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A REVIEW ON MULTILAYERED TABLET

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Abstract:
Bilayer tablets are a new era in the development of successful controlled release models and a variety of products that provide effective drug release. A multilayer tablet has two layers, a slow layer and an immediate release layer. It is based on the development of effective equipment that overcomes the disadvantages of single-layer tablets. Since the API is not compatible with each other, double-layer tablets should be prepared. Therefore, the use of double-layer tablets is very different from the anti-hypertensive drugs, diabetes, anti-inflammatory drugs and analgesic drugs that are often used in combination therapy. Many pharmaceutical companies are currently developing double-layer tablets for various reasons: patent extensions, medical, commercial, etc. The general principles of tablet manufacturing are still the same, but there is a lot to consider because multi-layer tablet manufacturing involves many different materials, accessories, and more designs and competition. This course presents bilayer tablet presses, the challenges in multilayer tablet production, the various tablet presses used, techniques used for bilayer tablet compression, and the latest advances in bilayer technology.

Keywords: *Multilayer tablet, Immediate release, Sustained release, Bilayer technology*

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INTRODUCTION:

A tablet can be defined as a solid unit dosage form of one or more medicinal products containing suitable excipients. It consists of a mixture of active ingredients and excipients, usually in powder form, compressed or compacted from a powder into a fixed dose.

Pharmaceutical research has focused on controlled drug delivery. This offers a distinct advantage over conventional release formulations of the same drug. Controlled-release systems that can provide zero-order drug delivery have the potential to maximize efficacy while minimizing dosing frequency and toxicity.

The multi-layer matrix system overcomes the inherent shortcomings of non-linearity associated with controlled diffusion matrix devices by providing additional emission surface over time to compensate for the reduced release rates. Multi-layer tablets are the latest concept for the successful development of controlled-release formulations with multiple functions that provide an avenue for successful drug delivery systems. Factors such as repeated dosing and unpredictable absorption of have led to concept-driven drug delivery systems.

Layered tablets consist of two or three compressed layers of granules. A single tablet consists of two or more layers, each layer having different colour.

For distinctive appearance,
There are two main types of layered tablets used for layered tablets in the pharmaceutical industry: bilayer and trilayer tablets. Bilayer tablets are suitable for him to release two drugs in a combined form. Two incompatible substances can be added to the bilayer tablet. One layer is immediate release as the initial dose and the second layer is the maintenance dose. Multilayer tablets are mainly used for miscible substances. Layered tablets allow for sustained release formulations containing an immediate release portion in one layer and a delayed release portion in a second layer. [1, 2, 3]

ADVANTAGES OF MULTI-LAYERED TABLETS [4, 5, 6]

- Low cost compared to all other oral dosage form.
- Better chemical and microbiological stability than any other oral dosage form.
- Unpleasant and bitter odour and tastes can be masked with coating technology
- They have the least hangover and are easy to swallow.
- Suitable for scale-up technology in pilot plants.
- For combination therapy, these tablets can be used without problems.
- Improved patient compliance.
- Bilayer execution with optional single layer conversion kit.

DISADVANTAGES OF MULTI-LAYERED TABLETS

- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Bitter testing drugs, drugs with an objection able odour or drugs that are sensitive to oxygen may require encapsulation or coating.
- Difficult to swallow in case of children and unconscious patients.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack and layer separation.
- Other challenges during development include establishing the order of layer sequence layers, first layer tamping force, and cross contamination between layers.
- The physician has a less flexibility on adjusting the dose regimes.
- Chances of cross contamination are high due to usage of multiple drugs.

VARIOUS KINETIC MODELS IN THE DEVELOPMENT OF MULTILAYERED TABLETS

The design of multi-layer through varying the geometry of the devices or modulating layers which allow different tablet design for the production with specific release properties to achieve different dissolution patterns like pulsatile, bimodal, delayed and multi modal delivery. Different designs have mentioned below:

- Zero order sustained release
- Quick/slow delivery system
- Time programmed delivery system
- Bimodal release profile

Zero order sustained release: System comprises hydrophilic or hydrophobic polymer as matrix or barrier layer in their formulation to control the release of drug via coating of polymer to both side of the matrix but leaving other sides for exposure to the

dissolution medium to sustain the release of the drug [7].

