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A REVIEW ON BILAYER TABLET FOR SUSTAINED DRUG DELIVERY SYSTEM

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ABSTRACT:

Bilayer tablet represents new era for the successful development of controlled release formulation along with various features to produce of the successful drug delivery system. According to the literature review of the past decade, bilayer tablets have been developed to achieve sequential release of two drugs in which one layer is immediate release layer and the second layer as sustained release layer. Bilayer tablets can be a primary option to avoid chemical incompatibilities between api by physical separation, and to enable the development of different drug release profiles like the immediate release with extended release. Bilayer tablet is suitable for sequential release of two drugs in combination or to incorporate two incompatible substances in same tablet. Bilayer tablet have improved beneficial technology to overcome the problems of the single layered tablets. Productions of quality bilayer tablets needs to be carried out and to reduce the common bilayer problems, such as layer-separation, insufficient hardness, Inaccurate individual layer weight control, cross- contamination between the layers, Therefore, now a day's bilayer tablet have been developed for combination therapy for treatment of various diseases such as anti-inflammatory, anti-hypertension, anti-diabetic and analgesic. And also disorder requiring long term therapy such as hypertension diabetes mellitus, rheumatoid arthritics. . The primary objective of bilayer tablet is sustained release drug delivery is to improve the oral therapeutic efficacy with optimal control of plasma drug level and also improve its bioavailability which in turn improve the patient compliance and convenience. . The present article explains introduction to bilayer tablets, Advantages, technology challenges in bilayer tablet manufacturing, various tablet presses used, quality and GMP requirements for their manufacturing various techniques used for bilayer tableting and recent advancement in the field of bilayer technology.

KEYWORDS:

Bilayer tablet for sustained drug delivery system, GMP requirement, Need of bilayer tablets, Novel drug delivery system Formulation and Evaluation of bilayer tablets, Bilayer tablet press, Technologies of bilayer tablets Duros Technology,Oros Push Pull Technology.

Introduction:

Now a days, various countries move towards succesfull development of a combination therapy for treatment of many type of diseases and disorders requiring longterm therapy such as Diabetes, Hypertension and Cardiovascular diseases.Over 90% of the formulations manufactured today are ingested orally. It shows that this class of the formulation is the most effective world wide and the major attention of the researcher is towards this direction. On the basis of these considerations, we have formulated a bilayer tablet, in which the one layer is modified to obtain immediate release of the drug, with the aim of obtaining a high serum concentration in a short period of time. The second layer is controlled release (sustained release hydrophilic matrix), which is designed to maintained an effective plasma level for a prolonged period of time.The main goal of controlled drug delivery is to reduce frequency of dosing, to localize the drug to the site of action, to reduce the dose required, or to reduce drug delivery by providing smooth drug delivery to increase effectiveness. The formulation of modified release drug product is to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval providing highest patient compliance and convenience. Bilayer tablet is the novel dosage forms a for the successful development of controlled release formulation and better than the traditionally used dosage forms. It includes super disintegrates, that increases the release rate of the drug and also attains the onset of action quickly. Whereas sustained release (maintenance dose) layer releases the drug in a sustained manner for a prolonged period of time by using various polymers as release in retardants. Diabetes, antihypertensive, antihistamines, analgesics, antipyretics and antiallergenic agents are mainly suitable for this type of drug delivery. Bilayer tablet is helpful for sequential release of two drugs in combination it is also suitable separating the two types of incompatible substances and for sustained release tablet in which one layer is immediate release as initial dose and the second layer is sustained release as maintenance dose. In certain cases bilayered tablets have 2 sustain release layers of of different drugs. Bilayer tablet is an improved technology to overcome the problems of the single layered tablet. Player tablets contain immediate, sustained release layers, and the immediate release layer delivers the initial dose, it contains superdisintegrates, which promotes the drug release rate and attains the onset of action quickly (loading dose) where as sustained release(maintenance dose) layer releases the drug in a sustained manner for a prolonged time period. The biphasic system isused mostly when maximum relief needs to be achieved quickly and it is followed by a sustained release phase. It also avoids repeated administration of a drug. Bilayer tablets have more advantage as compared to conventional tablets. These tablets are mostly used so as there is less use of chemical incompatibilities of formulation components by physical separation. [10]

