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RECENT APPROACHES OF BILAYER TABLET TECHNOLOGY: A REVIEW

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ABSTRACT:

Bilayer tablet is a new era for winning development of controlled release formulation along with various features to provide successful drug delivery system. Bilayer tablet may be the best option for avoiding chemical or physical incompatibilities between Active Pharmaceutical Ingredients (APIs) and to enable to the development of drugs are different drug release profiles. Bilayer tablet is suitable for the sequential release of two drugs in combination, as well as for the Sustained release of a tablet in which one layer is for immediate release as a loading dose and Second layer is maintenance dose. Bilayer tablet is continued improved beneficial technology to overcome the shortcoming of the single layerd tablets. Therefore, now a day's bilayer tablet is various developed and developing countries are moving towards 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. Bilayer tablet is involves both the compressibility and consolidation. 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 bioavailabilty which in turn improve the patient complience. The present object provide an introduction to bilayer tablet technology challenges in bilayer tablet manufacturing, various tablet presses used, quality and GMP reuirements for their manufacturing varioustechniques used for bilayer tableting and recent advancement in the filed of bilayer technology.

KEYWORDS:

Bilayer tablet, GMP requirement, DUREDAS^{TM} technology, Bilayer tablet press, Active Pharmaceutical Ingredients.

INTRODUCTION:

The development of two or more active pharmaceutical ingredients (APIs) combined in a single dosage form (bilayer tablet) is gaining importance in the pharmaceutical industry, facilitating patient convenience and compliance. Bilayer tablets may be a major option to avoid chemical incompatibilities between APIS by physical separation and facilitate the development of different drug release profiles (immediate release and sustained release) (Ghosh R. et al., 2014; Pujara ND et al., 2012) Bi-layer tablets represent a new era in the successful creation of controlled release formulations with a number of features to ensure successful medication delivery. Bi-layer pills may be a vital alternative to prevent chemical Active pharmaceutical ingredients (APIs) can be physically separated to resolve any incompatibilities between them and to make it easier to create various medication release profiles. A bi-layer tablet is suitable for the sequential release of

two medications taken together as well as for the sustained release of a tablet where the first layer is for immediate release as a loading dosage and the second layer is a maintenance dose. (Ghosh R. et al., 2014) The goal in the development of delayed or controlled-delivery systems is to reduce dosing frequency, or 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 primary goals of sustained drug delivery are to ensure safety and improve drug efficacy and patient compliance. Bilayer tablets are a major option for physical separation to avoid chemical incompatibilities between APIS and to allow development of different drug release profiles (immediate release and sustained release). Bilayer tablets are suitable for combining and sequentially releasing two drugs. It can also separate two incompatible substances. It can also be used for sustained release tablets, where one layer is the initial dose for immediate release and the second layer is the maintenance dose. Bilayer tablets contain immediate and delayed release layers. (Kale, S.S. et al.,2011; Payghan, S.A. et al.,2011)[4] The primary goals of sustained drug delivery are to ensure safety and improve drug efficacy and patient compliance. However, in many cases this controlled drug delivery system does not achieve the stated advantages because the initial bolus dose is not measured and site-specific drug delivery is not achieved. (Jaldhara, S.P. et al.,2012; Bhadange, M.D. et al .,2015) Immediate release drug delivery The system is said to disintegrate rapidly and exhibit immediate drug release. This is associated with fluctuations in plasma levels of the drug, leading to a decrease or loss of drug efficacy or an increased occurrence of side effects. leads to Therefore, multiple daily doses of DDS are required to compensate for the decrease in drug plasma concentration due to metabolism and excretion. A relatively constant plasma level of the drug is often preferred in order to keep the drug concentration within the therapeutic range. However, it is difficult to achieve, especially for once-daily dosage forms, in part because the environment for drug diffusion and/or absorption is limited along the gastrointestinal (GI) tract. Because it changes. Based on these considerations, we proposed bilayer tablets. (Jaldhara, S.P.et al., 2013)

