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RESEARCH ARTICLE

INLAY TABLET: A NOVEL APPROACH IN ORAL DRUG DELIVERY

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Abstract

Introduction:-

Tablet as a dosage form

1. Tablet is a solid dosage forms each containing a unit dose of one or more medicaments with or without suitable excipients.
2. Tablets may be swallowed whole or being chewed. Some are dissolved or dispersed in water before administration. Some are put in oral cavity, where the active ingredient is liberated at a predetermined rate. Implants or passerines may also be presented in form of tablet. Tablet may vary in shape and differ greatly in size and weight depending on the amount of medicinal substance and the intended mode of administration.

Advantages

1. Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.
2. Accuracy of dose is maintained since tablet is a solid unit dosage form.Tailor made release profile can be achieved.
3. Longer expiry period and minimum microbial spillage owing to lower moisture content.
4. As tablet is not a sterile dosage form, stringent environmental conditions are not required in the tablet department.
5. Ease of packaging (blister or strip) and easy handling over liquid dosage form.
6. Easy to transport in bulk. Emergency supply supplies can be carried by patients.
7. Organoleptic properties (taste, appearance and odour) are best improved by coating of tablet.
8. Product identification is easy and markings done with the help of grooved punches and printing with edible ink.
9. Different types of tablets are available like buccal, floating, colon targeting, effervescent, dispersible, soluble, and chewable, etc.
10. In composition to parenterals dosage form, a doctor or a nurse is not required for administration. i.e. self administration is possible.
11. In comparison to capsules, tablets are more tamperproof.

Disadvantages

1. It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
2. Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.
3. Slow onset of action as compared to parenteral, liquid orals and capsules.
4. The amount of liquid drug (e.g. Vitamin E, Simethicone) that can be trapped into a tablet is very less.

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5. Difficult to swallow for kids, terminally ill and geriatric patients.
6. Patients undergoing radiotherapy cannot swallow tablet

Types Of Tablets [3]

I. Oral tablets for ingestion

1. Standard compressed tablets
2. Multiple compressed tablets

• Compression coated tablet
• Layered tablet

• Inlay tablet

1. Modified Release tablet
2. Delayed action tablet
3. Targeted tablet
   • Floating tablet
   • Colon targeting tablet

a) Chewable tablet g. Dispersible tablet

II. Tablets used in the oral cavity

1. Lozenges and troches
2. Sublingual tablet
3. Buccal tablet
4. Dental cones Introduction
5. Mouth dissolved tablet

III. Tablets administered by other routes

1. Vaginal tablet
2. Implants

IV. Tablets used to prepare solution

1. Effervescent tablet
2. Hypodermic tablet
3. Soluble tablet

With advancement in technology and increase in awareness towards modification in standard tablet to achieve better acceptability as well as bioavailability, newer and more efficient tablet dosage form are developed.

1. Bi-layer tablet
2. Multilayer tablet
3. Inlayer tablet
4. Inlay tablet

Inlay tablet

1. Inlay tablet is a type of layered tablet in which instead of the core tablet being completely surrounded by coating, top surface is completely exposed. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet. Inlay tablet is a type of layered tablet in which instead the core tablet being completely surrounded by coating and the top surface is completely exposed. During the compression, some coating material is displaced to form sides and compresses the whole tablet.
2. The main body portion may consist of uncoated granules which are compressed around the enteric coated inlay portion. In this modification of tablet the main body portion is first released and assimilated in the gastrointestinal tract while other the enteric coating protects the inlay portion of tablet for a predetermined period of time so as to provide time delayed or sustained medication.
3. The present invention of inlay tablet also teaches the use of dual retard technique to effectively control the release rate of active ingredient by using small quantity of release controlling agents.
4. Due to this dual retard technique the size of dosage form sufficiently reduces, which is convenient for swallowing.

