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DESIGN AND OPTIMIZATION OF IMMEDIATE RELEASE TABLETS OF EFAVIRENZ USING MICRO CRYSTALLINE CELLULOSE

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ABSTRACT

The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment. Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its case of ingestion, pain, avoidance, versatility and most importantly patient compliance. In these solid formulations do not require sterile conditions and are these for less expensive to manufacture. Immediate release tablets are designed to disintegrate and release their medication with no special rate controlling features such as special coating and other techniques. Efavirenz being discussed is under Non-Nucleoside Reverse transcriptase inhibitor (NNRTI) used as part of highly active antiretroviral therapy (HAART) for the treatment of a human immunodeficiency virus (HIV) type 1.

KEYWORDS: Efavirenz, HIV, NNRTI, DDS, HAART.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment.

Oral Drug Delivery Systems

Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipment's choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights. Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities.

Oral administration is the most popular route for systemic effects due to its case of ingestion, pain, avoidance, versatility and most importantly patient compliance. In these solid formulations do not require sterile conditions and are these for less expensive to manufacture.

The development of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for delivery poorly soluble drugs high molecular weight protein and peptide.

Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required.

Compressed Tablets

In addition to the medical agent compressed tablets are usually contain a number of pharmaceutical adjuvants, including the following:

Diluents or fillers, which add the necessary bulk to a formulation to prepare tablets of the desired size.

Binders or adhesives, which promote adhesion of the particles of formulation, allowing a granulation to be prepared and maintaining the integrity of the final tablet.

Disintegrants or disintegrating agents, which promote. Breakup of the tablets after administration to smaller particles for ready drug availability. Antiadhrents, glidants,

lubricants, or lubricating agents, which enhance the flow of the material into the tablet dies, minimize wear of punches and dies, prevent fill material from sticking you the punches and dies, and produce tablets with a sheen after compression, tablets maybe coated with various materials as described later. Quality standards and compendial requirements.

In addition to the apparent features of tablets, tablets must meet other physical specifications and quality standards.

These include criteria for weight, weight variation, content uniformity, thickness, hardness, disintegration, and dissolution. These factors must be controlled during production and verified after the production of each batch to ensure that established product quality standards.

EVALUATION OF TABLETS

Tablet weight and USP weight variation Test

The quantity of fill in the die of a table press determines the weight of the tablet.
Example; if a tablet is to contain 20 mg of drug substance and if 100,000 tablets are to be produced, 2000g of drug is included in the formula.

After the addition of the pharmaceutical additives, such as the diluent, disintegrant, lubricant, and binder, the formulation may weigh 20 kg, which means that each Tablet must weigh 200 mg for 20 mg of drug to be present.

Thus, the depth of fill in the tablet die must be adjusted to hold a volume of granulation weighing 200 mg.

During production, sample tablets are periodically removed for visual inspection and automated physical measurement.

Content uniformity

10 doses units are individually assayed for their content According to the method described in the individual monograph.

Unless otherwise stated in the monograph, the requirements for content uniformity are met if the amount of active ingredient in each dose unit lies within the range of 85% to 115% of the label claim and the standard deviation ls less than 6%.

If one more dosage units do not meet these criteria, additional tests as prescribed in the **USP.**

Tablet Thickness

Thickness of the tablet is determined by the diameter of the die, the amount of fill permitted to enter die, the compaction characteristics of fill material, and the force of pressure applied during compression.

To produce tablets of uniform thickness during and between batch productions for the same formulation, care must exercised to employ the same factors of fill, die, and pressure.

Hardness is perhaps the more important criterion, since it can effect disintegration and dissolution. Thus, for tablets of uniform thickness and hardness, it is doubly important to control pressure.

Tablet hardness and friability

It is fairly common for a tablet press to exert as little as 3000 and such much as 40,000 Ib of force in production of tablets.

Certain tablets, such as lozenges and buccal tablets, that are intended to dissolve slowly, internationally are made hard; other tablets, such as those for immediate drug release, are made soft.

In general, tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing.

Special dedicated hardness testers are used to measure the degree of force required to break a tablet. Multifractional automated equipment can determine weight, hardness, thickness, and diameter of the tablet.

A tablets durability may be determined through the use of a friabilator. this apparatus determines the tablets friability, or tendency to crumble, by allowing it to roll and fall within the drum.