NEEDS OF BILAYER TABLETS:

1. To separate Incompatible Active Pharmaceutical Ingredients (APIs) from one another, as well as to control the release of API from one layer by utilizing the functional feature of the other layer (such as the osmotic property).
2. To provide fixed dose combinations of different APIs, prolong the life cycle of the drug product, and developed novel drug delivery methods such buccal/mucoadhesive delivery systems, chewing devices and floating tablets for gastro-retentive drug delivery system.
3. TO Modify the total surface area available for by sandwiching with One or two additional active layers to order to produce swellable/erodible barriers for modified release.
4. TO Control rate of delivery of one or two different active pharmaceutical ingredients.[12]

ADVANTAGES OF BILAYER TABLETS:

1. Since Bilayer tablets are unit dosage forms, they have the best capabilities of any oral dosage form for the most precise dosing and the least amount of content variability.
2. A high level of patient acceptance and patient convenience is improved because few daily doses are required compared to traditional delivery systems.
3. When two or more APIs are combined into a single bilayer tablet, the burden on the dosing unit is reduced, which enhanced patient compliance leading to improved drug regimen efficacy.
4. The drugs and excipients which causes incompatibility can be separated into different individual layers in single tablet thus minimizes physical and chemical incompatibilities.

5. Chemical and microbial stability among all other solid oral dosage forms and liquids.
6. Easy to swallow with a low tendency to hang up
7. Price is low in compared to all other dosage forms
8. Suitable for large-scale production.
9. Elegance to the product.
10. Objectionable odor and bitter taste can be masked by coating technique.
11. Treat different Diseases in the same patient, at the same time with one pill because It can be designed in such a manner so as to kept modified release of the layers as extended and the other as immediate release.
12. Flexible concept and self administration is possible.[9]

DISADVANTAGES OF BILAYER TABLET:

1. Drugs with , slow dissolution characteristics, poor wetting and optimal absorption, in the gastrointestinal tract (GIT) may be difficult to manufacture as tablets that provide acceptable or complete drug bioavailability.
2. Weight control for each individual layer is not accurate.
3. There is chances of cross contamination between the layers
4. Drugs that are oxygen sensitive, have an unpleasant taste may need to be coated or encapsulated.
5. Insufficient hardness may accures .Sometimes Reduced yield.
6. There is chances of layer separation or capping.
7. Adds complexities the situation and bilayer rotary presses are costly.
8. Children and unconscious patients cannot swallow tablets easily.[7]

LIMITATIONS OF BILAYER TABLETS:

1. In order to formulate bilayer tablets, There should be compatibility between the two active ingredients.
2. Some drugs having amorphous nature or low density character retards compression in dense compact.
3. There is no distinct visual separation between the two layers.
4. One of the most difficult problems in bilayer tablets manufacturing is a lack of complete bonding and adhesion at the interface between the layers.
5. Compacted layers that are either too soft or too hard will not adhere to one another firmly, which may compromise their mechanical integrity and cause layer separation.
6. If the first layer is compressed with high compression force, bonding will be too limited. In order for the first layer to interact with second layer during the final compression, proper binding can only be achieved when first layer is compressed at low compression force.[2]

TYPES OF BILAYER TABLET:

1.Homogenous Type:

When Drugs have distinct release profiles, Bilayer tablets are preferred option. Bilayer tablets are made with one layer of drug intended for immediate release while another layer designed for drug release , either as part of second dose or in an extended-release manner.

2. Heterogeneous Type:

Bilayer tablets can be used to separate two substances that are incompatible or to release two drugs in combination sequentially.

