FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLETS OF AN ANTI RETROVIRAL DRUG

A dissertation submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI- 600 032.

In partial fulfillment of the requirements for the award of Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted By

Reg No: 26118165

DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

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Under the guidance of

Prof.K.shahul Hameed Maraicar, M.Pharm., (Ph.D).,

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CERTIFICATE

This is to certify that the dissertation entitled **"Formulation and evaluation of extended release tablets of an anti retroviral drug"** submitted by **M. Swathik Srinivasan** (Reg No: 26118165) in partial fulfillment for the award of degree of Master of Pharmacy to the Tamilnadu Dr. M.G.R Medical University, Chennai is an independent bonafide work of the candidate carried out under my guidance in the Department of Pharmaceutics, Edayathangudy.G.S Pillay College of Pharmacy during the academic year 2012-2013.

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Place: Nagapattinam (**Prof.Dr.D.Babu Ananth, M.Pharm., Ph.D.,**)

Date:

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INDEX

TABLETS

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose and at a particular frequency. Thus drug may be administered by variety of routes in a variety of dosage forms.

Drugs are more frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost.

Drugs are administered by the oral route in a variety of pharmaceutical dosage forms. The most popular are tablets, capsules, suspensions, various pharmaceutical solutions. Among the drugs that are administered orally, solid dosage form represent the preferred class of product. They are versatile, flexible in dosage strength, relatively stable, present lesser problem in formulation, packaging and it is convenient to manufacture, store, handle and use. Solid dosage form provides best protection to the drug against light, temperature, humidity, oxygen, and stress during transportation. Amongst the solid oral dosage form tablets are widely used.

Tablets may be defined as solid pharmaceutical dosage forms containing medicament with or without suitable excipients and prepared either by compression or molding.

ADVANTAGES OF TABLET

Some of the potential advantages of tablets are as follows.

1. They are the unit dosage form having greatest capabilities amongst all the oral dosage form for the dose precision and least content variability.
2. Their cost is lowest amongst all the oral dosage forms.
3. They are the lightest and the most compact amongst all the oral dosage form.
4. They are easiest and cheapest for packaging and transportation.
5. They lend themselves to certain special release profile products such as enteric or delayed release products.
6. Tablets are better suited to large-scale production than other unit oral dosage forms.
7. They have the best-combined properties of chemical, mechanical, microbiological stability amongst all the oral dosage forms.

Disadvantages:

I. It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
II. Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.
III. Slow onset of action as compared to parenterals, liquid orals and capsules.
IV. The amount of liquid drug (e.g. Vitamin E, Simethicone) that can be trapped into a tablet is very less.
V. Difficult to swallow for kids, terminally ill and geriatric patients.
VI. Patients undergoing radiotherapy cannot swallow tablet.

1.1.1. TYPES AND CLASSES OF TABLETS

A. *Oral tablet for ingestion*

- Compressed tablets
- Multiple compressed tablets
- Sugar coated
- Film coated tablets
- Chewable tablets
- Delayed action tablets

B. *Tablet used in oral cavity*

- Buccal tablets
- Sublingual tablets
- Troches and Lozenges
- Dental cones

C. *Tablet administered by other routes*

- Implantation tablets
- Vaginal tablets

D. *Tablets used to prepare solution*

- Effervescent tablets
- Dispensing tablets
- Hypodermic tablets

A. Oral tablet for ingestion:

Compressed tablets: Standard uncoated tablets are manufactured by compression. The general methods are by wet granulation, dry granulation or direct compression, used for rapid disintegration and drug release. Both type of action – systemic effect and local effect.

Multiple compressed Tablets

The tablet-manufacturing machine is generally operated at relatively lower speeds than for standard compression tablet. There are three categories under this class:

- **Layered tablets** – two to three component systems.
- **Compression coated tablets** – tablet within a tablet.
- **Inlay tablet** – coat partially surrounding the core.

Repeat action tablet: Sugar coated or multiple compressed tablets are used for this purpose .The core tablet is usually coated with shellac or an enteric polymer so that it will not release its drug in stomach but intestine.

Delayed action and enteric-coated tablet: This dosage form is intended to release the drug after some time delay or after the tablet has passed one part of the GIT into another. All enteric coated tablets are type of delayed action tablet but all delayed action tablets are not enteric or not intended to produce enteric action.

Sugar coated tablet: Primary role is to produce an elegant, glossy, easy to swallow, widely utilized in preparing multivitamin and multivitamin mineral combination.

