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MULTI LAYERED TABLETS: INNOVATIVE TRENDS IN ORAL DELIVERY

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Abstract:

Multilayer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Controlled release dosage forms have been extensively used to improve therapy with several important drugs. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. 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 (immediate release with extended release). Despite their advantages, due to the use of different materials and complex geometric boundaries between the adjacent layers, the mechanical structures of this drug delivery system have become quite intricate, requiring complicated tablet architectures as well as patient-friendly. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. In the case of bilayered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper nonadhesive layer its delivery occurs into the whole oral cavity. This review explains fundamentals of bilayer tablet system along with its fabrication techniques, different approaches, characterization, and challenges in Bilayer tablet manufacturing and recent developments in the field of bilayer technology.

Keywords: *Multilayer tablets, Active Pharamaceutical Ingredient, Immediate Release, Drug release, Drug Delivery.*

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INTRODUCTION:

A diverse range of dosage forms and delivery systems has been developed for providing care and welfare for human beings. It is well known that modified release dosage forms may offer one or more advantages over immediate release formulations of the same drug. Depending on the method/route of administration, dosage forms come in several types. These include many kinds of liquid, solid, and semisolid dosage forms[1]. Common dosage forms include pill, tablet or capsule, drink or syrup, and natural or herbal form such as plant or food of sorts, among many others. Notably, the route of administration for drug delivery is dependent on the dosage form of the substance in question. The design of modified release drug product is usually intended to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval whilst also providing greater patient compliance and convenience. Sustained release dosage forms cover a wide range of prolonged action preparations that provide continuous release of their active ingredients for a specific period of time. By prescribing sustained release systems, it is possible to achieve several desirable therapeutic advantages[2]. As the frequency of dosage is reduced, patient compliance can be improved, and drug administration can be made more convenient.

Drug Delivery system is becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biological parameters pertinent to their performances[2,3]. Controlled Drug Delivery System provides drug release at a predetermined, predictable and controlled rate to achieve high therapeutic efficiency with minimal toxicity. Despite tremendous advancement in drug delivery, oral route remains the preferred route for the administration of therapeutic agents and oral drug delivery is by far the most preferable route of drug delivery because of low cost of therapy and ease of administration leads to high levels of patient compliance as well as the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes, consequently much effort has been put into development of strategies that could improve patient compliance through oral route[4].

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bi-layer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance[5]. Multi-layer tablets or bi-layer tablets can be a primary option to avoid chemical incompatibilities between API'S by physical separation, and to enable the development of different drug release profiles (immediate release with extended release).4 multi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Multi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. So use of bi-layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few[6]. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependent polymers.

Figure 1 Multi-layer Tablets

However, these drug delivery devices are mechanically complicated to design/manufacture and harder to predict their long term mechanical properties due to the poor mechanical and compression characteristics of the constituent materials in the compacted adjacent layers, elastic mismatch of the layers, insufficient hardness, inaccurate individual mass control, cross contamination between the layers, reduced yield, and their tendency to delaminate at the interface between the adjacent compacted layers during and after the various stages of production downstream of the compaction process. One of the major challenges is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack driven by residual stresses in the tablet propagating a finite distance within the tablet and leads to delamination[7].

Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, firstlayer tamping force, and cross contamination between layers. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per sec (inefficient or uncontrolled process) and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control).

NEED OF MULTILAYER TABLETS [7,8]:

- For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/mucoadhesive delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.
- Controlling the delivery rate of either single or two different active pharmaceutical ingredient(s)
- To modify the total surface area available for API layer either by sandwiching with one or two in active layers in order to achieve swellable/erodible barriers for modified release.
- To separate incompatible Active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).

MERITS OF MULTILAYER TABLETS:

- Bi-layer execution with optional single-layer conversion kit.
- Cost is lower compared to all other oral dosage form.
- Greatest chemical and microbial stability over all oral dosage form.
- Objectionable odour and bitter taste can be masked by coating technique.
- Flexible Concept.
- They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Easy to swallowing with least tendency for hang-up. Suitable for large scale production

CHALLENGES IN MANUFACTURING MULTI LAYERED TABLETS:

- Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In Practice, there are some manufacturing challenges[9].
- Delamination: Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.
- Cross-contamination: When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.
- Production yields: To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layer tablets.