GENERAL PROPERTIES OF BILAYER TABLET DOSAGE FORMS:

1. A bilayer tablet should have a attracts product identity while free of defects like discoloration, and contamination chips and cracks.
2. Bilayer tablets should be strong enough to withstand mechanical shock during production, shipping, packaging, and dispensing.
3. It should be sufficiently stable both chemically and physically to maintain its physical properties over time.
4. Bilayer tablets need be able to release the active ingredients in consistent and repeatable way.
5. Bilayer tablets need to have a shelf life that is chemically stable to prevent changes to the medicine.[1,15]

TYPES OF BILAYER TABLET PRESS:

1. Single Sided Tablet Press
2. Double Sided Tablet Press
3. Bilayer Tablet Press with Displacement Monitoring
4. Multilayer Compression.

1**. Single Sided Tablet Press:**

Although there are many presses available for producing bilayer tablets, but the most simplest design is a single sided tablet press. In this tablet press double feeder chambers separated from each other. Each chamber operates in accordance with gravity or force fed with a different powders, thus producing the tablet with two layers .As the die passes beneath the feeder, The first layer of powder is loaded followed by pre compression and then the second layer of powder is added followed the second precompression and finally main compression. As a result the entire tablet is formulated in one or two stages (precompression and main compression). While manufacturing bilayer tablets, there should be enough bonding between two layers so that there is no layer separation at the time when the tablet is produced.[12]

Limitation of Single Sided Tablet press:

1. The individual layer's weight is not properly monitored or controlled.
2. Sometimes there is no clear visual distinction between the two layers.
3. Dwell Time (Duration of stay).
4. Compression force.
5. Poor deration, Capping and Hardness issues.

Dwell Time:

Its defined as period of time that the compression force is more than 90% of its maximum value. Significant element in production of quality bilayer tablets is longer dwell time.

Compression force:

Compression force of 100daN is needed for numerous bilayer tablets for first layer compression for retaining ability's to create a bond with second layer.100daN Compression force enough to ensure appropriate bonding between the two layers but above this force, there is possibility of loss of bonding. Due to this separation of two layers may accures due to low hardness of bilayer tablets.

2.Double Sided Tablet Press:

The majority of double-sided tablet presses use automated production control, which works well for monitoring and managing tablet weights when combined with compression force. The control system is used to calculate peak compression force at the stage of exertion on each individual tablet or layer at stage of final main compression of bilayer tablets. This system is useful for rejection outside of the tolerance tablets and die fill depth correction when required with the help of signal produced by control system.

Advantages

1. Increased dwell time at precompression of both first and second layer provide sufficient hardness to bilayer tablet.
2. To prevent capping and layer separation by applying a low compression force to the first layer.
3. Control system is very helpful in accurate and independent weight control of the individual layer.
4. Cross-contamination between two layers is avoided to greatest extent.
5. High Production yield.
6. In bilayer tablets there is possibility of clear visual separation between the two layers.

3. Bilayer Tablet Press with Displacement Monitoring

This tablet press operated on principle of displacement tablet weight control that is fundamentally different from the compression force control principle. According to the principle sensitivity of control system doesn't really depend on the tablet weight but actually depends on the applied precompression force. In this case risk of capping and separation increases with increases with production speed, but it can be reduced by there is enough dwell time at all four compressions.

Advantages:

1. Increased dwell time at precompression of both first and second layer provide sufficient hardness to bilayer tablet.
2. To prevent capping and layer separation by applying a low compression force to the first layer.
3. Control system is very helpful in accurate and independent weight control of the individual layer.
4. Cross-contamination between two layers is avoided to greatest extent.
5. High Production yield.
6. In bilayer tablets there is possibility of clear visual separation between the two layers
7. On bilayer tablet,There is no any effect of stiffness.