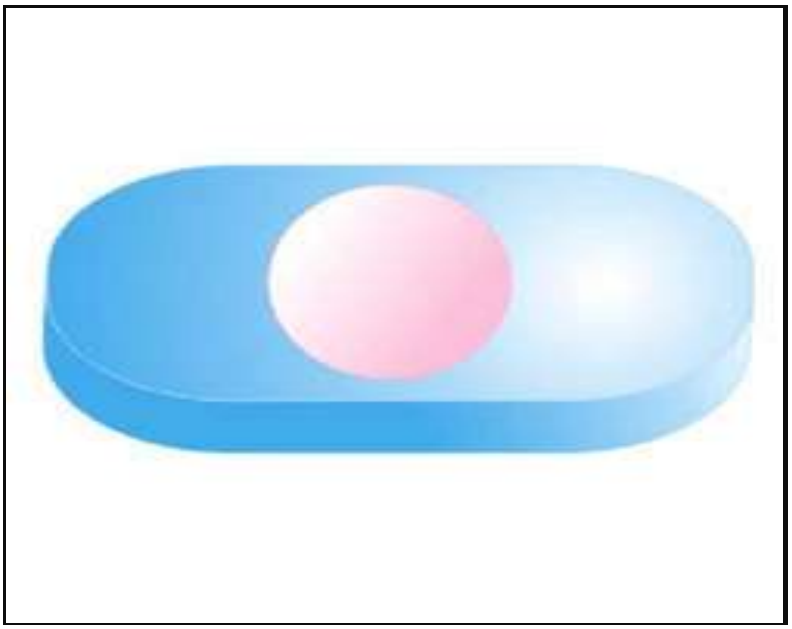

Figure 1:- Inlay tablet.

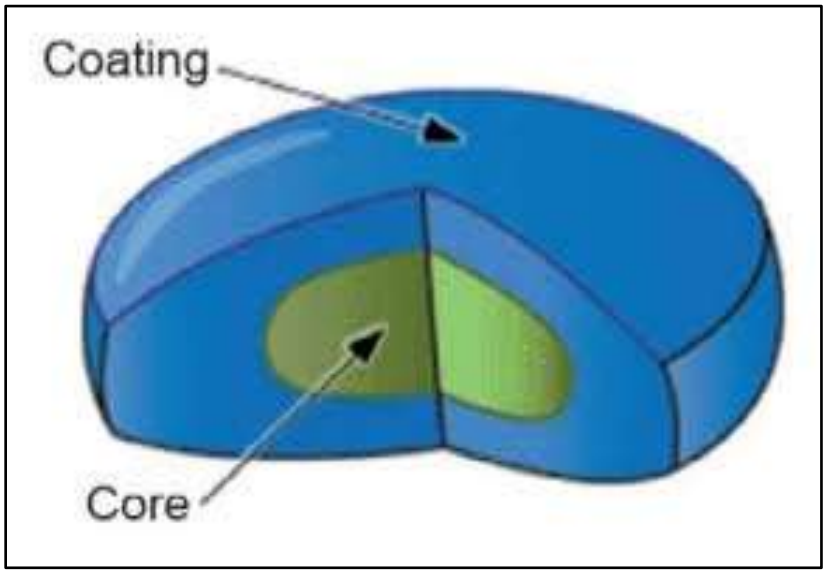

Figure 2:- Inner picture of inlay tablet.

Advantages

1. Dosage form comprising of an active ingredient as modified release and an active ingredient as immediate release can be prepared.
2. Plasma level can be maintained constant and within the therapeutic window throughout the period of treatment.
3. Adverse effects due to sub therapeutic plasma concentration can be avoided.
4. The burst effect, namely, large release within a short period of time, is common in highly soluble drugs, and shall be avoided, as it may lead to high concentration of active ingredients in the blood stream.
5. Has the ability to release soluble and insoluble drugs at a zero-order rate of release in dissolution media .Dosage frequency of highly water soluble drugs con be reduced providing same efficacy.
6. Tablets of different shape such as triangular, rectangular, or capsule shaped tablets can be manufactured.

Advantages of Inlay Tablets over Other Compressed Tablets

1. Less coating material is required.

2. Core is visible, so coreless tablets can be easily detected.
3. Reduction in coating forms a thinner tablet and thus freedom from capping of top coating.
4. The layered tablet is preferred over compression coated tablet as the surface contact is less and the production is simple and more rapid.