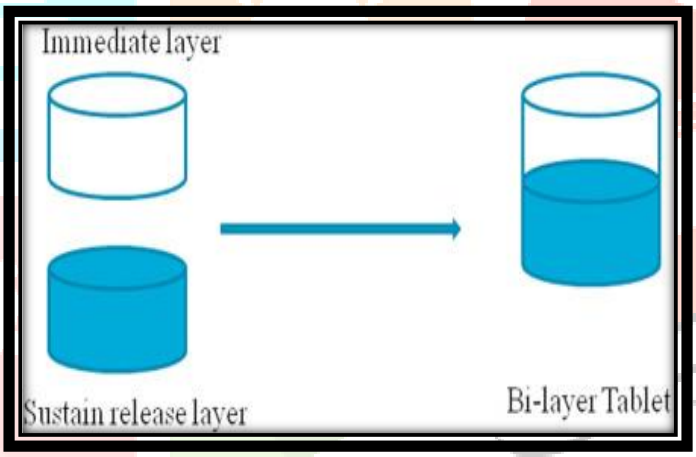

Fig. 1 Bilayer Tablet

NEEDS OF BILAYER TABLETS:

1. To separate Active Pharmaceutical Ingredients (APIs) that are incompatible from one another, control the release of API from one layer by applying the functional feature of the other layer (such as the osmotic property).
2. To provide fixed dose combinations of various APIs, extend the life cycle of the drug product, and create novel drug delivery methods such chewing devices, buccal / mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery.
3. One or two additional active layers to create swellable/erodible barriers for adjustable release, hence modifying the overall surface area available for the API layer.
4. Controlling the rate of delivery of one or two active pharmaceutical ingredients. (Gopinath, C. et al., 2013 ; Patel, M.)

ADVANTAGES OF BILAYER TABLET:

1. Since they 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. Easy to swallow with a low tendency to hang up
3. A high level of patient acceptance
4. When two or more APIs are combined into a single bilayer tablet, the burden on the dosing unit is reduced, which improves patient compliance.
5. The highest level of chemical and microbiological stability among all oral dosage forms
6. Low price in compared to other dose forms.
7. The use of coating technologies can cover up offensive tastes and smells.
8. Suitable for large-scale manufacturing (Gopinath, C. et al.,2013; Pooja Nair et al., 2019; Panchal, H.A. et l.,2012)

DISADVANTAGES OF BILAYER TABLET:

1. Drugs with poor wettability, slow dissolution characteristics, optimal absorption, and high GIT content can be difficult to formulate or manufacture as tablets that provide adequate or complete drug bioavailability.
2. Bitter-tasting, unpleasant-smelling, or oxygen-sensitive drugs may require encapsulation or coating.
3. Inaccurate weight control for each individual layer.
4. Cross contamination between the layers.
5. Adds complexities the situation and bilayer rotary presses are expensive.(Rameshwar, V. et al., 2014)

LIMITATION OF BILAYER TABLET:

1. It should be chemically and physically stable enough to sustain its physical properties over time. The bi-layer tablet must be capable of releasing the therapeutic ingredients in a predictable and repeatable manner.
2. Drugs with poor wetting, slow dissolution characteristics, and optimal absorption in the gastro intestinal track (GIT) may be challenging to formulate or manufacture into a tablet that provides acceptable or full drug bioavailability.
3. One of the most difficult issues in bilayer formulation is a lack of adequate bonding and adhesion at the interface between the layers. Neighbouring compressed layers, which is frequently the outcome of a layer separation and an interfacial crack.
4. A bilayer tablet's neighbouring layers are biomechanically joined to one another, so it's crucial to understand what determines the stress state. The mechanical characteristics of each layer and the tablet, the compression parameters used in conjunction with specific techniques, and the compression situation all play a significant part in the same.
5. The administration of a sustained release bilayer tablet does not allow for the early conclusion of therapy.
6. 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 layer separation.
7. Must have a chemical stability shelf life to prevent the change of the therapeutic agents.
8. The bilayer tablet must release the drug in a predictable and repeatable manner. (Sarma, A. t al., 2013; Jaldhara, S.P. et al., 2013; Sushma, NSV et al., 2016)

CHALLENGES IN BILAYER MANUFACTURING:

Bilayer tablets are conceptually two single-layer tablets squeezed into one. There are various manufacturing difficulties in real life.

DELAMINATION –
Tablet delamination occurs when there is insufficient bonding between the two halves of the tablet. When the two granulations are compressed, they should stick together.