DEMERITS OF MULTILAYER TABLETS:

- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Bitter tasting drugs, drugs with an objectionable 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[10]
- If the compacted layers are too soft or too hard, they will not bind securely with each other which can lead to compromised mechanical integrity and also the separation of the layers

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- Production yields: To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layer tablets.
- Cost: bilayer tableting is more expensive than single- layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation[12].
- Taste- Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.
- Properties- Drugs with poor wetting, slow dissolution properties, increased absorption in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability

MANUFACTURING ASPECTS OF MULTILAYERED TABLETS:

The manufacturing process of bi-layer tablets requires special rotary presses where the first layer is fed into the die and partially pressed, but not ejected from the die. Then the second layer is fed followed by compaction and ejection. Apart from the critical material attributes of individual components and final blend, the tablet press has large influence on the manufacture of multilayer tablets[13].

Single sided press:

The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder.

Figure 2 Single sided press

Then the entire tablet is compressed in one or two steps. Individual layer-weight control on a single-sided press requires some form of measurement of the first layer and of the total tablet. The first control loop indirectly monitors weight and controls the fill depth of the first layer. The second loop indirectly

monitors the total tablet weight, but adjust only second- layer fill depth. In general, compression force is used to monitor tablet or layer-weight. But to do so it is necessary to apply a compression force to the first layer before adding the second layer-powder[14]. Limitations of the single sided press-No weight monitoring / control of the individual layers.

Double sided Tablet press:
In most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required. Bilayer tablet press with displacement monitoring[15]

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied precompression force.

Bilayer tablet press with displacement monitoring:
The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied precompression force[16].

Advantages:
- Weight monitoring / control for accurate and independent weight control of the individual layers.
- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- Independence from the machine stiffness.
- Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross-contamination between the two layers.
- Clear visual separation between the two layers and maximized yield.

Compression force-controlled tablet presses:
Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of the bi-layer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet. Bonding is severely restricted if the first layer is compressed at a too-high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with "compression force measurement". Most double-sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at maincompression of that layer[17,18]. This decreasing sensitivity is inherent to an exponential relationship and therefore inherent to the compression force-controlled system. The rate at which the sensitivity decreases depends on the formulation or powder characteristics. This is the very reason why a compression force control system is always based on measurement of compression force at main-compression and not at pre-compression since a higher compression force is required to obtain sufficient sensitivity, thus allowing a more accurate control.

TECHNOLOGIES USED IN MULTILAYER TABLETS:

A) OROS® Push Pull Technology:
This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core[19].

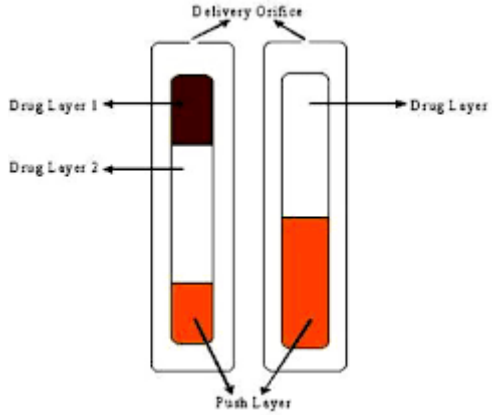

Figure 3 Bilayer and Trilayer technology

B) L-OROSTM Technology:

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and then a semi permeable membrane, drilled with an exit orifice.

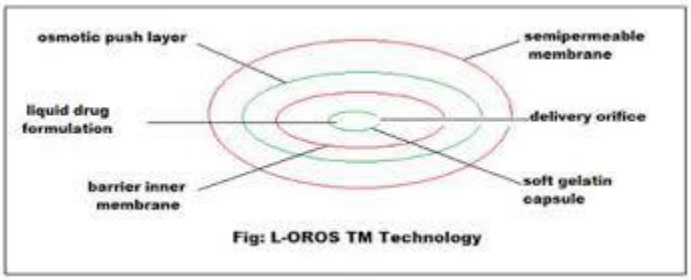

Figure 4 L OROSTM Technology

C) DUREDAS™ Technology:

This system is also known as Elan drug technologies' Dual release drug delivery system. DUREDAS™ Technology is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tableting process can provide an immediate release granulate and a modified release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers[20].