4. Multilayer Compression Basics

The idea of Multiple Layer tablets is one that has two or more layers can provide multiple drug release patterns. Multilayer tablets are made on Presses modified multilayer compression, or a standard conventional double press can be converted to multilayer press. The multilayer tablet technology helpful for sustained release of drugs. The drug release pattern is determined by granules. The pharmacokinetics advantage relies on the fact that drug release from fast releasing granules leads to sudden rise in blood concentration works as loading dose however plasma drug blood level maintained at a steady state as the drug is released from the sustained granules.[6,8,18]

VARIOUS TECHNIQUES FOR BILAYER TABLET:

1. OROS® Push pull Technology
2. L-OROS^{TM} Technology
3. PRODAS or Programmable Oral Drug Absorption System
4. EN SO TROL Technology
5. DUROS Technology
6. DUREDAS^{TM} Technology
7. GEMINEX TECHNOLOGY
8. GEOMATRIX TECHNOLOGY

1. OROS® Push pull Technology:

This system made up of two or three layers, one or more of which is necessary for drug and remaining layers are consist of push layer. The drug layer is primarily composed of drug along with two or more excipients. So this drug layer consist of drug that is in a poorly soluble form. There is also further addition a suspending agent and a osmotic agent. The tablet core is covered by a semi-permeable membrane.

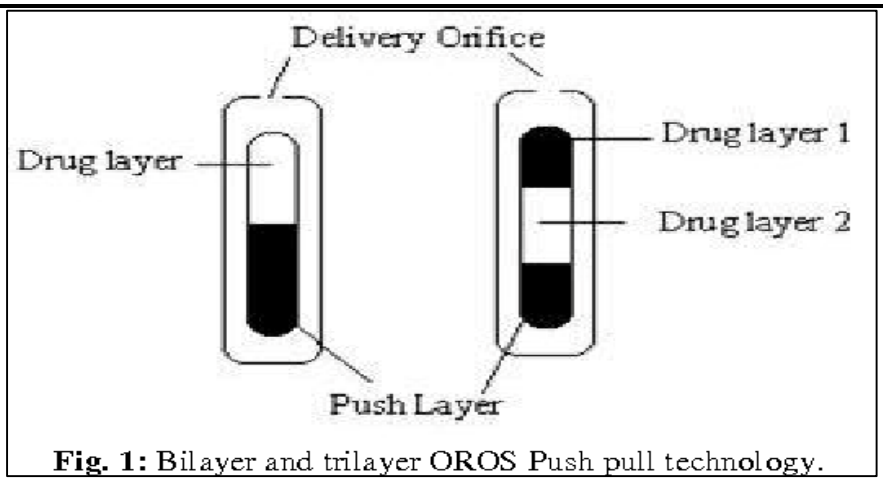

Fig. 1: Bilayer and trilayer OROS Push pull technology.

2. L-OROS^{TM} Technology :

This system used for the solubility Problem alza developed the L-OROS system which uses drug-containing lipid soft gel product in a dissolved state is initially created and then coated with a barrier layer, then osmotic push layer and finally a semi permeable membrane, drilled with an exit orifice.

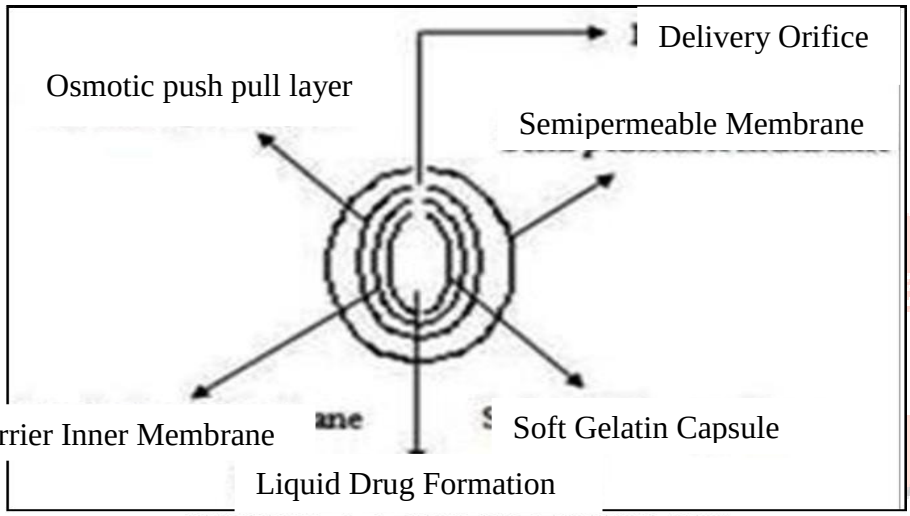

FIGURE 2: L-OROS TM TECHNOLOGY

3) PRODAS or Programmable Oral Drug Absorption System:

PRODAS (Elan Corporation) is another name for multi particulate drug technology. Controlled release mini tablets (size range from 1.5 to 4 mm) are encapsulated in this technology. This technology is hybrid of a multi particulate and hydrophilic matrix tablet technologies used to provide above mentioned usefulness technologies in single dosage forms. PRODAS Technology is helpful for targeted drug delivery. Minitab has different release rates for targeting GIT. Minitab (Immediate, delayed release and controlled release) lets combine them in single dosage form to set the desired release rate.

4. EN SO TROL Technology:

Solubility enhancement of an order of magnitude or to developed optimised dosage form Shire laboratory takes an integrated approach to drug delivery that focuses on identifying and administration of the identified enhancer into controlled release technologies.

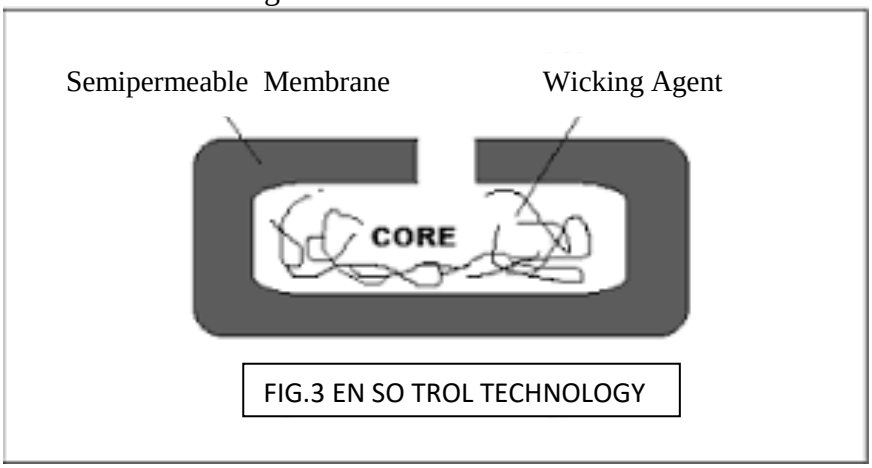

FIG.3 EN SO TROL TECHNOLOGY

5. DUROS Technology:

The system composed of an external external cylindrical reservoir made up of titanium alloy.. This reservoir shields the drug molecules from enzymes and has high impact strength. The DUROS technology is the tiny drug dispensing system that opposes like small syringe and irregularly sized amount of concentrated form that has been ongoing and consistent from over months or the year.