CROSS-CONTAMINATION -

Cross-contamination occurs when the granulation of the first layer mixes with the granulation of the second layer or vice versa. The fundamental goal of the bilayer tablet might be defeated. Cross contamination can be significantly reduced by using appropriate dust collection.

PRODUCTION YIELDS -

To prevent cross contamination, dust collection is required which leads to losses. As a reason, single-layer tablets provide higher yields than bilayer tablets.

COST -

There are various factors that make bilayer tableting more expensive than single layer tableting. The tablet press is firstly more expensive. Second, in bilayer mode, the press often operates more slowly. Third, developing two compatible granulations is necessary, which needs additional time to develop, evaluate, and validate the formulation. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, in order to enable the design of a reliable product and process, it is imperative to gain insight into the core causes.(Gopinath, C. et al., 2013; Akhtar, M. et al.,2020)

BILAYER TABLET: QUALITY AND GMP REQUIREMENT:

The selected press must be capable of, in order to make a quality bilayer tablet in an approved and GMP manner:

- Preventing the bilayer tablet's two layers from capping and separating from one another.
- Providing enough tablet hardness.
- Preventing cross-contamination between the two layers.
- Producing a clear visual separation between the two layers.
- High yield
- Controlling the weight of the two layers precisely and individually. (Kumar et al.,2013; Aggarwal, S. et al.,2013)

TYPES OF BILAYER TABLET:

1. Homogenous Type

   Bilayer tablets are preferred when the release profiles of the drugs are different from one another. Bilayer tablets enable the design and modulation of dissolving and release properties. Bilayer tablets are prepared with one layer of drug for immediate release while second designed to release drug later, either as second dose or in an extended-release manner. (Patil et al.,2019; Syed et al., 2013;Gopinath et al.,2013)

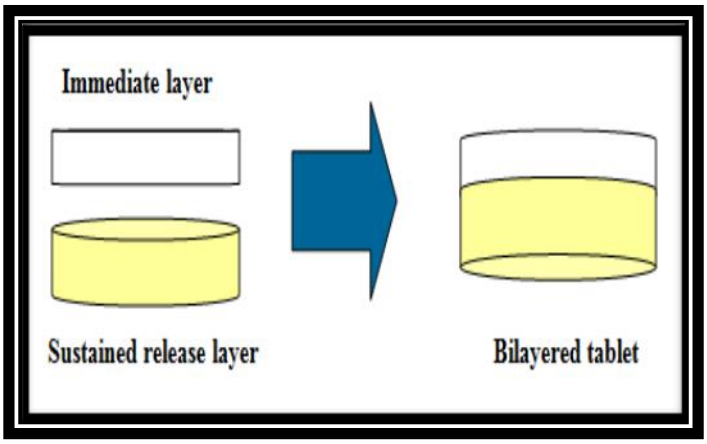

Fig. 2 Bilayer tablets (same drug with different release pattern-homogenous)

2. Heterogeneous Type

   Bilayer tablet is suitable for sequential release of two drugs in combination, distinct two incompatible substances. (Syed et al., 2013;Gopinath et al.,2013)

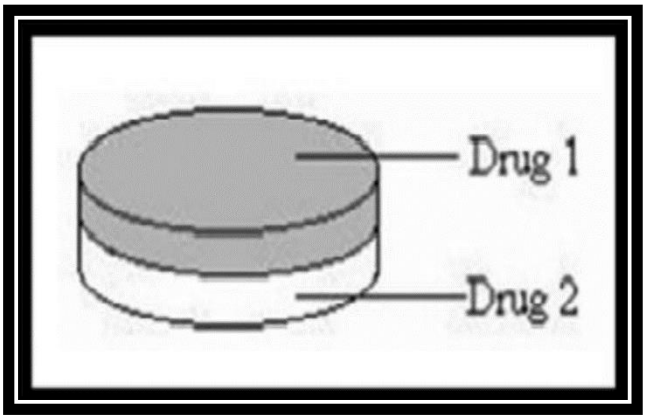

Fig. 3 Bilayer tablets (with two different drugs-heterogeneous)