Quick/ slow delivery system: This system is characterized by initial rapid release followed by extended / prolonged release of the drug to achieve immediate therapeutic effect and to sustain a constant release of drug to maintain plasma level concentration. This concept is applied on where dose regimen does not satisfy simple release of the drug [8].

Time programmed delivery system: Time programmed delivery system provide immediate release of drug followed by time-controlled release, when the delivery of the drug is required in a time-controlled fashion in the gut, rather than release of drug in continuous manner according to circadian rhythm. This system consists of core which is coated with different polymeric barriers. The release of drug from the core tablet after swelling of hydrophobic or hydrophilic barrier of coating that show pulsatile release of the drug [9].

Bimodal release profile: This system shows an initial rapid release followed by slow release and again, a second phase of rapid drug release i.e., sigmoidal release profile. This system compensates the slow absorption in the stomach and small intestine and for programmed pulse releases that perform more effectively at the site of action to undertake periodic changes [1].

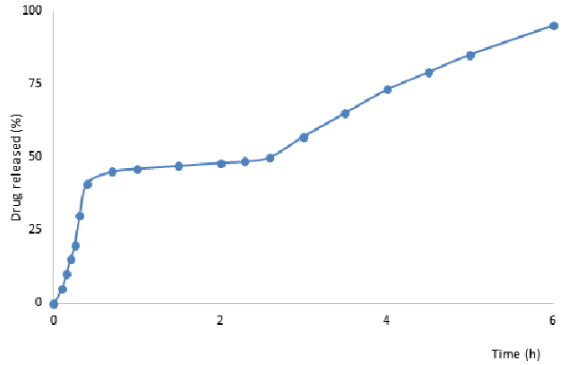

Fig 1: Bimodal release profile

TYPES OF MULTILAYER TABLETS [10]

Bilayer tablets to quadruple layered tablets are available.

a) Bilayer Tablet
Bilayer tablets are suitable for sequential and simultaneous release of two different API'S. One layer is immediate release, and another layer is sustained release which acts as a maintenance dose. Bilayer tablet is suitable to deliver two drugs at one time without any dynamic pharmacological interaction.

Fig 2: Bilayer tablets

b) Triple layer tablet
Triple layer tablet consists of three layers of which first layer is immediate release of drug and the second layer are sustained release. These two layers in trilayer tablet are
separated with middle barrier layer. For the delivery of two drugs, it is more suitable which have interactions in them.

Fig 3: Triple layer tablets

DIFFICULTIES IN MANUFACTURING MULTI-LAYER TABLET

In addition to having desirable therapeutic properties, multi-layer tablets should also possess sufficient mechanical strength and hardness to withstand the normal rigors of processing, handling, packaging, and shipping [11, 12]. A multi-layer tablet may consist of a core and more barrier layers and/or a core and shell in the case of compression coated tablets. Because it is not easy to develop and produce, some problems may arise during production that affects the properties of the formulation. Some of the main issues are – inadequate hardness, imprecise regulation of layers and tablet weight, elastic mismatch between

conterminous layers, and susceptibility to delaminate during the various stages of manufacture.

Improper manufacturing process of multilayer tablet may contribute to delamination clear separation of layers along the interface. Delamination can occur immediately after compaction, following steps in a technological process, or during storage [13, 14], can occur between adjacent layers interlaminar delamination, or can occur within layers delamination. As a result, the patient may not receive any of her substance as intended. Or may receive the wrong dose. Therefore, special attention should be paid to the properties of the materials used and the parameters of the formulation process in order to minimize the likelihood of their occurrence. These include tools and materials that can be incorporated into the design of multilayer tablets, factors that cause delamination, layer order, and weight ratios, mechanical strength of the tablet and each layer, and interphase adhesion.

1. Active ingredients and excipients

The physiochemical properties of active ingredients and excipients are important for the successful production of multilayer tablets [11, 15]. Material properties play an important role in the strength and fracture properties of multilayer tablets. Parameters such as brittleness, viscoelasticity, plasticity and compression properties have a significant impact on the compression process [16]. The formulation of each layer of the multi-layer tablet should be chosen so that it exhibits sufficient volume reduction so that is mechanically strongly cohesive into a solid form. They should be characterized by good compressibility (the ability of the substance to reduce its volume under pressure) and tolerability (the ability of the powder substance to transform into a tablet). When used to manufacture layered tablets, it is important to optimise the particle size distribution, flow properties, and compressibility of the material to precisely control the weight of each layer. The latter is an important factor in ensuring acceptable API uniformity. In addition, it is recommended to prioritize layer compression with lower drug doses or weights to obtain satisfactory API content homogeneity. Unfortunately, modern commercial presses are equipped with weight control mechanisms that can only control the first layer and total tablet weight.