Resistance to loss of weight indicates the tablets ability to withstand abrasion in handling, packaging, and shipment. A maximum weight loss of no more then 1% generally is considered accepted for most products

Tablet Disintegration

For the medical agent in a tablet to become fully available for absorption, the tablets must first disintegrate and discharge the drug to a body fluids for dissolution. Tablet disintegrating also is important for tablets containing medicinal agents (such as antacids and antidiarrheal) that are not intended to be absorbed but rather to act locally within the GIT. In these instances, tablet disintegration provides drug particles with an increased surface area for activity within the GIT. All USP tablets must pass a test for disintegration, which is conducted in vitro using a testing approaches such as the one. The approaches consists of basket and rack assembly containing six opened transparent tubes of USP specified dimensions, held vertically upon a 10 mesh stainless steel wire screen. Enteric coated tablets are similarly tested except that tablets are tested in stimulated gastric fluid for 1 hour after which no sign of disintegration. They are then actively immersed in the stimulated intestinal fluid for the time stated in individual monograph, which time the tablets disintegrate completely for a positive test.

Tablet Dissolution

In vitro dissolution testing of solid dosage forms is important for a number of reasons (5).

1. It guides formulation and production development towards product optimization. Dissolution studies in early stages of a products development allow differentiation b/w formulations and correlations identified with in vitro bioavailability data.
2. Manufacturing may be monitored by dissolution testing as component of the overall quality assurance program. The conduct of such testing from early product development through approval and commercial production.
3. Constituents in vitro dissolution testing ensures bio equivalence from batch to batch. In ascending such bioequivalence, the U.S food and drug administration (FDA) allows manufacturers to examine scalp up batches of 10% proposed size of actual production.
4. It is requirement of regulatory approval of marketing for products registered with the FDA and regulatory agencies of other countries. NDS are submitted to FDA contain in vitro dissolution data generally obtained batches used in pivotal clinical and bio availability studies and human studies conducted during product development. USP Specifications for all subsequent batches and bioequivalent products.

The goal of in-vitro dissolution testing is to provide inosfar as is possible a reasonable prediction of or correlation with the product in vivo bio-availability. The system relates combination of a drug's solubility and it's intestinal permeability as a possible basis for

predicting the likelihood of achieving a successful in vivo - in-vitro correlation. Considered are drugs determined to have

High solubility and high permeability

Low solubility and High permeability

High solubility and low permeability

Low solubility and low permeability

For a high- solubility and high-permeability drug, an IVIVC may be expected if the dissolution rate is slower than the rate of gastric emptying.

A number of formulation and manufacturing factors can affect the disintegration and dissolution of a tablet, including particle size of the drug substance; solubility and hygroscopity of the formulation type and concentration of the disintegrant, binder, and lubricant; manufacturing method, particularly the compactactness of the granulation and compression force usedin tableting; and any process variables.

The equipment consists of a variable speed stirrer motor, a cylindrical stainless steel basket on a stirrer shaft, a 1000-ml vessel of glass or other inert transparent material fitted with a cover having a center port for the shaft of the stirrer and three additional ports, a water bath to maintain the temperature of the dissolution medium in the vessel.

Definition

Immediate release tablets are designed to disintegrate and release their medication with no special rate controlling features such as special coating and other techniques.

Efavirenz being discussed is under Non-Nucleoside Reverse transcriptase inhibitor (NNRTI) used as part of highly active antiretroviral therapy (HAART) for the treatment of a human immunodeficiency virus (HIV) type 1.

Human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/AIDS) is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV). During the initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses, it interferes more and more with the immune system, making the person much more likely to get infections, including opportunistic infections and tumors that do not usually affect people who have working immune systems.

HIV is transmitted primarily via unprotected sexual intercourse, contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding. Some bodily fluids, such as saliva and tears, do not transmit HIV.

Virology

HIV is the cause of the spectrum of disease known as HIV/AIDS. HIV is a retrovirus that primarily infects components of the human immune system such as $CD4^+$ T cells, macrophages and dendritic cells. It directly and indirectly destroys $CD4^+$ T cells.

HIV is a member of the genus *Lentivirus*, part of the family *Retroviridae*. Lentiviruses share many morphological and biological characteristics. Many species of mammals are infected by lentiviruses, which are characteristically responsible for long-duration illnesses with a long incubation period. Lentiviruses are transmitted as single-stranded, positive-sense, enveloped.

LITERATURE REVIEW

1. ***Snehal b. Kulkarni, ashutosh tripathi.*** *et al.,* **(2019).** Immediate release tablets of efavirenz were successfully enhanced the solubility by using micellar solubilization technique to improve solubility and dissolution rate of poorly water soluble efavirenz. Drug - excipient compatibility study was performed by using FTIR and DSC. Various post compression parameter like general appearance, thickness, hardness, weight variation, uniformity content, disintegration time and in-vitro drug release were determined. Among these coated F9 batch gave best result. Coated F9 batch showed better disintegration time 1:30 and in vitro drug release 98.99%.
2. ***Adele S. Benzaken*** *et al.,* **(2019).** Antiretroviral therapy composed of the most modern art drugs, which is largely disseminated to the HIV population through a unified, universal and free charge public health system. HIV transmitted and acquired drug resistance are also contained to low to moderate levels, resulted from the rational distribution and use of ARV drugs in the country. Despite the successful price negotiations with international pharmaceutical ARV manufacturers and significant local production of ARVs, the costs of a universally free health system for HIV/AIDS.
3. ***Jessica Yee; charles V. Preuss.*** *et al.,* **(may 30,2019).** Efavirenz therapy, as with all ART, requires an inter-professional team approach, including physicians, specialists, specially trained nurses, and pharmacist, all collaborating across disciplines to achieve optimal patient results.