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 Basics

1. Single Sided Tablet Press

Over time, different kinds of bilayer presses have been developed. The most basic design is a single-sided press with two distinct chambers for the double feeder. Each chamber is gravity or force fed with a separate powder, resulting in the two separate layers of the tablet. The first layer of powder and the second layer of powder are put onto the dye as it passes under the feeder, and then the entire tablet is compressed in one or two steps. The two layers in the dye mix slightly at their interface and, in most circumstances, connect sufficiently such that no layer separation happens when the tablet is made; this is the easiest method of generating a bilayer tablet. (Kiran et al., 2015; Kumar et al.,2013)

Fig. 4 Single Sided Tablet Press

Limitation

- Dwell time because of the short compression roller may cause issues with hardness and poor deaeration capping.
- There is no weight monitoring or control over the separate layers.
- Between the two levels, there is no obvious visual separation.
- The dwell duration can be increased by decreasing the turret rotation speed, although doing so will result in a reduced tablet output. (Das et al., 2017;Gupta et al., 2021; Nazim et al., 2015)

Dwell time

Dwell time is defined as the time during which compression force is above 90% of its peak value. Extended dwell times are a major factor in producing as quality tablet, especially when compressing a difficult formulation. (Rameshwar et al., 2014)

Compression force

Many bilayer formulations need a first layer compression force of less than 100 daN in order to maintain their ability to link with the second layer. Above 100daN, this ability may be lost and the bonding between the two layers may not be strong enough to prevent the separation of the two layers and low hardness of the bilayer tablet.(Rameshwar et al., 2014)

2. Double Sided Tablet Press

Most double-sided tablet presses that automate production control monitor and control tablet weights using compression force. The effective compression force applied on each individual tablet by the compression mechanism at the layer's main compression. This system helps into reject out the tolerance tablets and correct the dies fill depth when required. (Rameshwar et al.,2014)

Fig. 5 Double Sided Tablet Press

Advantages

1. Increased dwell time at first and second layer precompression to give sufficient hardness at highest turret speed.
2. Low compression force is applied to the top layer to prevent chapping and individual layer separation.
3. Displacement weight monitoring allows accurate and independent weight control of the individual layer.
4. Maximum cross-contamination prevention between two layers
5. Maximized yield
6. A clear visual separation between the 2 layers. (Abebe, A. et al., 2014)

Limitation

1. Correct bonding is only achieved when the first layer is compressed at a low compression force, allowing it to interact with the second layer during the final compression.
2. Bond strength is too restricted if the first layer is compressed at a high compression force.
3. Unfortunately, in the case of tablet presses with compression force measurement, the low compression force needed to compress the first layer decreases the accuracy of the weight monitoring/control of the first layer. (Kiran et al., 2015)

3. Bilayer Tablet Press with Displacement Monitoring

The displacement tablet weight control principle is fundamentally different from the compression force control principle. When measuring displacement, the control system sensitivity doesn't really depend on the tablet weight but depends on the applied precompression force. (Gopinath et al., 2013)

Fig. 6 Bilayer Tablet Press

Advantages

1. Weight monitoring and control for accurate and independent weight control of individual layers.
2. Low compression force applied to the first layer to prevent capping and layer separation.
3. Increased dwell time during precompression of the first and second layers to give enough hardness at the fastest turret speed. Maximum cross-contamination prevention between the two layers.
4. Maximum yield and clear visual separation between the two layers. (Gopinath et al., 2013)

4. Multilayer Compression Basics

Presses can be modified for multipliers, or a conventional double press can be specifically made for multi-layer compression. The idea of a multilayer tablet has been used for a long time to create formulations for prolonged release of drugs. These tablets may feature a fast-releasing layer as well as double or triple layers to sustain drug release from the tablet. The pharmacokinetics advantage relies on the fact that drug release from fast releasing granules leads to sudden rise in blood concentration, however the blood level remains in a steady state as the drug is released from the sustained granules.(Kiran et al.,2015)

PREPARATION OF BILAYER TABLETS:

Bilayer tablets are manufactured with one layer of drug for immediate release and the second layer for later release, either as a second dosage or in a prolonged release form. Bilayer tablets with two incompatible drugs can also be made by compressing individual layers of each drug to restrict the area of contact between two layers. An extra intermediate layer of inert material may also be included.

