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A REVIEW ARTICLE ON DELAYED RELEASE TABLETS

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Abstract:

A delayed release dosage form is designed/intended to release the drug from the dosage form at a time other than promptly after administration or after the tablet pass GI tract. A common example for the delayed release tablets is Enteric coated tablet such that all the enteric coated tablets are Delayed release tablet's but not all delayed release tablets are enteric coated. Delayed release dosage form is best formulations which are used for drugs that are destroyed in the gastric fluids, or cause gastric irritation, or are absorbed preferentially in the intestine. Such preparations contain an alkaline core material comprising the active substance, a separating layer and enteric coating layer. This review focus on the types of ER tablets, Method of preparation of tablets, defects in tablets, mechanisms involved for release of drug in extended release tablets and advantages of DR tablets over conventional tablet.

Key word: Extended release, Tablet, Concentration, Defects, Granules, Coating etc.,

INTRODUCTION:

1. ORAL DRUG DELIVERY:

Oral route is the most preferred route of drug administration among all routes that have been explored for the systemic delivery of drug via various pharmaceutical products of different dosage form as they being user friendly route of administration. Powders, pills, cachets, capsules or tablets administered orally as Solid medicaments. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms. The stringent formulation requirements of modern medicaments, the many advantages of tablet and capsule medication and currently they account for well over two third of the total number and cost of medicines produced all over the world.

2. TABLETS

Tablets are solid dosage forms usually obtained by single or multiple compression of powders or granules. They are uncoated or coated. Tablets are normally right circular solid cylinders, the end surfaces of which are flat or convex and the edges of which may be bevelled. Tablets containing active ingredients having a narrow therapeutic window should generally not be presented with break-marks for subdivision. Tablets containing active ingredients having a narrow therapeutic window should generally not be presented with break-marks for subdivision.

Advantages:

1. The unit dosage form having greatest capabilities amongst all the oral dosage form.
2. Low cost, Lighter and compact.
4. Easiest and cheapest to package and strip.
5. Easy to swallowing with least tendency for hang- up.
6. Sustained release product is possible by enteric coating.
7. Objectionable odour and bitter taste can be masked by coating technique.

Disadvantages:

1. When the dose of drug is large, tablets might be too big for children & adults to swallow.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT.

3. ADDITIVES USED IN TABLETS

1. **Diluents:**

Diluents are normally used as a filler, in order to increase the bulk of the tablet. Example for diluents includes lactose, starch, mannitol etc.

2. **Binders and adhesives:**

Binders are either added in wet form or dry form, which serves as a binding agent in the formulation. The type of the binder added vary with the formulation. The amount of binder added and type of binder influences the tablet properties.

3. **Disintegrants:**

These are added, in order to aid in disintegration or breaking of tablet in GIT. Disintegrants like starch, clays, cellulose are used.

4. **Lubricants:**

Lubricants prevents sticking of tablets to dies and punches. : Talc, stearic acid, magnesium stearate.

5. **Glidants:**

They reduce the friction, thus aid in free flow of granules or powder. Commonly used glidants includes starch and talc.

6. **Colouring agents:**

Helps in elegant appearance of the product. Examples of colouring agents like brilliant blue.

7. **Sweeting agent:**

Sweeting agent are added in order to mask the bitter taste of the drug. Ex: aspartame, mannitol, lactose.

8. **Flavouring agent:**

Added in order to impart flavour or odour to the table formulation. Ex: Menthol, clove oil, vanilla.

4. TYPES OF TABLETS

1. Tablet ingested orally
    - a. Compressed tablets
    - b. Multiple compressed tablets
        - i. Layered tablet
        - ii. Compression coated tablet
    - c. Repeat action tablet
    - d. Delayed action and enteric coated tablet
    - e. Sugar and chocolate coated tablet
    - f. Film coated tablet
    - g. Chewable tablet
2. Tablet used in the oral cavity
    - a. Buccal tablet
    - b. Sublingual tablet
    - c. Troches and lozenge
    - d. Dental cones
3. Tablet administrated by other routes

a. Implantable tablet
b. Vaginal tablet

4. Tablet use to prepare solution
   a. Effervescent tablet
   b. Dispensing tablet
   c. Hypodermic tablet
   d. Tablet triturate.