Preparation Of Inlay Tablet [4]

It can be done in the three steps;

1. Preparation of core tablet
2. Preparation of cup portion
3. Preparation of inlay tablet

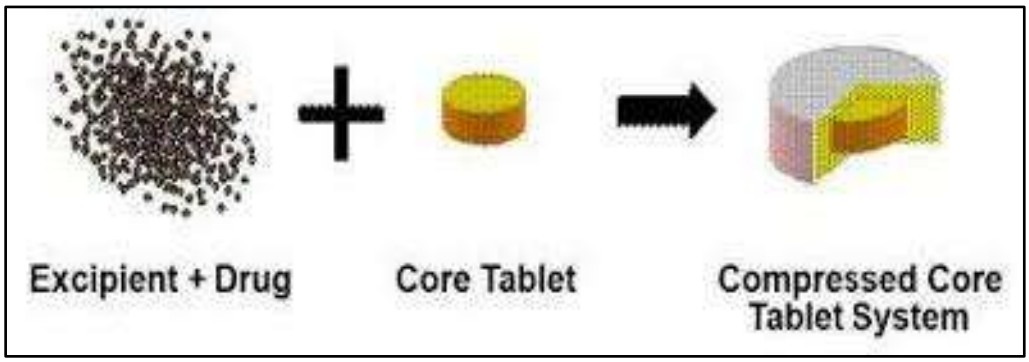

Figure 3:- Preparation of inlay tablet.

Sustained Release Oral Drug Delivery [5]

1. There is a continuously growing interest in the pharmaceutical industry for sustained release oral drug delivery systems. There is also a high interest for design a dosage formulation that allows high drug loading, particularly for actives with high water solubility.
2. This type of tablets are also called prolonged action tablet, repeat action tablet.
3. In this type of dosage forms, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response. The remaining fraction is released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess of time expected from usual single dose.
4. The basic rationale of a sustained drug delivery system is to optimize the biopharmaceuticals, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route.
5. Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect.
6. The sustained plasma drug levels provide by sustained release products often times eliminates the need for night dosing, which benefits not only the patients but the care given as well. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration.
7. Oral route has been the most popular and successfully used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system.
8. The sustained release systems for oral use are mostly solid and based on dissolution, diffusion or a combination of both mechanisms in the control of release of drugs.
9. They can often be taken less frequently than instant release formulations of the same drug, and that they keep steadier levels of the drug in the bloodstream.

Advantages of sustained release tablet

1. Reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery.

2. It would be a single dose for the duration of treatment whether it is for days or weeks, as with infection, or for the life time of the patient, as in hypertension or diabetes.
3. It should deliver the active entity directly to the site of action, minimizing or eliminating side effects.
4. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.
5. The safety margin of high potency drug can be increase and the incidence of both local and systemic adverse side effects can be reduced in sensitive patient.
6. If the active compound has a long half-life (over 6 hours), it is sustained on its own.
7. If the pharmacological activity of the active compound is not related to its blood levels, time releasing has no purpose.
8. If the absorption of the active compound involves an active transport, the development of a time-release product may be problematic.
9. Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity; otherwise, the risk is unwarranted and another mode of administration would be recommended.

Problems

1. More complicated formulation may be more erratic in result. A sustained release product may contain a larger dose, i.e. the dose for two or three (or more) 'normal' dosing intervals. A failure of the controlled release mechanism may result in release of a large toxic dose.
2. More expensive technology.

Immediate Release Oral Drug Delivery

1. Immediate release formulations are designed to disintegrate and release the drug in absence of any controlling features such as coatings or other formulation techniques.
2. Despite a rising interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole, disintegrating and releasing their medicaments rapidly in the gastrointestinal tract.
3. A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids.
4. Such a rapid rupture of the tablet matrix increases the surface area of the tablet particles, thereby increasing the rate of absorption of the active ingredient and producing the desired therapeutic action.
5. The proper choice of disintegrant and its consistency of performance are critical to formulation development of immediate release tablets. In the past, starch was one of the most widely used, inexpensive, and effective tablet disintegrant.
6. A high concentration of starch is required to bring about effective disintegration. Scientists search for disintegrating agents with efficient disintegrating properties at relatively low concentrations has led to the development of some new compounds with excellent disintegrating properties.