To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. Because of the drug's poor flow and compatibility

qualities, which will result in capping and/or lamination, it may be difficult for the formulator to achieve these conditions on occasion, especially in the case of bilayer tablet formulation, when double compression technique is applied. A material's consolidation and compressibility both contribute to its compaction**.**

Compression: It is defined as a reduction in bulk volume caused by the elimination of voids and the bringing of particles into relatively close contact.

Consolidation: It is the property of the material in which there is increases the mechanical strength due to interparticulate interaction (bonding). The compression force on layer one was discovered to be a significant element determining tablet delamination. (Agiba, A.M. etal., 2021; Bhadange, M.D.et al.,2015;Gopinath et al.,2013)

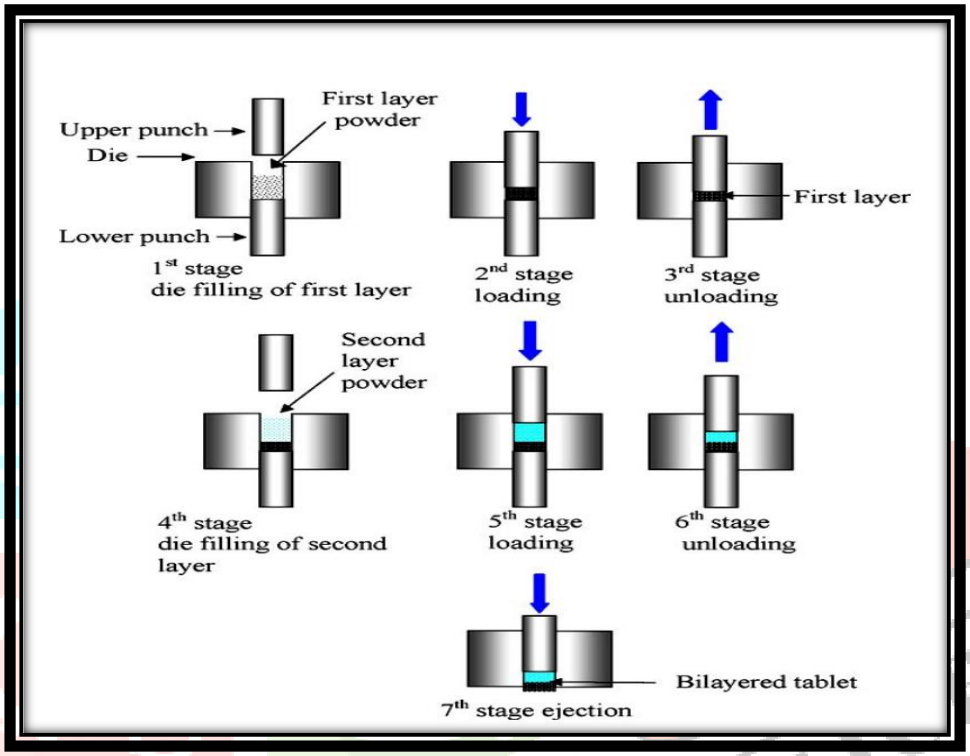

Fig. 7 Preparation of Bilayer Tablet Compaction

V**ARIOUS TECHNISHQUES FOR BILAYER TABLET:**

1. OROS® Push pull Technology
2. L-OROS™ Technology
3. EN SO TROL Technology
4. DUROS Technology
5. DUREDAS™ Technology

1. OROS® Push pull Technology

This system accommodates primarily two or three layers among which the one or more layer is essential of the drug and other layer are consist of push layer. The drug layer is made up of drug and two or more distinct agents. As a result, the medication in this layer is in a poorly soluble form. There is also a suspending agent and a diffusion agent added. The tablet core is surrounded by a semi-permeable membrane. (Jaldhara et al.,2013)