5. MODIFIED DRUG DELIVERY SYSTEM:

Modified release DDS include systems with pH–dependent, extended, delayed or pulsed drug release. Sustained, extended or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery.

6. DELAYED RELEASE SYSTEM:

The design of such system involves release of drugs only at a site in the gastrointestinal tract. The drugs contained in such a system are those that are:

a) Destroyed in the stomach or by intestinal enzymes.
b) Known to cause gastric distress.
c) Absorbed from a specific intestinal site.
d) Meant to exert local effect at a specific gastrointestinal site.

The two types of delayed release systems are:

Intestinal release systems:

A drug may be enteric coated for intestinal release for several known reasons such as to prevent gastric irritation, prevent destabilization in gastric pH etc.

Colonic release systems:

Drugs are poorly absorbed through colon but may be delivered to such a site for two reasons.

a) Local action in the treatment of ulcerative colitis.
b) Systemic absorption of protein and peptide drugs

Delayed release drug delivery systems (DRDDS) indicates that the drug is not released immediately but is being released at a later time. Therefore, the formulation is designed in order to increase the stability of the drug and optimizing the therapeutic effect of a drug by controlling its release in the body in the lower part of the gastrointestinal tract.

These formulations are basically aimed to deliver the drug to a particular area of gastrointestinal tract, instead of delivering the drug immediately after ingestion.

In general, delayed delivery systems attempts to: -

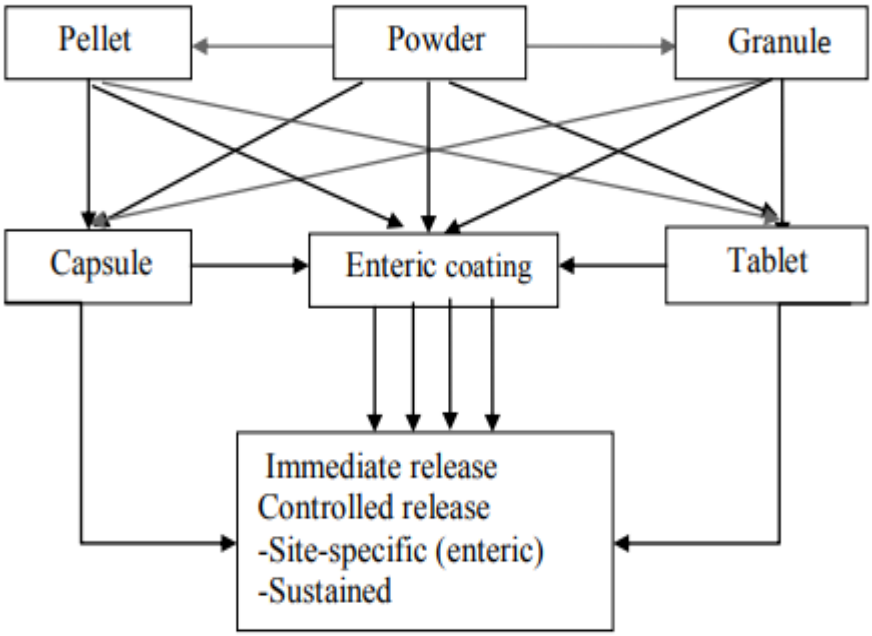
a) Delay the drug action and effective drug level in the body with minimization of undesirable side effects associated with kinetic pattern.

b) Drug action can be localized using delayed release formulation, as they delay the delivery of drug using appropriate polymers and localize drug action by spatial placement in the system.

c) Various carriers or chemical dramatizations are used in order to target particular type of cell for drug action.