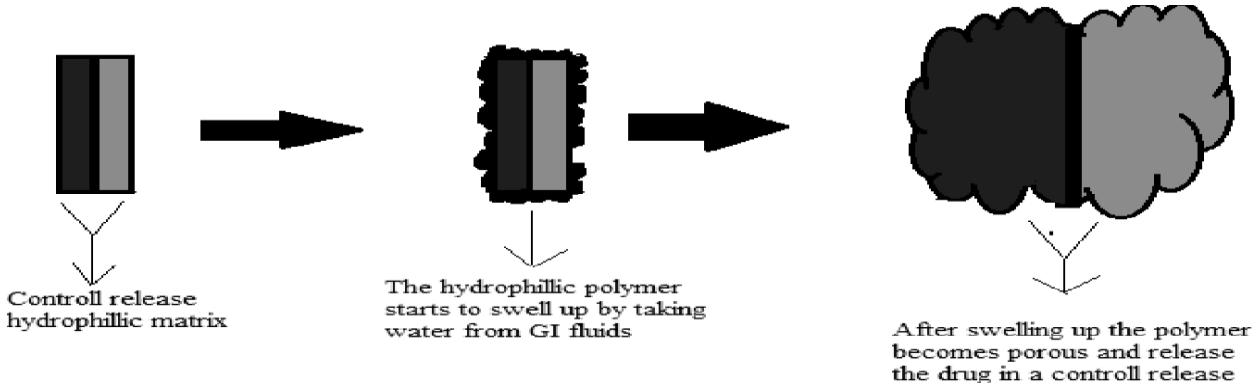

Figure 5 DUREDAS TECHNOLOGY

D) Duros Technology:

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature

syringe and reglious minute quantity of concentrated form in continues and consistent from over months or year[21]

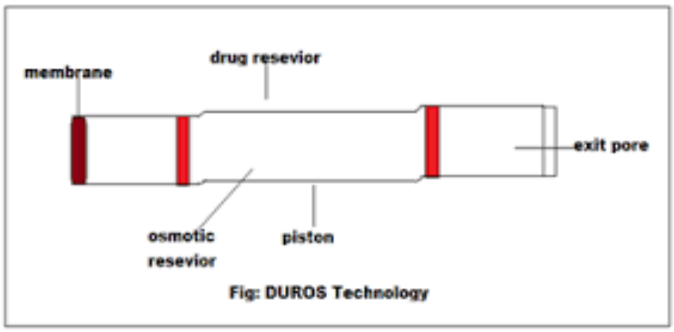

Figure 6 DUROS Technology

EVALUATION OF MULTI LAYERED TABLETS:

Precompression studies:

General Appearance:

The visual identity and overall 'elegance' of a tablet is essential for consumer acceptance. The general appearance includes tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Angle of Repose:

The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

Ɵ = tan-1 (h/r)

Where 'h' and 'r' are the height and radius of the powder cone.

Moisture Sorption Capacity:

All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity was performed by taking 1 g of disintegrate uniformly distributed in Petri-dish and kept in stability chamber at 37±1°C and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by difference between weights[22,23].

Density:

The bulk density (BD) and tapped density (TD) were determined and calculated using the following formulas.

Bulk density= $\frac{wieght\ of\ the\ powder}{bulk\ volume}$

Tapped Density =$\frac{wieght\ of\ the\ powder}{tapped\ volume}$

Compressibility:

The compressibility index of disintegrate was determined by Carr's compressibility index[24].

Carr's Index % = $\frac{TD-BD}{TD}$ **x 100**

Hausnser's ratio:

It is calculated by the formula, **Hausner's Ratio =** $\frac{TD}{BD}$

Post compression parameters:

Tablet thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism[25]. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of weight:

Twenty tablets were selected at random and the average weight was determined. Weight Variation was calculated and was compared with I. P. standards.

Friability:

Friability is the measure of tablet strength. Friction and shock are the forces that most often cause tablets to chip, cap or break[26]. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. Electrolab EF-2 Roche friabilator (USP) was used for testing the friability using the following procedure[27]. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a

distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined[28].

% loss = [(Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets] ×100

Hardness:
The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The Strong-Cobb Pfizer and Schleuniger apparatus which were later introduced measures the diametrically applied force required to break the tablet[29,30]. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 Kg is usually considered to be the minimum for satisfactory tablets[30].

Stability Study (Temperature dependent):
The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability and Dissolution etc.) and drug content[31]. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C [32].

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5%	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

CONCLUSION:

Bi-layer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate (e.g. IR and ER) can be incorporated in a single unit. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. A well-developed product will effectively address these issues by including appropriate control strategies and establishing the functional relationships of the material attributes and process parameters critical to the bilayer tablet quality as discussed in the article. The preparation of bi-layer tablet dosage form could be a potential formulation for delivery of drugs from a single dosage form which could reduce the dosing frequency, improve patient compliance and give better disease management. Hence, multilayered tablets will definitely throw a new limelight for researchers who are interested to design modified sustained release dosage form in a cost effective manner.

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