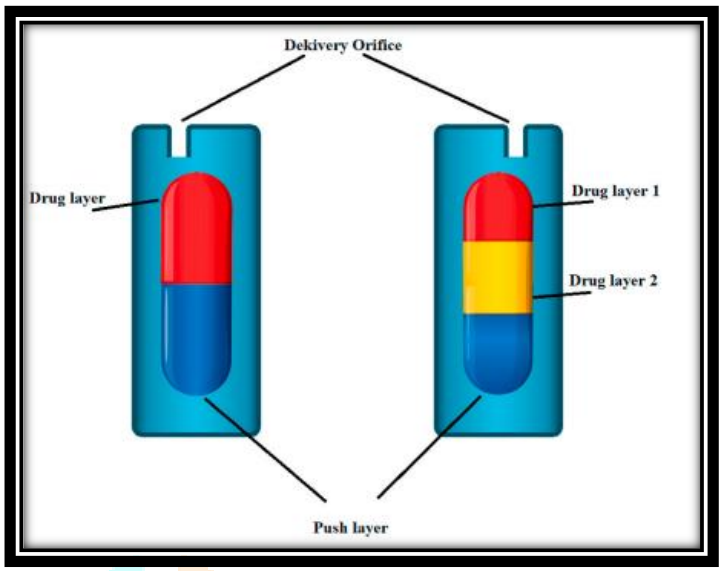

Fig. 8 OROS® Push pulls Technology

2. L-OROS™ 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 layer, then osmotic push layer and then a semi permeable membrane, drilled with an exit orifice.(Kumar et al.,2013)

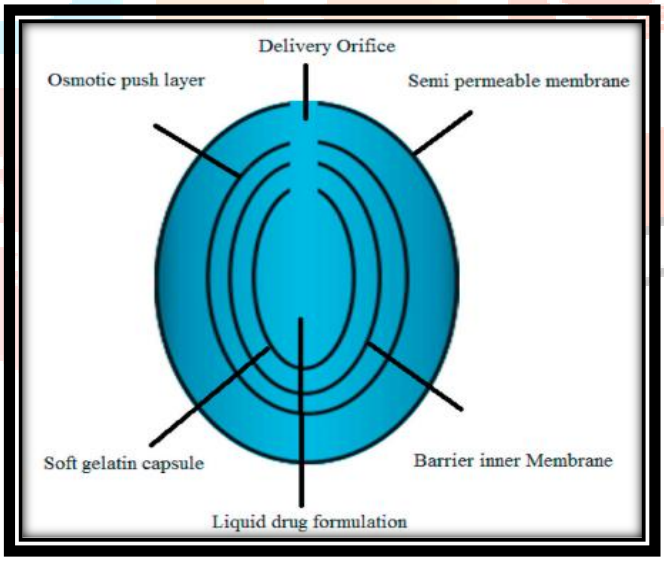

Fig. 9 L-OROS™ Technology

3. EN SO TROL Technology

Solubility enhancement of an order of magnitude or to create optimised dosage form Shire laboratory uses an integrated strategy to drug delivery that focuses on identifying and incorporating the identified enhancer into controlled release technologies.(Akhtar et al., 2020;Pooja Nair et al., 2019)

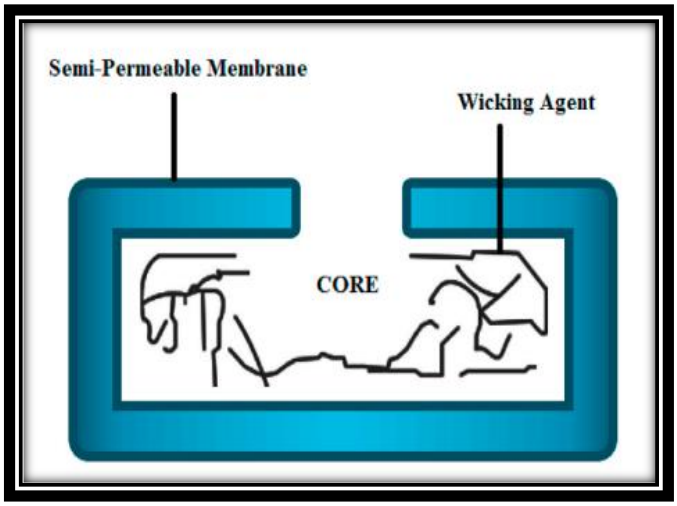

Fig. 10 EN SO TROL Technology

4. 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 amount of concentrated form in continues and consistent from over months or the year. (Panchal et al., 2012)