If it is not possible to keep the weight of each layer comparable (e.g., if the amount of drug in only one layer is high for clinical reasons, or if the layer weight is high for formulation reasons), the compositions of layers should be created using some common excipients. The similarity of the weight/formulation of the two layers then leads to the similarity of the physical properties of the materials used in the tablet formulation. Additionally, this procedure helps to obtain layers with similar compression profiles, improving the physical integrity of multi-layer tablets. If different formulations must be used for each layer, it is often necessary to adjust the compression process to obtain acceptable physical properties.

2. Layer ratios and orders

Another aspect of multilayer tablet compression is the relationship of the layers and the order of their arrangement for the same purpose of reducing the possibility of delamination of intralayer capping between layers. Most commonly, bilayer tablets are made with a 1:1 or 1:2 weight ratio of layers. Layer ratios of 1:3 or 1:4 are sometimes used, and unbalanced layers up to 1:6 were formulated during development studies. When using much more first layer weight than second layer, it is more difficult to maintain integrity. Therefore, it is desirable to compress the lightweight layers first. Unfortunately, current available presses are not capable of compressing the lightweight first layer. Therefore, there is no way around the problems associated with adding weight to the first layer of the tablet [11].

Making the first layer with methyl cellulose and the second layer with starch significantly reduced the surface roughness of the methyl cellulose layer and reduced the intramolecular attractive forces between the two adjacent layers. After reversing the layer order (starch in the first layer, methylcellulose in the second layer), the tablets featured relatively high tear resistance compared to the previous ones. Thus, a series of layers with different compressive properties allows us to control the roughness of the interface, thus affecting the strength of the interface. A common practice in the manufacture of multi-layer tablets is to use a material with a high fracture tendency to form the first layer and a material with a high deformability for subsequent layers. The compressive properties of each layer can be estimated based on the powder/granule compressibility (curve of compressive tensile strength against solids content) [17].

3. Tablet hardness

Tablet hardness is expressed as tensile strength and calculated according to the Fell and Newton formula.

$$\sigma = 2P/\sigma Dt$$

σ- tensile strength [kg/cm^2]; **D** - tablet diameter [cm]; **t** - tablet thickness [cm]; **P** = fracture force [kg][18].

Tensile strength of bilayer tablets made with common excipients can be accurately specified using a simple model based on the Ryshkewitch-Dukworth equation. Investigation of layered tablet properties in early formulation development can be done using a variety of tools. Among other things, we determined the interfacial strength, recognized the unusual extreme properties of the compression layer, ensured the consistency of the resulting tablets, elucidated the mechanism of material damage that occurred during manufacturing, and analysed the impact of relevant factors. It's important to understand, punching speed, compression force, etc.), reducing energy consumption by minimizing the production of defective tablets and optimizing environmental conditions [11].

4. Compressive Force

The compressive force of each layer has a great effect on the strength and interfacial adhesion between layers, thus, it contributes to the mechanical integrity of the subsequent multilayer tablet [14]. Therefore, it is necessary to set the optimal compression force in order to mould the final product with desired physical properties. Tablets may also delaminate during the compression process, particularly during remoulding and extrusion, due to differences in mechanical stress between the plastic layers.

The most important parameter in the manufacturing process of multilayer tablets is the value of compression force used for the first layer, which affects the adhesion of the layers. Compaction pressure and punch speed have a significant effect on compressibility and resistance to compressibility into the die. The role of the first layer of compressive force (usually in the range of 2-18 kN) is to compact the powder/granules to reduce their volume, smooth the first layer surface of the first layer, and provide a support for laying it down. It's about creating space. Second layer. In general, applying greater compressive force increases tensile strength and decreases surface roughness. Smoothing the surface of the first layer limits the intermolecular adhesion between adjacent layers and thus may increase delamination [19, 20].