In order to achieve constant plasma concentration, the most common conventional method used is intravenous infusion. Sometimes Oral & Transdermal route are preferred as it would be inconvenient for most of the therapeutic situation.

In a delayed release product one aims for release of drug at a later time in order to release the drug at a particular site and avoiding degradation of the drug at lower pH. Here, drug availability is controlled by the kinetics of drug release and as well absorption.



7. CLASSIFICATION OF DELAYED RELEASE SOLID ORAL DOSAGE FORMS:

Delayed release solid oral dosage forms are available either as single unit (non divided formulations– tablets, capsules) or as multiple unit (divide formulations-pellets, mini -tablets) forms.

a) Single unit dosage forms:

The single-unit dosage forms usually refer to diffusion-controlled systems which include monolithic systems. Where the diffusion of the drug through polymer coating or layer of the system is the rate limiting step. However, generally, release of drugs will occur by a mixture of these two mechanisms.

b) Multi-unit dosage forms:

Types of multi-unit dosage forms comprise,

a. Granules

b. Pellets

c. Microparticles (microspheres or microcapsules) and Nanoparticles.

d. Mini tablets and mini depots (dispersed and distributed throughout the gastro intestinal tract when the capsule or tablet disintegrates).

e. Multi-unit tablets (divided at ingestion without loss of the depot effect, as the sub unit act as a self-contained depots).

Therapeutic Advantage of Multi units over single units:

- When taken orally, multi-unit dosage forms
- Disperse freely in the gastro intestinal tract.
- Provides less risk of dose dumping.
- Reduces localized concentration of irritative drugs.
- Reduce risk of inter and intra patient variability.
- Improves safety and efficacy of a drug.

8. ENTERIC COATING:

A tablet that has a special outer covering designed to dissolve in the small intestine. Once the enteric-coating is dissolved the tablet disintegrates and drug can be absorbed by the patient.

An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed. The word “enteric” indicates small intestine; therefore, before the reaches the small

intestine enteric coating prevent release of medication. At low pH, the enteric coated polymers remain unionize and therefore remain insoluble.

Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibers.

There are four reasons for coating a tablet or capsule ingredient:

- Protection of active pharmaceutical ingredients, from the acidic environment (e.g. enzymes and certain antibiotics).
- To prevent gastric distress or nausea from a drug due to irritation (e.g. sodium salicylate).

9. MANUFACTURING OF TABLETS:

1. Dispensing (weighing and measuring):

Dispensing is the first step in any pharmaceutical manufacturing process. Dispensing is one of the most critical steps in pharmaceutical manufacturing; as during this step, the weight of each ingredient in the mixture is determined according to dose.

2. Sizing:

The sizing (size reduction, milling, crushing, grinding, pulverization) is an impotent step (unit operation) involved in the tablet manufacturing.

Advantages:

- Improved flow properties of raw materials.
- Improved colour and/or active ingredient dispersion in tablet excipients.
- Uniformly sized wet granulation to promote uniform drying.

3. Powder blending:

The successful mixing of powder is acknowledged to be more difficult unit operation because, unlike the situation with liquid, perfect homogeneity is practically unattainable.

4. Granulation:

Following particle size reduction and blending, the formulation may be granulated, which provides homogeneity of drug distribution in blend.

5. Drying:

Drying is a most important step in the formulation and development of pharmaceutical product. It is important to keep the residual moisture low enough to prevent product deterioration and ensure free flowing properties.

10. TECHNIQUES FOR TABLET PREPARATION:

a. Wet granulation method
b. Dry granulation method
c. Direct compression

a. Wet granulation method:

i. It's the foremost common and widely used method and involves various steps like weighing of ingredients, mixing, granulation, and screening of damp pass, drying, lubrication and compression of tablets.
ii. The active ingredient, diluent, disintegrants are blended together, then it's allowed to go through the sieve (sifting).
iii. Solutions of the binding agent are added to the initial mixture with stirring.
iv. The binding agents added should be sufficient, to avoid over wetting of the tablet.
v. Tray drying is most typical method of drying the tablet granules.
vi. After drying the granules, they're allowed to go through the screen, usually 60-100.

vii. After dry granulation, lubricant is added as fine powder, which is required for correct filling of the die cavity.