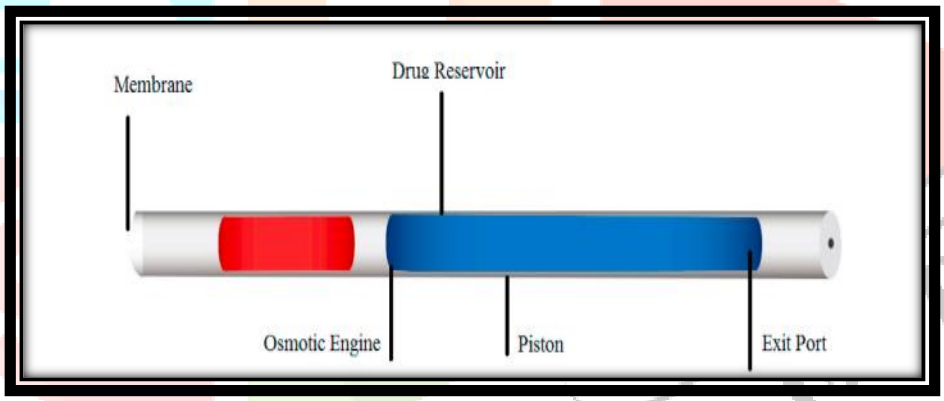

Fig. 11 DUROS Technology

5. DUREDAS™ Technology
   (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. A modified-release hydrophilic matrix complex and an immediate release granulate can be provided by the tab letting method as different layers within a single tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers. (Kumar et al., 2013)

   Benefits offered by the DUREDAS™ technology include:

   - Bilayer tableting technology.
   - Tailored release rate of two drug components.
   - Capability of 2 different CR formulations combined.
   - Capability for immediate release and modified release components in one tablet.
   - Unit dose, tablet presentation.

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bi-layer. It is possible to achieve two separate release rates from either side. Greater sustained release prolonging is possible in this way. Typically, an instant release granulate is compressed initially, followed by the addition of a controlled release element, which is compressed onto the initial tablet. The final dose form obtains the distinct bi-layer effect as a result. A further extension of the DUREDAS™ technology is the production of controlled release combination dosage forms whereby two

different drugs are incorporated into the different layers and drug release of each is controlled to achieve maximum the therapeutic effect of the combination. Again, both immediate release and controlled release combinations of the two drugs are possible. A number of combination products have been explored using this technology approach. The DUREDAS™ technology was initially employed in the development of a number of OTC controlled release analgesics. In this instance, rapid analgesic release is required for a quick onset of therapeutic impact. As a result, one layer of the tablets is formulated as an immediate release granulate. By contrast, the second layer of the tablet, through use of hydrophilic polymers, releases drug in a controlled manner. The controlled release is due to a combination of diffusion and erosion through the hydrophilic polymer matrix. (Singh, S.D. 2011;Kumar et al.,2013)

VARIOUS APPROACHES USED IN THE BILAYER TABLET:

a) Floating Drug Delivery System

These are designed to have a low density and therefore float on gastric contents after administration until the system either disintegrates or the device absorbs fluid to the point where its density is sufficient that it loses buoyancy and can pass more easily from the stomach with a wave of Motility responsible for gastric emptying. The bilayer tablet is made in such a way that one layer delivers the drug immediately, resulting in a rapid start of effect, while the other layer is designed as a floating layer that floats in the stomach.

Approaches to design Floating Drug Delivery System: The following approaches have been applied to the design of floating dosage forms of single- and multiple-unit systems.

Intra gastric bilayered floating tablets: These are also compressed tablets with immediate and sustained release in two layers, as shown in the figure 12.(Bhadange et al., 2015;Ghosh et al., 2014)

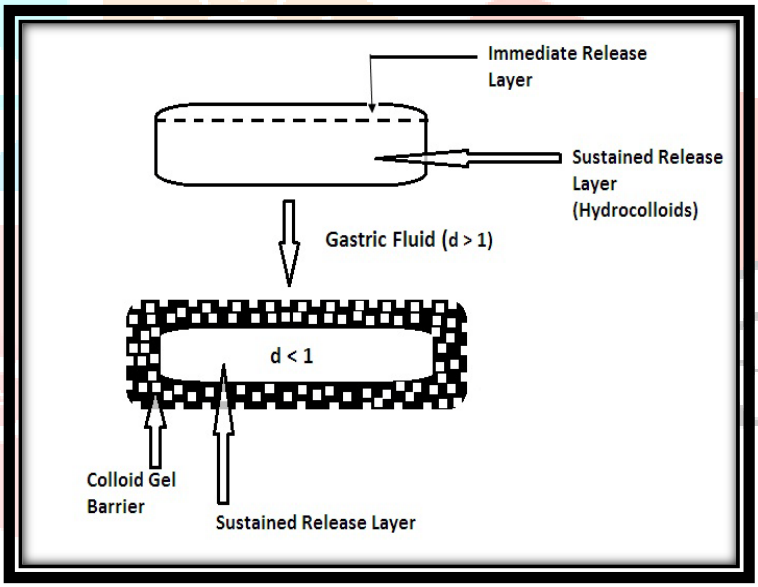

Fig. 12 Intra gastric bilayer floating tablet.