5. Interfacial Strength

A major cause of sealing, cracking, lamination and failure of multilayer tablets is related to interfacial cracking caused by residual stress. Note that these changes are not always noticeable immediately after the compression process. The presence of the above changes at the interface reduces the overall stiffness and increases tablet brittleness. The difference in elastic modulus between adjacent layers of the tablet contributes to the elastic mismatch, which causes radial stress and consequent delamination of the multilayer tablet. However, using a plastic material for each layer provides the weakest interfacial strength. Furthermore, if the material forming the first layer is more elastic, the stress introduced into the system weakens the strength of the multilayer tablet. Such tablets can delaminate even when removed from the die. The lack of flexibility of the brittle material has been shown to significantly reduce the deformability of the particles on the first tablet layer, thus maintaining adequate layer porosity. This provides nesting sites for mechanical latches. It has also been pointed out that for plastically deformable materials, the bonding strength between adjacent layers decreases as the interface roughness decreases.

The amount of granulating liquid and the drying temperature greatly affect the properties of the final product. These include the following granulation properties - particle size distribution, flowability, bulk density, sedimentation capacity, etc. As a result, the physical properties of each tablet, such as weight variation, thickness and hardness, as well as specific analytical results (such as grade uniformity and dissolution profile) are all affected [21].

6. Adhesion

Adhesion is a factor to be considered in the technological process of simply layered multi-layer tablets (composite tablets). In the first step, the central tablet layer (tablet core) is produced during pre-compression. In the second step, the top and bottom layers are compressed into the middle layer. As the middle layer is already a compressed tablet and its release rate is controlled by the outer layers, it is difficult to achieve proper adhesion between layers, but the physical integrity of multilayer tablets is necessary to maintain [22].

STEPS INVOLVED IN THE FORMULATION OF MULTILAYER TABLETS

The various steps involved in the formulation of tablets are

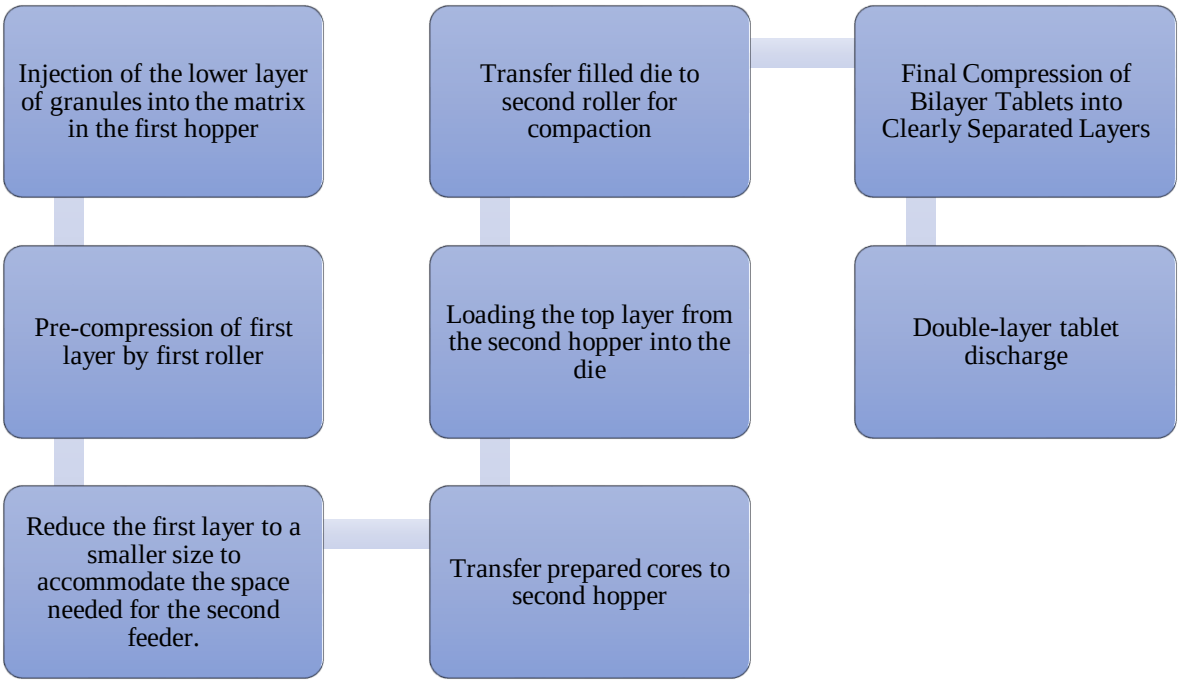

Figure 4: Formulation of Multilayer tablet

TYPES OF BILAYER TABLET PRESS [23, 24]