Important steps involved in wet granulation:

i. Mixing of drug(s) and excipients.
ii. Preparation of binder solution.
iii. Mixing of binder solution with powder mixture to create wet mass.
iv. Course screening of wet mass employing a suitable sieve (6-12 screens).
v. Drying of moist granules.
vi. Screening of dry granules through an appropriate sieve (14-20 screen).
vii. Mixing of screened granules with disintegrants, glidants, and lubricant.

Special wet granulation techniques:

i. High shear mixture granulation.
ii. Fluid bed granulation.
iii. Extrusion-spherization
iv. Spray drying.

b. Dry granulation method:

i. This method is employed for tablet preparation, just in case tablet ingredients are sensitive to moisture, or unable to with stand elevated temperatures.
ii. This, usually eliminates various steps, which involves slugging of the powder mass.
iii. The active ingredient, diluent and lubricant are blended together, to create the slug and it is skilled the mesh or through the mill, and also the remaining lubricant is added to the granulation, blended properly and compressed to create the tablets.

c. Direct compression:

i. Direct compression involves direct compressing the powdered material into tablets.
ii. This method is adopted, if drug constitutes major portion of tablet total weight.
iii. Tablets prepared by above method are subjected to compression machine which can be single station or multiple station.

• Advantages:

a. Direct compression is more efficient and economical process as compared to other processes, as it involves only dry blending and compaction.

b. The foremost important advantage of direct compression is that it's a cost-effective process reduced interval, reduced labour costs, fewer manufacturing steps, and fewer number of equipment's, less process validation, reduced consumption of power.

c. Elimination of warmth and moisture.

d. Ideal characteristics of tablets:

A. Should be free from defects like cracks, discoloration, chips etc.

B. Should ready to withstand mechanical stress

C. Physically and chemically stable.

e. Manufacturing defects in tablet compression:

During processing of tablets during compression, there several processing problems encountered such as: Picking, sticking, capping, lamination, mottling.

A. Picking: The tablet surface material could also be removed by a punch during compression leads to picking.

B. Sticking: Adhesion of tablet to the die wall, which can occur thanks to excessive moisture within the tablet.

C. Capping: It is partial or complete separation of tablet from the highest or bottom crowns of the tablet from the most body.

D. Lamination: Segregation of a tablet into two or more distinct layers. Capping and lamination may occur thanks to air entrapment during processing.

E. Mottling: Unequal distribution of color on tablet surface leads to mottling.

11.TABLET COATING:

- Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits that broadly ranges from facilitating product identification to modifying drug release from the dosage form.
- The tablet coating has number of benefits like masking odor, taste, color of the drug, providing physical and chemical protection to drug, Protecting drug from the gastric environment.
- Three primary components of tablet coating are tablet properties, coating process and coating composition.
- Tablets are usually coated in horizontal rotating pan with coating solution is either directly poured or sprayed on to them.
- The number of coating on the surface of a tablet is critical to the effectiveness of the oral dosage form.

12.EVALUATION PARAMETERS:

- Tablets when formulated may undergo physical and chemical changes, which may alter their bioavailability.
- Therefore, the tablets are to be evaluated before dispensing to ensure their stability and bioavailability throughout their shelf life.
- Evaluation of tablets can be carried out by the following test.

Pre-compression Parameters:

- Loss on drying.
- Bulk density.
- Tapped density.
- Carr's index.
- Hausner's ratio

Evaluation of Tablets:

- Tablet appearance.
- Hardness.
- Thickness.
- Friability Weight variation test.
- Disintegration test.
- Drug content.
- In-vitro Dissolution test.

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