Problems faced during manufacturing of compression coated and inlay tablets

Preparation of core tablet can be done in similar manner as that of for other immediate release tablet after compression of core tablet, one has to place this core tablet in to middle of the outer layer powder blend or granules (cup portion) at the time of final compression manually or by use of mechanical device that can place a core tablet and them compression will carry out to prepare inlay or core in cup tablet. In this procedure there are certain drawbacks which are discussed below;

1. By any of above two methods placing of core tablet at exact centre of the outer layer is quite difficult, Thus misalignment of core tablet is quite often.
2. Uniform thickness of outer layer at every side of core tablet can’t be maintained.
3. If core tablet has to place manually, so it is time consuming and also required skilled personal.
4. As tablet has to place manually by hand; there may a chance of accidental hazards.
5. Hardness of core tablet is difficult to maintain.
6. Incorporation of poor compressible material as core tablet can’t be possible.
7. Preparation of inlay tablet or compression coated tablet with more than one core tablet is quite difficult or not possible.
8. Due to such manufacturing problems there may be a cost effective.

OSDRC (One Step Dry Coating Technique)

OSDRC is one step dry coating technology that opens a door to a new world of pharmaceutical tablet manufacturing.

1. OSDRC is the great innovation towards compression coated tablets and inlay tablets.
2. OSDRC provides unique, high quality products at low coast.
3. OSDRC is novel variable double punch tableting technology, simply by changing the punch of rotary tablet compression machine, product development scientists can create new formulations and tablet configurations that are not possible with current tablet manufacturing technology.

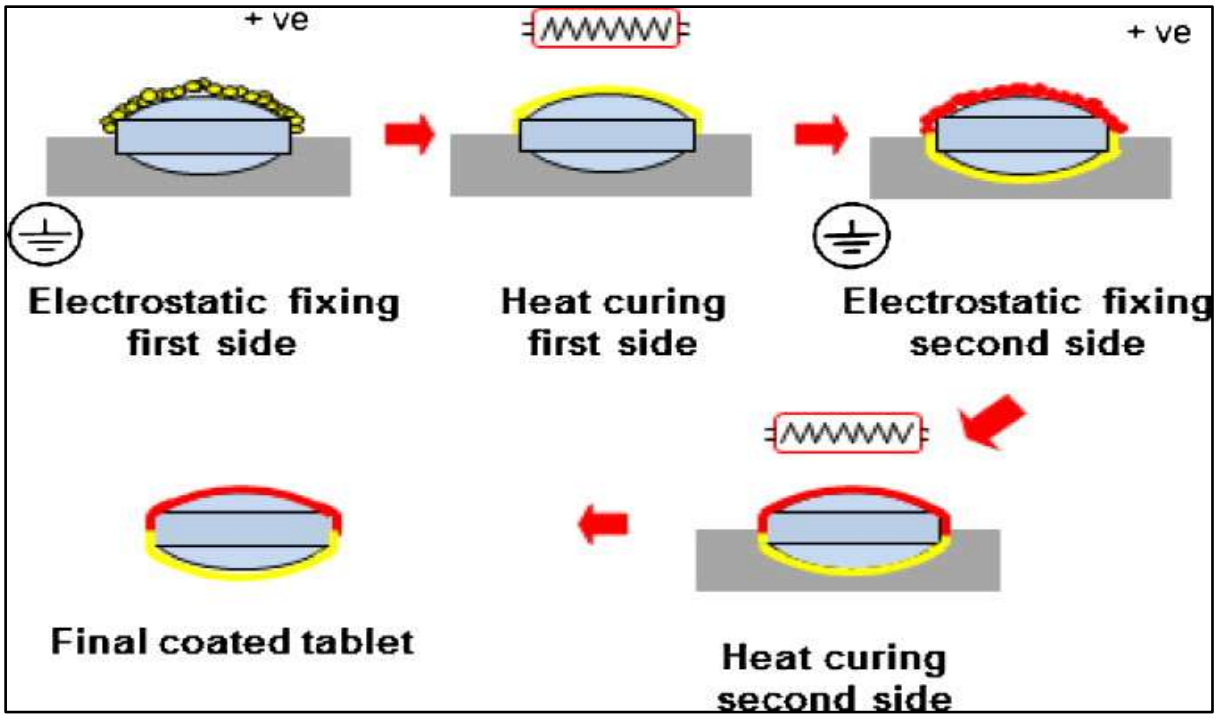

Figure 5:- One step dry coating technique.