- Single sided tablet press
- Doubled sided tablet press
- Bilayer tablet press with displacement monitoring

1. Single sided tablet press

The simplest design is a single-sided press in which the two chambers of a double feeder are separated from each other. A different gravity or restraint is applied to each chamber, creating two separate purification layers within it. As the die passes under the feeder, the first layer of powder is loaded into the die, followed by the second layer of powder. The entire tablet is then compressed in one or two steps.

Fig 5: Single sided tablet press

Limitations of single sided tablet press

- No weight monitoring/control of individual layers.
- There is no clear visual separation between the two layers.
- Due to the small compaction rollers, the residence time of the first layer is very short, which can lead to problems of degassing, capping and hardness.

Residence Time

Residence time is defined as the time during which the compressive force exceeds 90% of its peak value. Longer residence time is a key factor in producing high quality tablets, especially when compressing difficult formulations.

Compressive Force

In many two-layer formulations, the compressive force of the first layer should be less than 100 daN to maintain bonding with the second layer. Above 100 daN, this ability is lost and the bonding between both layers may not be sufficient, resulting in low hardness of bilayer tablets and possible separation of the two layers.

2. Double sided tablet press

Most automatic production control double-sided tablet presses use compression force to monitor and control tablet weight. The effective peak compression force applied to an individual tablet or layer is measured by the control system at the main compression of the layer. This measured peak compression force is the signal used by the control system to eliminate out-of-tolerance tablets and correct the mould filling depth as necessary.

Fig 6: Double sided tablet press

3. Bilayer tablet press with displacement

The weight control principle of displacement tablets is fundamentally different from that based on compressive force. When measuring displacement, the sensitivity of the control system does not depend on the weight of the tablet, but on the applied pre-compression force.

Fig 7: Bilayer tablet press with displacement

PREPARATION OF BILAYER TABLETS [25, 26]

Bilayer tablets are manufactured with one layer of drug for immediate release and a second layer to later release the drug as a second dose or in sustained release form. It is intended for Bilayer tablets containing two incompatible drugs can also be made by compressing separate layers of each drug to minimize the contact area between the two layers. An additional intermediate layer of inert material may also be included. Certain requirements, such as sufficient mechanical strength and a desirable drug release profile, must be met in order to produce a suitable tablet formulation. In some cases, it may be difficult for formulators to achieve these requirements. Especially in the bilayer tablet formulation, which requires double compression technology, capping occurs due to the poor flow and compatibility characteristics of the drug. Material Densification includes both compressibility and consolidation.

Compression

It is defined as the reduction of gross volume by removing voids and bringing particles closer to the contact points.

Consolidation

It is a property of a material in which the mechanical strength is increased by due to the interaction between particles (bonding). The compressive force on layer 1 was found to be the main factor affecting the delamination of pellet.

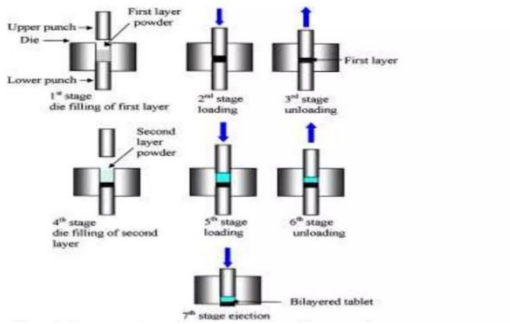

Fig 8: Formulation of multilayer tablets

VARIOUS TECHNIQUES FOR BILAYER MANUFACTURING [27, 28]

OROS Push Pull Technology

The system is mainly composed of 2 or 3 layers, one or more of which is composed of drug and another layer is composed of printing layer. A drug layer consists primarily of a drug and two or more different drugs. This drug layer therefore consists of the poorly soluble form of drug. Suspending agents and penetrating agents are further added. A semi-permeable membrane surrounds the tablet core.