Film coated tablet: One type of coated tablet in which drug is not required in coating. This is an attractive method within one or two hours. Polymers such as hydroxypropylcellulose, hydroxypropylmethyl cellulose, and colloidal dispersion of ethyl cellulose are commonly used. A 30% dispersion of ethyl cellulose is known as aqua coat. Advantage of film coated over sugar coated tablets is better mechanical strength and flexibility of the coating, little increase in tablet weight.

Chewable tablet: These are intended to be chewed in the mouth before swallowing. Used for large tablet of antacid, bitter or foul testing drugs are not suitable for this type tablet.

B. Tablets used in oral cavity:

Buccal and sublingual tablet: These tablets are small, flat and are intended to be held between the cheek and teeth or in cheek pouch (Buccal tablet) or below the tongue (sublingual tablet). Drugs used by this route are for quick systematic action. The tablets are designed not to be disintegrate but slowly dissolve.

Troches and lozenges: These are used in the oral cavity to exert local effect in mouth and throat. They are commonly used to treat sore throat or to control coughing in

common cold. They may contain local **anesthetics**, **antiseptic**, **antibacterial agents**, **demulcents**, **astringent** and **antitussive**. The tablets are dissolving slowly over a period of 30 minutes.

Dental cone: These tablets are designed to be placed in the empty socket remaining after tooth extraction. Main purpose is to prevent microbial growth in the socket or to reduce bleeding.

C. Tablets administered by other route:

Implantation tablets: These are designed for substances implantation to provide prolonged drug effect from one month to a year; tablets are usually small, cylindrical not more than 8mm length. These methods require special surgical technique for implantation and discontinuation of therapy. Generally used for administration of growth hormone to food producing animal.

Vaginal tablets: These are designed to undergo slow dissolution and drug release in vaginal cavity. Tablets are wide or pear shaped, used to antibacterial, antiseptic and astringent to treat vaginal infection.

D. Tablets used to prepare solution:

Effervescent tablets: Tablets are designed to produce a solution rapidly with the release of carbon dioxide. The tablets are prepared by compressing the active ingredient with mixture of organic acid such as citric acid or tartaric acid and sodium bicarbonate.

Dispersing tablets: Tablets are intended to be added to a given volume of water to produce a solution of a given drug concentration.

Hypodermic tablets: These tablets are composed of one or more drugs with water-soluble ingredients. Drug is added to sterile water to prepare sterile solution, which is injectable.

Tablet triturates: Usually are made from moist materials using a triturate mold, which gives them the shape of cylinder. Such tablet must be completely and rapidly soluble.

1.1.2. COMMONLY USED EXCIPIENTS IN TABLET MANUFACTURING:

Excipient means any component other than the active pharmaceutical ingredient(s) intentionally added to the formulation of a dosage form. Many guidelines exist to aid in selection of nontoxic excipients such as IIG (Inactive Ingredient Guide), GRAS (Generally Regarded As Safe), Handbook of Pharmaceutical Excipients and others. While selecting excipients for any formulation following things should be considered wherever possible: keep the excipients to a minimum in number minimize the quantity of each excipient and multifunctional excipients may be given preference over unifunctional excipients.

Excipients play a crucial role in design of the delivery system, determining its quality and performance. Excipients though usually regarded as nontoxic there are examples of known excipient induced toxicities which include renal failure and death from diethylene glycol, osmotic diarrhea caused by ingested mannitol, hypersensitivity reactions from lanolin and cardio toxicity induced by propylene glycol.

Diluents or Fillers

Fillers are used to make tablets of sufficient size for easy handling by the patient and to facilitate production. Tablets containing a very potent active substance would be very small without additional excipients. Good filler will have good compactability and flow properties, acceptable taste, will be non-hygroscopic and preferably chemically inert. It may also be advantageous to have filler that fragments easily, since this counteracts the negative effects of lubricant additions to the formula.

E.g. mannitol, lactose, sorbitol, sucrose, and inositol, microcrystalline cellulose (Avicel®)

Binders or Granulating agents or Adhesives

A material with a high bonding ability can be used as a binder to increase the mechanical strength of the tablet. A binder is usually a ductile material prone to undergo plastic (irreversible) deformation. Typically, binders are polymeric materials, often with disordered solid state structures. Of special importance is the deformability of the peripheral parts (asperities and protrusions) of the binder particles .Thereby, this group of materials has the capacity of reducing inter particulate distances within the tablet, improving bond formation. If the entire bulk of the binder particles undergo extensive plastic deformation during compression, the inter particular voids will, at least partly, be filled and the tablet porosity will decrease. This increases the contact area between the particles, which promotes the creation of inter particular bonds and subsequently increases the tablet strength. However, the effect of the binder depends on both its own properties and those of the other compounds within the tablet. A binder is often added to the granulation liquid during wet granulation to improve the cohesiveness and compactability of the powder particles, which assists formation of agglomerates or granules. It is commonly accepted that binders added in dissolved

form, during a granulation process, is more effective than used in dry powder form during direct compression.