Technology Attributes

1. OSDRC includes variable double punches those can manufacture compression coated or inlay tablet in a single step and can go beyond the parameters of current tableting machines.
2. This technology has ability to manufacture this compression coated and inlay tablet configuration at a rate of up to 100,000 tablets per hour with the avoidance of problem faced with conventional manufacturing process such as misalignment of cores, mass variability and cross contamination.
3. This variable double punch rotary tableting machine has up to 54 double punches and two or three feeders.
4. Because the tablet is prepared in a single step while the punches make one rotation on a turret there is no longer any need for separate step to deliver a core tablet. Because the core tablet is held in place by lower punch until the final compression, thus misalignment does not occur.
5. There are many types of tablet configurations can be made with OSDRC, depending only on double punch variations.
6. OSDRC allow the formulators to freely control the size, shape, thickness and position of core tablet as well as that of outer cup tablet.
7. This facilitates the manufacturing of completely new types of drug products that were not possible with conventional technology.
8. In addition of this one can include cameras, automation and advance in process control functions to provide precision, high speed tableting, also prevent cross contamination of powders, auto sampling and auto exclusion mechanism can meet Good Manufacturing Practice (GMP) standards.
9. This technology not only produces higher quality cored tablets than previously possible, but also enables development of various new solid dosage forms; it also allows product development scientists to device new novel dosage forms.

Controlled Release Tablets:
This technology facilitates the control of API by altering the thickness of outer coating. Capability to precisely position multiple cores allows the manufacture of tablet product with variety of pulsatile drug delivery profiles.

Divided Core Tablets:
There also possible to make divided tablets with separate cores in one step operation, which is not possible with current technology. For example divided enteric coated tablets are the world's first dividable enteric coated tablets. Dividable core tablets so called because the core fully encased in the coating even when the tablet is divide, even though the release profile is remain unaffected by dividing the table.

Cored Tablets with Poorly Compressible:
Cores By using this technology there is no need of separate manufacturing of core tablet even using of powders with poor compressibility as the core matrix. As it possible to directly encase core pharmaceutical ingredients with the outer covering, these ingredients can be used in oral rapid disintegration tablets. Pellets can also be used instead of powder as core material, drugs normally formulated as capsule dosage form can be formulated as tablet dosage form.

Sugar and Film Coating
It can be Replaced Tablet with extremely thin coat can be produce in one step, thus sugar and film coating can be replaced which substantially reduce manufacturing steps and cost. Core and Coat Shapes are also Variable The shape, thickness and tablet configuration of core and coat can be varied simply by changing the punches.

Advantages of OSDRC
- The OSDRC is rotary tableting machine with variable double punch configuration facilitate single step manufacturing of pharmaceutical products.
- In addition to commercial production of compression coated and inlay tablet it is also ideal for manufacturing a variety of high quality pharmaceutical product at low cost.
- In addition to overcome of misalignment of core tablet this technology allows placement of any number of cores of any shape into the tablet just where they positioned for optimum drug delivery of API such as divide tablets with two cores, pulsatiles tablets with three cores and other combination products.
- Core ingredients with poor compressibility, pellets as core material to replace conventional capsule dosage form, development of new oral rapid disintegrating tablet can be possible with OSDRC technology.
- Variety of pulsatile drug release profile can be achieved.
- Dividable enteric coated tablet with two cores can be formulated in such a way that after division of tablet each core is fully encased by coat material and release profile will be unaffected.
- By using this technology extremely thin coated tablet can be formulated so sugar coating and film coating can be replaced.
- Variety of core and coat tablet can formulate in single step just by changing double punches.
- By including cameras, automation technique and advanced in process control one can achieved GMP standards.

General formulation of inlay tablet
- Diluents: Microcrystalline cellulose, lactose , mannitol , hypromellose , calcium phosphate , calciumsulphate , kaolin , dry starch etc.,
- Binders: Povidone, starch, stearic acid, hydroxyl propyl methyl cellulose, poly vinyl pyrrolidine etc.
- Anti Oxidants: Citric acid, propyl gallate, tocopherol, butyl hydroxyl toluene etc.
- Disintegrants: Starch, cross caramellose, cross povidone, sodium starch glycollate etc.
- Coating Polymers:

1. **Seal coat polymers:** Hydroxyl propyl methyl cellulose , hydroxyl propyl cellulose, poly vinyl pyrrolidine etc.,
2. **Enteric coating polymers:** Methyl methacrylate ,eudragits , carboxy methyl cellulose, cellulose actate phthalate , hydroxyl propyl methyl cellulose phthalate etc.