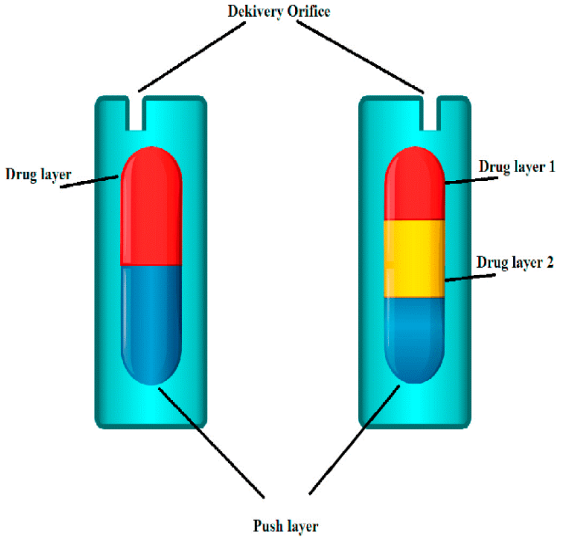

Fig 9: OROS Push Pull technology

L-OROSTM Technology

This system is the L-OROS system developed to solve the solubility problem. A lipid soft gel containing the drug in dissolved state is first made and then coated with a barrier membrane, followed by an osmotic push layer and then a semi-permeable membrane with the exit hole.

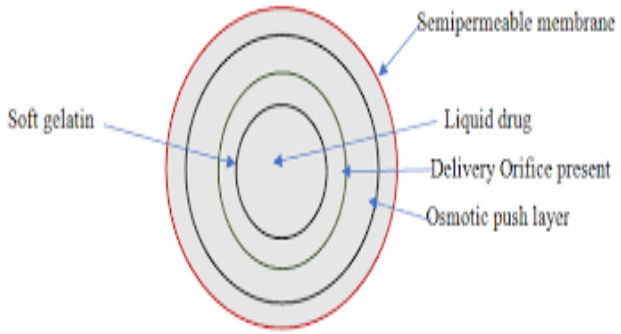

Fig 10: L-OROSTM Technology

ENSOTROL Technology

Increased solubility for custom or optimised formulations Shire Labs takes a holistic approach to drug delivery with a focus on identification and incorporating identified enhancers into controlled release technology.

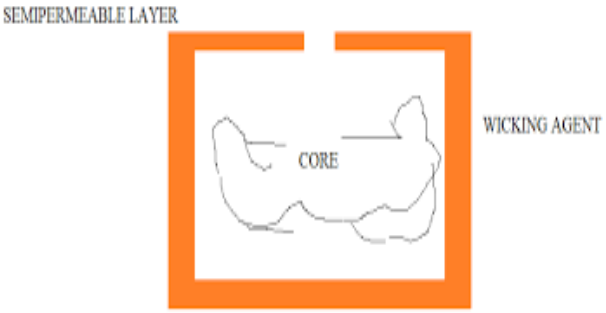

Fig 11: ENSOTROL Technology

DUREDAS Technology

This system is also known as the Elan dual release drug delivery system. DUREDAS™ technology is a bi-layer tablet that can provide immediate or sustained release of two drugs or different release rates of the same drug in a single dosage form. The tableting process can provide the immediate release granules and modified release hydrophilic matrix complex as separate layers in a single tablet. The modified release formulation properties of are provided by a combination of hydrophilic polymers.

DUROS Technology

The system consists of an outer cylindrical tank made of titanium alloy, which has high impact strength and protects drug molecules from enzymes. DUROS technology is a compact drug delivery system that resists the tiny syringe and delivers continuous, reliable release of small amounts of concentrated form over months or years.

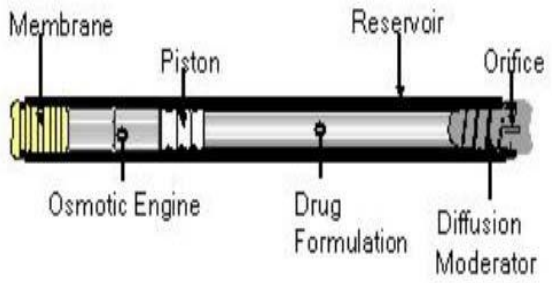

Fig 12: DUROS Technology

EVALUATION OF MULTILAYER TABLETS

Pre-compression evaluation [29-32]

Particle size distribution: The particle size distribution is measured using sieving method.

Photo-microscope study: Photo-microscope image of TGG and GG is taken (X450 magnifications) by photomicroscope.

