophilic matrix tablets after ingestion is complex but it is based on diffusion of the drug through, and erosion of, the outer hydrated polymer on the surface of the matrix. Typically, when the matrix tablet is exposed to an aqueous solution or gastrointestinal fluids the surface of the tablet is wetted and the polymer hydrates to form a gelly like structure around the matrix, which is termed as the ' gel layer'. This process is also called as the glassy to rubbery state transition of the polymer. This leads to relaxation and swelling of the matrix which also contributes to the mechanism of drug release. The core of the tablet remains essentially dry at this stage. As the outer later becomes fully hydrated, the polymer chain become completely released and can no longer maintain the integrity of the gel layer, thereby leading to erosion and disentanglement of the surface of the matrix. A new

inner layer replaces it and is cohesive and continuous enough to retard the influx of water and control drug diffusion.[8,10]

CONCLUSION:

Queliapine fumarale is a prescription antipsychotic drug used in the treatment of schizophrenia and bipolar disorder.Quetiapine fumarate is a dibenzothiazepine derivative, & a recent antipsychotic drug with an atypical neuropharmacological profile. It has the highest serotonin dopamine binding ratio, being the serotonin type 2. ($5HT_2$) receptor blocking effect about twice as strong as the dopamine D2-receptor blocking effect, thereby leaving more active neurotransmitter in the synapse. It is widely prescribed for the treatment of schizophrenia & bipolar disorder.

Quetiapine fumarate is a BCS class II (poorly soluble, highly permeable) drug. It has a plasma half life of 6±1h. & a bioavailability of 83% in 1.5 h. For such drug hydrophilic matrix systems are more suitable. Matrixing agents for developing the sustained released tablets. The dose of the conventional tablet available in market is tid or bid depending on the pharmacological condition of the patient. From the vast range of polymers in the hydrophilic systems hydroxylpropyl methyl cellulose is one of the most wide used semi synthetic polymer. The solubility of HPMC is PH-independent. It has been found as a versatile material for the formulation of soluble matrix tablets.. It is accepted excipient by FDA, is available easily & is a eco-friendly as well as economic to use.[3,4] The present work involves considearation of facotrs involved in designing of drug.

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