- Surfactants: Polyoxy ethylene, castor oil, glycerin monostearate, sorbitonmonostearate, polysorbates, macrogols, sodium lauryl sulphate etc.
- Lubricants: Magnesium stearate , zinc stearate , calcium stearate , stearic acid , hydrogenated vegetable oil etc.,
- Glidants: Talc , colloidal silicon dioxide , corn starch etc.,
- Colorants: Brilliant blue and other FDA approved colors

Targeted disease by inlay tablet

Table 1:- Targeted disease by inlay tablet.

Targeted disease	Example of drugs
Diabetes	Metformin HCL Glipizide Sitagliptin phosphate Gliclazide
Hypertension	Losartan Potassium Diltiazem Felodipine Isradipine Nicardipine Nifedipine
Anti-TB	Isoniazide Rifampicin
Hyperlipidemia	Atorvastatin Pravastatin Rosuvastatin calcium Simvastatin

Methods:-

Pre-formulation studies

A pre-formulation study is the first step in the rational development of dosage forms of a drug substance. It can be defined as phase of research and development process of physical and chemical properties of a new drug substance alone and when provide a rational for formulation design, or support the need for molecular combined with excipients, in order to develop stable, safe and effective dosage form. The overall objective of preformulation studies is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

A thorough understanding of physicochemical propertiesmay ultimately modification or merely confirms that there are no significant barriers to the compounds development. The goals of the pre-formulation study are:

1. To establish the necessary physicochemical characteristics of a new drug substance.
2. To determine its kinetic release rate profile.
3. To establish its compatibility with different excipients.

Compatibility study

The drug and the excipients choose for the formulation are screening for compatibility by physical methods and Fourier Transform infrared spectrometric method (FTIR).

Physical Compatibility study

The physical compatibility studies are conducting to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It is done by mixing the drugs and the excipients in the proper ratio. Any change in color of the physical mixture is observed by visually.

Fourier transforms infrared spectrometry (FT-IR)

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. Pure drugs, polymers, excipients, drug excipient mixtureis subjected to the FTIR study.

Evaluation

A. Organoleptic characters

Color,odor, taste of the new drug must be recorded.

B. Pre-compression study

Angle of repose is defined as the maximum angle viable between the surface of a pile of the powder and horizontal aircraft. The frictional pressure in a unfastened powder or granules can be measured by using angle of repose.

$\text{Tan } \Theta = h/r$

Θ = tan -1 (h/r)
Where,
Θ-is the angle of repose his height of pile
r-is radius of the base of pile

Table 2:-

Angle of Repose (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Method:-

A funnel became filled to the brim and the take a look at sample changed into allowed wafting easily through the orifice under gravity. From the cone shaped on a graph sheet turned into taken to measure the location of pile, thereby comparing the glide capability of the granules. Height of the pile became also measured.

a) Bulk density

Bulk density is described because the mass of a powder divided via the bulk volume. The majority density of a powder relies upon primarily on particle length distribution, particle shape, and the tendency of the particles to stick to one another.

Method:-

Loose bulk density (LBD) and tapped bulk density (TBD) both are determine. Quantities of accurately weighed powder (bulk) from every method, formerly shaken to interrupt any agglomerates formed become introduced into a 25 ml Measuring cylinder. After the initial extent changed into observed, the cylinder changed into allowed falling underneath its very own weight onto a difficult surface from the peak of 2.5cm at 2 sec c language. The taping changed into endured until no in addition exchange in extent was cited.

LBD and TBD were calculated using following formula;

TBD=Weight of powder Volume of packing
LBD= Weight of powder Tapped packing

b) Percentage Porosity

This can be calculated by taking the value of bulk density and true density Percent
Porosity = 1- Bulk density × 100
True density

c) Carr's compressibility index

Carr's index (%) =Tapped density–bulk density × 100
Tapped density

- By decreasing the bulk and tapped density good flow properties can be obtained.