Angle of repose: The angle of repose is determined to determine the flow property. The maximum angle between the free-standing surface of the powder heap and the horizontal plan is called the angle of repose.

$$\tan \theta = h/r$$

OR

$$\theta = \tan h/r$$

Where, **θ**=Angle of repose, **h**= height of the pile, **r**= radius of the powder cone

Table 1: Angle of repose I.P limits

Angle of repose	Powder flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density and Tapped density: A quantity of the powder (W) form is introduced into a measuring cylinder. After the initial volume, the cylinder is allowed to fall under its own weight onto a hard surface from the height for the fixed intervals. The tapping should be continued until further change in the volume will not occurs then it can be noted. The bulk density and the tapped density can be calculated using the following formulas.

Bulk density = $\mathbf{W/V_0}$

Tapped density = $\mathbf{W/V_t}$

Where **W** = Weight of powder, $\mathbf{V_0}$ = initial volume, $\mathbf{V_t}$ = final volume

Compressibility: Compressibility measured with the help of Carr's index. For measurement of Carr's index, values of bulk density and tapped density must be known.

$$\mathbf{CI = (TD-BD)/TD*100}$$

Where, **TD**= Tapped density, **BD**= Bulk density

Table 2: Carr's index I.P limits

Carr's index	I.P limits value
<10	Excellent
11-15	Good
16-20	Fair
21-25	Possible
26-31	Poor
32-37	Very poor
>38	Very very poor

Hausner's ratio: It includes the flow properties of the powder and is measured by the ratio of tapped density and the bulk density.

Hausner's ratio = Tapped density/Bulk density

Table 3: Hausner's ratio I.P limits

Hausner's ratio	I.P Limits value
Excellent	1.00-1.11
Good	1.1-1.18
Fair	1.19-1.25
Possible	1.26-1.34
Very poor	1.35-1.45

Moisture sorption capacity: All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity can be performed by taking 1g of disintegrate. Uniformly distributed in petri-dish and can be put in stability chamber at 37+1^{0}c and 100% RH for 2 days and can be investigated for moisture uptake by difference between weights.

Post compression evaluation [33-35]

General appearance of tablets: The overall look and feel of any tablet is its visual identity, and its overall "elegance" is paramount to consumer acceptance. The general appearance of tablets includes colour, smell, taste, size, shape, surface texture, physical defects, texture, and readability of identification marks.

Size and shape: The size and shape of compressed tablets are examined with a magnifying glass.

Tablet thickness: The thickness of the tablet is an important characteristic appearance and counting of the filling equipment to ensure the same thickness of the tablet. Ten tablets are taken, and their average thickness is recorded using micrometer.

Friability test: the friability of tablets is determined using the Roche friabilator. It is expressed as a percentage (%). If the mass (unit, mass) of the tablet is 650 mg or less, the entire 6.5 g tablet is used as a sample, and if the mass (specific gravity) of the tablet exceeds 650 mg, it is used as a sample. Ten whole tablets should then be taken as a sample, weighed (initial two) and transferred to the mill. The friabilator runs for 4 minutes at 25 rpm. This means up to 100 spins in less than 4 minutes. The weighed tablet is now re-weighed (w).
The percentage friability then calculated by: Percentage of friability = 100(1-w/w0) Percentage friability of tablets less than 1% is considered acceptable.

Weight variation test: Randomly select 20 tablets to determine their average weight. No more than two individual weights deviate from the average weight by more than the percentage deviation indicated in the table, and neither differs more than twice the percentage.

Swelling studies: The degree of swelling of the tablet is measured by putting it in the dissolution test apparatus, in 900 ml of 0.1N HCl at 37+20^{0}c. The weight and volume achieved by matrix tablet overtime is determined by periodically withdrawing the tablet from the dissolution medium. The tablet should be weighed on an analytical balance after lightly dampening with tissue paper to remove excess test solution. The volume of a tablet is obtained by measuring its thickness and diameter, considering the shape of an ordinary round cylinder. The determined weight and volume should be used to calculate the tablet's density during the dissolution study and swelling at the end of a specific time point. Performance is expressed as water absorption rate (WU) according to the following equation:

WU % =Wt. of swollen tablet -initial weight of tablet/ initial wt. tablet * 100

Hardness or crushing strength: Monsanto hardness tester measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. The Schleuniger and Strong-Cobb Pfizer apparatus can measure the diametrically applied force required to break the tablet.