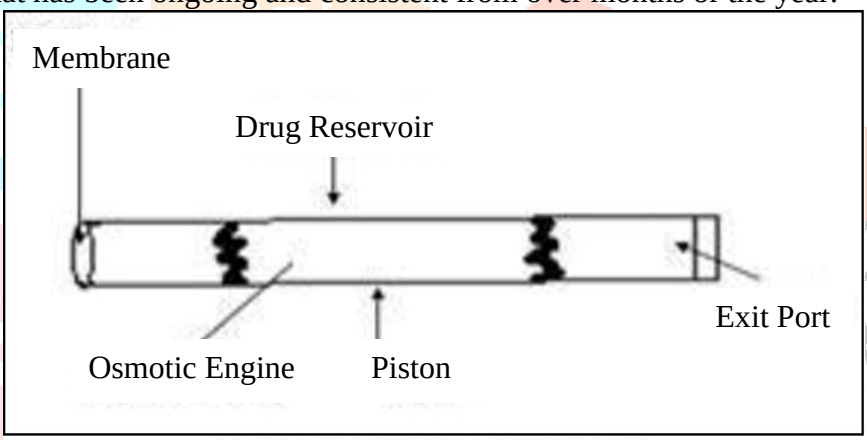

Fig 4.DUROS Technology

6. Elan Drug Technologies' DUREDAS™ Technology:

(DUREDAS™ Technology) is Bilayer tablet that offers two drugs in one dosage form at different release rates with immediate and sustained release. Tableting process can yield a modified-release hydrophilic matrix complex and an immediate release granulate as different layers within a single tablet. The modified-release properties of the dosage form are provided by a blend of hydrophilic polymers.

Benefits offered by the DUREDAS™ technology include:

- Bilayer tableting technology.
- Two drug components release at different rate
- Combined ability of two distinct CR formulations.
- Ability to release immediate release and modified release ingredients in one tablet.

7. GEMINEX Technology:

This technology helps massively in increasing the therapeutic effectiveness of drugs while also reduce their side effects. It administered one or more drugs having different release rates through a single dose. It is extremely helpful for patients and industry. It is widely used by pen west for cardiovascular diseases, CNS disorders, diabetes, cancer, and central nervous system disorders.

8. GEOMATRIX Technology :

Using Geomatrix Technology multiplayer tablets are produced in which the active ingredient contained within a matrix core and is surrounded by one or more barrier-forming modulating layers that are bonded to central matrix throughout the tablet's manufacturing process. These barriers have primary function is to prevent contact between core and dissolution agent.[3,11,15,21]

METHOD OF PREPARATION OF BILAYER TABLETS :

Wet Granulation:

Wet granulation is process in which powder blend converted in large regular aggregates called granules. This process Enhances: 1) Flow properties
2) Prevent segregation.
3) Facilitates compression.

Steps involved in wet Granulation:

1) Grinding: Drug is added to the granulator and grinded.

2) Blending: Suitable adjuvants (Diluents and excipients) are added and mixed in blender.

3) Preparation of Damp mass: Involves addition of binder solution with powder mixture to form coherent mass.

4) Wet Screening: Wet mass powder blend screened using sieve no.8 or 10.

5) Drying: Wet granules are dried in oven at 60^0c.

6) Dry Screening: Dried granules passed through sieve no.20 to get uniform sized granules. It results in size reduction.

7) Blending: Lubricating agent are added and mixture is thoroughly mixed in blender. Remaining amount of additional disintegrants are also added at this stage.

8) Compression: Resultant granules are compressed by tablets punching machine.

Steps for compression of Bilayer tablets:

1) Filling of First layer.

2) Compression of first layer.

3) Ejection of upper punch.

4) Filling of second layer.

5) Compression of both layer together.

6) Ejection of Bilayer Tablets.[16,20]

GMP Requirements of Quality Bilayer Tablets:

1. Maximum granules size should be less than 16 mesh for smooth, uniform scrape off at the die. Materials that smear, chalk or coat on the die table must be avoided to obtain clean scrape-off and uncontaminated layers.

2. Low moisture is required if incompatibles are used.

3. Weak granules that break down easily must be avoided .Excessive amounts of lubrication especially metallic stearates should be avoided for better adhesion of the layers.

4. Formulation of multiplayer tablets are more demanding than that of single layer tablets .For this reason, selection of additives is more critical.

5. Dust fines particles must be limited.

6. Avoidance of cross contamination between two layers.

7. Tablets hardness must be sufficient.

8. Correct and individual weight control of two layers.

9. Producing a transparent visual separation between two layers.

10. Avoidance of capping and separation of layers of bilayer tablets. Producing More Yield.[5,17]

Challenges Involved in Manufacturing of Bilayer Tablets:

Bilayer tablets are conceptually equivalent to two single-layer tablets compressed into one. There are certain manufacturing challenges in practice.

1. Delamination:

When two halves of a tablet do not fully bind to each other, Tablet falls apart. Granules should stick tightly when compressed.