Table 3:-

Carr's index	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor

>40	Extremely poor

d) Hausner's ratio

Hausner`s ratio = Tapped density × 100
Bulk density

Table 3:-

Hausner`s ratio	**Type of flow**
< 1.25	Good flow
> 1.5	Poor flow
1.25-1.5	Glidant addition required
1.5	Glidant doesn't improve flow

C. Post-compression study

a) Hardness

"Hardness is defined as the resistance of the tablet against the applied force till it breaks"

Tablet hardness and strength are the essential to see that the tablet can with the shock and stress during manufacturing, packing and transportation, and while handled by the patient. To test the hardness of the tablet Monsanto Hardness Tester or Stokes Hardness tester, Strong-Cobb Tester, the Pfizer Tester, the Erweka Tester, the Heberlain Hardness Tester or Schlesinger Hardness tester are used. Measure of the mechanical integrity of tablets is their breaking force, which is the force required to cause them to fail (i.e., break) in a specific plane. The tablets are generally placed between two platens, one of which moves to apply sufficient force to the tablet to cause fracture. For conventional, round (circular cross-section) tablets, loading occurs across their diameter (sometimes referred to as diametric loading), and fracture occurs in that plane.

Unit: kg/cm^2 or Newton
Criteria: Tablet hardness should lies between 5 to 10 kg/cm^2

b) Friability:

FRIABILITY is the phenomenon where the surface of the tablet is damage or shown a site of damage due to mechanical shock. It is tested by using Roche friabilator. This is made up of a plastic drum fixed with a machine which rotated at 25 rpm for 100 revolutions (25X4=100). Tablet falls from 6 inches height in each turn within the apparatus. "Roche Friabilator".

Procedure

For tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablets corresponding as near as possible to 6.5 g. For tablets with a unit weight of more than 650 mg, take a sample of 10 whole tablets.
Percentage Friability = W1 – W2 /W1 × 100
W1 = weight of tablets before testing.
W2 = weight of tablets after testing.

Limits

According to B.P/I.P = Percentage of friability should be not more than 0.8% - 1.0% According to U.S.P = Percentage of friability should be not more than 4%.

c) Weight Variation

Weight variation test is performed to check that the manufactured tablets have a uniform weight.

Procedure
Weigh individually 20 units selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage given in the pharmacopoeia and none deviates by more than twice that percentage. IP/BP & USP limits for tablet weight variation are given below.

Sr. No	USP	Max % difference allowed	IP/BP
1	130mg > or less	±10%	80mg > or less
2	130mg-324 mg	±7.5%	80mg-250mg
3	324mg < or more	±5%	250mg < or more

d) Disintegration
Disintegration is the first physical change observed for a drug when it enters into the body, Disintegration test helps in knowing the API solubility in the gastric fluids of the digestive system. As per USP the disintegration apparatus consist of 6 glass tubes (77.5mm±2.5mm long & 21.5mm internal diameter) with a 10 number mesh (1.8-2.2mm) at the bottom. This arrangement of 6 tubes is placed in a medium simulated to the disintegration environment which is maintained at $37^{o}C\pm 2^{o}C$, in 1 liter vessel. This system is made to move up and down through a distance of 5-6 cm at a frequency of 28-32 cycles per minute. Tablet remains 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. The disintegration time of the tablet is compared with the values in the monograph.

- D.T. is not applicable for Sustain Release or Modified Tab.& Chewable Tablet
- Recommended temperature for D.T. of Dispersible tablet is $25^{0}c \pm 1^{0}c$ (IP) & $15^{0}c - 25^{0}c$ (BP)

e) Chromatographic conditions
High Performance Liquid Chromatography can be performed for inlay-tablets.

f) In-vitro drug release
The rate and extent of drug release form the inlay-tablet (under standardized condition of temperature and solvent composition) is estimated by dissolution test. It is a dynamic property that changes with time and describes the process by which a homogeneous mixture of solid or a liquid can be obtained in a solvent. Dissolution testing is a critical pre-formulation solubility analysis research tool in the process of drug discovery. Drug Dissolution testing plays an important role as a routine quality control test, for characterization the quality of product and also plays a major role in drug development. Different types of apparatus are used to study the dissolution test of the tablet. As per IP apparatus I (paddle) and apparatus II (basket) are used.

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