E.g. Starch, gelatin, sucrose, glucose, dextrose and lactose are frequently used as binders. Natural and synthetic gums that have been used include acacia, sodium alginate, ghatti gum, CMC, veegum etc. Starch paste in varying concentration from 10-20% is used as a binder. HPMC, which is more soluble in cold water as compared to hot water, is also used in special cases.

Glidant, antiadherent and lubricant (Antifrictional Agents):

Glidants are added to increase the flowability of the powder mass, reduce inter particular friction and improve powder flow in the hopper shoe and die of the tableting machine. An anti adherent can be added to decrease sticking of the powder to the faces of the punches and the die walls during compaction, and a lubricant is added to decrease friction between powder and die, facilitating ejection of the tablet from the die. However, addition of lubricants (here used as a collective term, also including glidants and anti adherents) can have negative effects on tablet strength, since the lubricant often reduces the creation of inter particular bonds. Further, lubricants can also slow the drug dissolution process by introducing hydrophobic films around drug and excipient particles. These negative effects are especially pronounced when long mixing times are required. Therefore, the amount of lubricants should be kept relatively low and the mixing procedure kept short, to avoid a homogenous distribution of lubricant throughout the powder mass. An alternative approach could then be to admix granulated qualities of lubricant. Commonly used lubricants are talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil and PEG. The method of adding lubricant is an important factor for satisfactory results. The quantity of lubricant significantly varies from 0.1 to 5%. The additions of lubricant to granules in the form of emulsion or suspension are used to

reduce the processing time. The primary problem in the preparation of water soluble tablet is the selection of satisfactory lubricant. Soluble lubricants include Sodium benzoate, sodium acetate, sodium chloride and carbowax 4000.

The most commonly used glidants are colloidal silicon dioxide (Cabosil®, Cabot®) and asbestos free talc. They are used in concentration less than 1%. Talc is also used and may serve the dual purpose of lubricant/glidant.

Disintegrants

Disintegrating agent: A disintegrant is normally added to facilitate the rupture of bonds and subsequent disintegration of the tablets. This increases the surface area of the drug exposed to the gastrointestinal fluid; incomplete disintegration can result in incomplete absorption or a delay in the onset of action of the drug. There are several types of disintegrants, acting with different mechanisms:

- Promotion of the uptake of aqueous liquids by capillary forces,
- Swelling in contact with water,
- Release of gases when in contact with water and
- Destruction of the binder by enzymatic action.

Starch is a traditional disintegrant; the concentration of starch in a conventional tablet formulation is normally up to 10% w/w. The starch particles swell moderately in contact with water, and the tablet disrupts. So-called superdisintegrants are now commonly used; since these act primarily by extensive swelling, they are effective in only small quantities. Cross-linked sodium carboxymethyl cellulose (e.g. Ac-Di-Sol®), which is effective in concentrations of 2-4%, is a commonly used superdisintegrant. Larger particles of disintegrants have been found to swell to a

greater extent and with a faster rate than finer particles, resulting in more effective disintegration.

Other ingredients like veegum, methyl cellulose, agar, bentonite, cellulose, citrus pulp and CMC are also used. They are mostly added into two portions, one part is added prior to granulation and the remainder is mixed with the lubricant and finally both are mixed just before the compression.

Miscellaneous

- Wetting agents
- Dissolution retardants
- Dissolution enhancers
- Buffers
- Antioxidants
- Chelating agents
- Preservatives
- Colouring agents
- Flavors
- Sweeteners

1.1.3. TABLET: MANUFACTURING METHODS

A. Direct Compression

B. Granulation

A. Direct compression

Processing steps are**:**

Raw material →weighing → screening → mixing → compression.

In early days, most of the tablets require granulation of the powdered Active Pharmaceutical Ingredient (API) and Excipients. At the availability of new excipients or modified form of old excipients and the invention of new tablet machinery or modification of old tablet machinery provides an ease in manufacturing of tablets by simple procedure of direct compression.

Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression. Thus offering advantage particularly in terms of speedy production. Because it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability.

Merits:

- Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.