2. Cross-Contamination:

When the granulation of the first layer is integrated with the second layer, cross contamination happens. It might defeat the primary goal of bilayer tablets. Appropriate dust collection greatly contributes to avoiding the spread of infection.

3. Production Yields:

To avoid contamination by other substances, there must be a dust collection, which results in losses. Consequently, compared to single-layer tablets bilayer tablets yield less tablets.

4. Cost:

Cost of bilayer tableting is higher than that of single layer tableting for various purposes. Tablet presses are expensive. [8,12,21,23]

EVALUATION OF BILAYER TABLETS:

Precompression Evaluation:

1.Particle size distribution:

The particle size distribution is measured using sieving method. [13,09]

2.Photo-microscope study:

Photo-microscope image of TGG and GG(X450 magnifications) was taken by photomicroscope. [13]

3.Angle of Repose:

The powder cone's diameter was determined and angle of repose was obtained by using equation,

$$Ø = \tan^{-1(h/r)}$$

Where 'r' and 'h' stands for powder cone's radius and height respectively. [09]

4. Moisture Sorption Capacity:

Every disintegrants has ability to take moisture from air which influences moisture sensitive drugs. To measure the moisture sorption capacity, take 1 g of uniformly disintegrated material dispersed in petri dish and kept in stability chamber maintained at 37±1°C and 100% relative humidity for 2 days and looked into hoe much moisture was absorbed based on weight variations.[09]

5. Density

Following formulas were used to determine the bulk density (BD) and tapped density (TD)

Bulk Density =Weight of powder /Bulk volume.

Tapped Density=Weight of powder/Tapped volume. [13,09]

6. Compressibility:

Carrs Index (CI) used to calculated compressibility.

$$CI = (TD - BD) / TD \times 100.$$

Whereas

TD = Tapped Density

BD = Bulk Density. [13]

7. Hausner's Ratio :

It is crucial to specify the flow properties of powders and granules.

Hausner's Ratio = Tapped Density / Bulk Density. [09]

Post-compression Evaluation:

1.General Appearance:

The general appearance of tablet, its visual identity and overall 'elegance' are crucial factor for determining consumer acceptance which includes tablet size, shape, colour, presence or absence of an adour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.[14]

2.Size and Shape:

The size and shape of tablet can be dimensionally specified, monitored and controlled.[15]

3.Tablet Thickness:

Tablet thickness is important property in reproducing appearance and also in counting by using filling machinery as counting system. A Micrometer used to measure the thickness of ten tablets. In general, a tablet's thickness should be between 30% and 50% of its size. [14]

4.Tablet Hardness:

The hardness of a tablet determines resistant to breakage or shipping during handling, storage, and transportation prior to use. Using a Monsanto hardness tester, the tablet hardness of each formulation was determined. The tablet hardness was measured in kg/cm^2. The tablet is too hard, it might not dissolve in amount of time needed to meet dissolution requirements; if it is too soft it might not be able to withstand handling during further processing like coating or packing activities. Crushing strength of 4 kg is typically considered to be minimum amount necessary for satisfying tablets. The typical hardness of oral tablets is in between 4 to 10 kg. Usually hypodermic and chewable tablets are much softer (3kg). Some sustained released tablets are much harder (10-20kg). Hardness of tablets has been linked to additional tablets characteristics like porosity and density.

5.**Friability:**

It defined as capacity of tablet to withstand abrasion in packaging, handling and shipping. Friability is measured by using Rache friabilator. A number of tablets is calculated and placed in the apparatus in which they are subjected to rolling and shocks as they drop 6 inches in each turn within the apparatus. Following four minutes of this treatment or after 100 revolutions, the tablets are weighed and weight is recorded compared with the initial weight. The loss as a result of abrasion is measure of tablet friability. The result value is expressed in percentage %. During friability testing weight loss of up to not more than 1% of total weight of tablets are generally considered acceptable and any cracked or smashed tablets are not picked up. Friability is measured in percentage as:

% Friability = 1- (loss in weight / initial weight) × 100.[15]

6.Drug Content and release:

To assess the efficacy of tablets, the amount of the drug per tablet must be monitored from tablet to tablet and batch to batch as well as ability of tablets to release drug need to be determined.