4. ***Marwan Almoiliqy and Puneet Utreja***. *et al.,* **(2019).** Conventional drug delivery involved in antiretroviral, such as compressed tablet for oral administration solution for Iv administration, such as dosage form have several limitations such as requirement of high dosage, dose, frequency, low effectively, high adverse effects. In the last decades different novel and controlled delivery systems are being investigated to overcome the limitations of conventional drug delivery, to decrease drug degradation, to minimize the side effects and side effects to improve drug bio availability. As conclusion of this review paper introduce the most recent approaches of drug delivery systems for anti HIV drugs.
5. ***Sanju Dhawan.*** *et al.,* **(2018).** formulated solid lipid nanoparticles of quercetin were formulated using Comprisal as the lipid and Tween 80 as the surfactant through a micro emulsification technique, and optimized employing a 3(2) central composite design (CCD). Selection of the optimized SLN formulation, using brute-force methodology and overlay plots, was based on its efficiency of entrapping quercetin inside the lipophilic core, particle size, surface charge potential and ability of the SLNs to release the entrapped drug completely. The optimized formulation was subjected to various in-vivo behavioural and biochemical studies in Wister rats. The studies demonstrated successful targeting of the potent natural antioxidant, quercetin, to brain as a novel strategy having significant therapeutic potential to treat Alzheimer's disease.
6. ***Abhay Guptha.*** *et al.,* **(2016).** studied correlation between disintegration and dissolution for immediate release tablets containing a high solubility drug and to identify formulations where disintegration test, instead of the dissolution test, may be used as the acceptance criteria based on International Conference on Harmonization Q6A guidelines. A statistical design of experiments was used to study the effect of filler, binder, disintegrating agent, and tablet hardness on the disintegration and dissolution of verapamil hydrochloride tablets. At constant filler or disintegrating agent, an increase in disintegration time led to slower tablet dissolution.

Potur Rg. *et al.,* **(2016).** formulated immediate release tablets of Metformin hydrochloride and Gilbenclamide by using Design of Experiment approach. The investigation was based on the latest quality by design principles, using the design of experiments technique. The aim was to attain an immediate release formulation of metformin hydrochloride and glibenclamide and to optimize the delivery of these two different antidiabetic agents within a single-tablet combination. For the assessment of the level of fitting and Anova tests were

performed. The desired drug release pattern can be achieved by using a proper percent of superdesintegrant, by reducing the filler and by the presence of extragranulary added binder.

AIM AND OBJECTIVES

Aim

The main aim of the work is to optimize the immediate release tablets of EFAVAVIRENZ drug also used in treatment of HIV/AIDS by Design of Experiments so as to overcome the drawbacks of OVAT.

Objectives

Optimization of formulation using Design of experiment
(DOE).
Physical and In-vitro evaluation of optimized formulation for the release characteristics.

DRUG PROFILE

EFAVIRENZ

Molecular mass	**315.675 g/mol**
Route of administration	Oral
Uses	Treatment of HIV infection
Description	Efavirenz is a white to off-white crystalline powder
Solubility	Insoluble in water n soluble in lower alcohol like methanol
Strengths	600mg
Melting Point	138-14 $2^{o}C$
Storage Conditions	should be stored under normal conditions

- Sold under the brand names sustiva among other is an antiretroviral medication used to treat and prevent HIV/AIDS.
- It may be used for prevention after a needle stick injury or other potential exposure.
- It is sold both by itself and in combination as efavirenz/emtricitabine/tenofivir.
- It is taken by mouth once a day.

❖ **Common side effects**: rash, nausea, headache, feeling tried and trouble sleeping. Some of the rashes may be serious such as Stevens - Johnson syndrome Other serious side effects include depression thoughts of suicide, liver problems and seizures. It is not safe for use during pregnancy.

❖ **Medical uses:** Efavirenz is also used in combination with other antiretroviral agents as part of an expanded post- exposure prophylaxis regimen to reduce the risk of HIV infection in people exposed to a significant risk.

Bio-availability: - 40-45percent.

Protein binding: - 99.5 - 99.75 percent.

Metabolism: - Hepatic.

Onset of action: - 3-5hrs.

Elimination Half-life:- 40 - 55hrs.

Excretion: - Urine (14-34percent).

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