Hardness is also called crushing strength during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is harder, it is difficult to disintegrate in the required period to meet the specifications; and if the tablet is soft, it is difficult to handle during other processes such as coating, packaging and shipping operations. The force required to break the tablet is measured in kilograms and strength of 4 kg is usually considered to be the minimum for satisfactory tablets. Oral tablets are typically 4 to 10 kg in hardness, but subcutaneous and chewable tablets are generally much softer (3 kg), and some extended-release tablets are much harder (10 to 20 kg). hardness is controllable and depends on the shape, chemistry, binder and pressure applied during compression.

Disintegration studies: A disintegration tester is commonly used to measure the disintegration time of tablets. Disintegration time is measured by placing one tablet in each test tube and placing the basket arc in a 1 litre beaker of water at 37-12^{0}c. to meet USP standards, all the tablets must disintegrate, and all particles must pass 10 mesh within a specified time.

Dissolution studies: Drug release studies were performed at 100 rpm, 37+ 0.5^{0}C and pH 1.2 buffer (900 ml) (i.e., 1N HCl) for 2 hours. Replace the lysis medium with phosphate buffer pH 6.8 (900 ml) and continue the experiment for another 10 hours. Samples taken during dissolution testing are analysed

by UV spectrophotometry using the multi-component analysis mode.

Stability studies: Bilayer tablets are packaged in appropriate packaging and stored under the following conditions for the period specified in the ICH recommendations for accelerated studies. The purpose of the stability study was to determine the proposed storage conditions, retest period and expiration date life. Stability test can analyse key parameters such as physical performance in the presence of visual defects, appearance, colour, tablet hardness, tablet weight, friability studies, dissolution profile, percentage drug content and impurity profile. Optimised formulations can be packaged in suitable induction-sealed HDPE blisters or bottles and subjected to temperature and humidity stability studies per ICH recommendations.

FUTURE ASPECTS

Floating drug delivery system: From a formulation and technology perspective, floating drug delivery systems provide a very simple and consistent approach to developing gastric retention dosage forms (GRDFs).

Approaches to design floating drug delivery system: The following methods have been used to design floating dosage forms for single unit and multiple unit systems.

Intra gastric bi-layered floating tablets: These are also compressed tablet contain two layers i.e.

i. Immediate release layer
ii. Sustained release layer

Multiple unit type floating pills: These systems consist of slow release pills, like "seeds surrounded by a double layer". The inner layer is made of an effervescent agent, while the outer layer is made of an expendable film layer. When the system is immersed in a dissolution medium at body temperature, it sinks immediately and then forms swollen balloon-shaped particles which float due to their lower density.

- To study the formulation and evaluation of a combination of sustained release microsphere and immediate release microsphere in a tablet formulation.
- Stability study in accelerated conditions and long term stability studies.
- In-vivo study in animals and IVIVC.

Pharmacokinetics studies by assessment of bioavailability by rapid analytical methods like HPLC, LC-MS etc.

CONCLUSION:

Formulation for different types of tablets viz. Bilayer/multi-layer, primarily to produce drug delivery systems that are relatively simple and inexpensive to manufacture, and to provide convenient dosage forms from patient's perspective. Multi-layered tablet works better than a single immediate-release or extended-release formulation. Multi-layered tablets are prepared to provide delivery systems for incompatible drugs and to provide controlled release tablet formulations by providing peripheral or multiple swellings. Bilayer tablets offer the possibility and the means to combine incompatible drugs and the same drug with release rates in a single unit. For the formulation and development of bilayer tablets using different methods such as direct compression, dry granulation and wet granulation. The influence of selected process parameters on the key properties of bilayer tablets can be investigated. Based on tablet optimisation, the effects of disintegrates, lubricants, binders and polymers on the performance of bilayer tablets should be investigated. We can determine the best method for proper disintegration time, in vitro/in vivo dissolution profile, satisfactory physical parameters, i.e., the size, shape, colour, weight, thickness, hardness and friability of the prepared formulation. Multi-layered tablet formulation should have the following main expected results:

- An immediate release of drug for quick onset of action and sustained release of drug in a specific site where it is best absorbed.
- Overall reduction in the dose.
- In-vivo efficiency in terms of bioavailability and steady state blood levels.

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