7.Weight Variation:

To check weight variation twenty tablets are chosen at random from each batch and weighed individually. Determine the average weight and compare the individuals tablet weights with the average. The tablet fulfills the USP If no more than 2 tablets are found the outside the percentage limits and if no tablet differs by more than 2 times the percentage limit. Small amount of variation is permitted in weight of tablet according to the US united states pharmacopoeia. Following percentage deviation is allowed in weight variation as shown in table no.1 [14]

Average weight of tablets	Percentage deviation
130 mg or less	±10
>130 mg and <324 mg	±7.5
324 mg or more	±5

Table no. 1 weight variation parameters.

8. In-vitro dissolution study:

A in vitro dissolution study is carried out in simulated gastric and intestinal fluids to evaluate their ability to provide the desired controlled drug delivery. The vitro drug release studies are carried out using USP dissolution test apparatus test at 100 rpm, 37±0.5°C, and PH 1.2 buffer (900 ml) (i.e. 0.1N HCL) for 2 hours because average gastric emptying time is around 2 hours. The medium of dissolution was replaced with 6.8 phosphate buffer (900ml) and the experiment was repeated for another 10 hours. At various time intervals, 5ml of samples were withdrawn and replaced with 5 ml of drug-free dissolution medium. UV spectrophotometer was used to analyzed the withdrawn samples using multi-component mode of analysis.[13,15]

Recent developments in field of Bilayer tablets:

Development of pre-determined released profiles of active ingredients and incorporation of incompatible active ingredients into single unit dosage form has been made possible by advancement of bilayer tablets in the pharmaceutical industry. [4,12,13,9]

1.	Metformin HCL, Glimipiride.	Bilayer Tablets	Synergistic effects in diabetes.
2.	Pioglitazone HCL, Gliclazide.	Bilayer Tablets	Treatment of Type II Diabetes.
3.	Metformin HCL, Pioglitazone.	Bilayer Tablets	Synergistic effects in diabetic mellitus.
4.	Diclofenac, Cyclobenza-prine.	Bilayer tablets.	Synergistic effects in pain.
5.	Metformin HCL , Atorvastatin Calcium	Bilayer tablets.	To develop polytherapy for treatment of NIDDS and hyperlipidemia.
6.	Diclofenac sodium, Paracetamol.	Bilayer tablets.	Synergistic effects in pain
7.	Ibuprofen, Methacarba-mol.	Bilayer tablets.	Synergistic effects in back pain.
8.	Guaifenesin.	Bilayer tablets	Biphasic released profile.
9.	Tramadol, Acetaminophen	Bilayer tablets	Synergistic effects in pain
10.	Montelukast, Levocetrizine	Bilayer tablets	To improve stability of drugs in combination.
11.	Telmisartan, Hydrochlor-thiazide.	Bilayer tablets	To minimized contact between hydrochlor-thiazide and telmisartan.
12.	Amlodipine and Atenolol	Bilayer Tablets	To improve stability of drugs in combination.
13.	Misoprostol, Diclofenac	Bilayer tablets	To minimize contact between drugs.
14.	Cefuroxime axetil, Potassium clavulanate	Bilayer tablets	Synergistic effects of drugs against microbial infections
15.	Metformin HCL' Glipizide.	Bilayer tablets.	To avoid interaction between in-compatible drugs .

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the short coming of the single layered tablet. There are various application of the bilayer tablet, it consist of monolithic partially coated or multilayered matrices. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The preparation of tablets in the form of multilayer is used to provide systems for the administration of drugs, which are incompatible and to provide control release tablet preparations by providing surrounding or multiple swelling layers. Bilayer tablet quality and GMP-requirements can vary widely. This explains why many different types of presses are being used to produce bilayer tablet, ranging from simple single-sided presses to highly sophisticated machines.

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