Multiple unit type floating pills

In these systems, the "seeds" are sustained release pills that are surrounded by two layers. Effervescent agents make up the inner layer while swellable membrane layers make up the outer layer. The system lowers immediately when immersed in dissolving liquid at body temperature, then generates swollen pills that resemble balloons and float because they have a reduced density. (Bhadange et al., 2015)

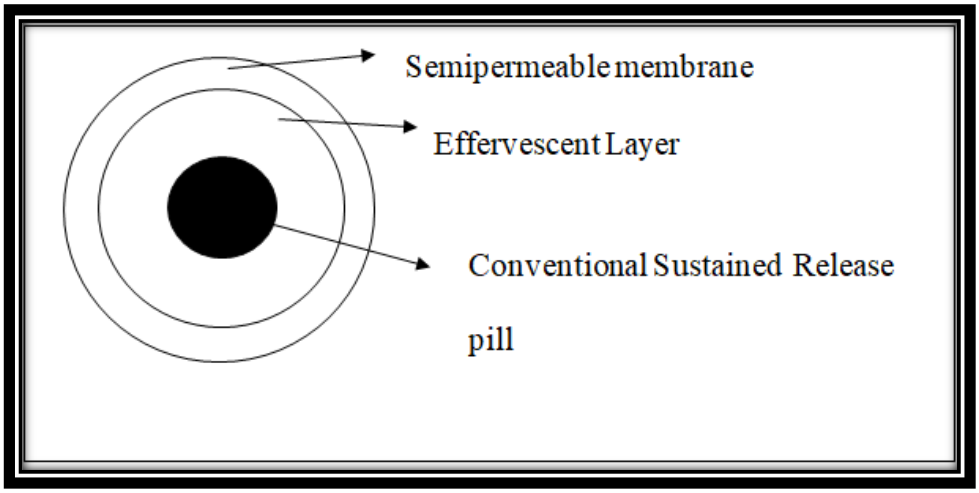

Fig. 13 Multiple units of oral FDDS

b) Polymeric Bio adhesive System

These are designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. While the adhesive forces are being reduced, this should promote stomach retention. These are composed of two layers, one with rapid dosing and the other with bio adhesive capabilities.

Disadvantages: The success is seen in animal models with such system has not been translated to human subjects due to the differences in mucous amounts, consistency between animals and humans. The system adheres to mucous rather than mucosa. The mucous layer in humans would appear to slough off readily, carrying any dosage form with it. As a result, bio adhesive dosage form does not appear to offer a solution for long-term administering drugs over a few hours. (Bhadange et al., 2015)

c) Swelling system

These are designed to be small enough when administered to allow ingestion of the dosage form easy (e.g., less than approximately 23 mm long and less than 11 mm broad for an oval or capsule-shaped tablet, whereas 10- 12mm in diameter for round tablets). On ingestion they rapidly swell or dissolve or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree.

The system's gradual erosion or disintegration into tiny particles allows it to depart the stomach. The basic bilayer tablet may have an immediate release layer and a prolonged release or conventional release layer. (Gopinath et al., 2013)

RECENT ADVANCEMENTS IN BILAYER TABLET TECHNOLOGY:

The introduction of bilayer tablets into the pharmaceutical industry enabled the development of pre-determined active ingredient release profiles as well as the combination of incompatible active ingredients into a single unit dosage form. Large number of works has been done in this field. Some of the recent findings are explained in the table 1. (Ghosh et al., 2014; Bhadange, M.D. et al., 2015)

Table 1 -: Various Advancements in the Field of Bilayer Tablets

DRUG(S)	DOSAGE FORM	RATIONAL	REF. NO.
Paracetamol, Diclofenac Sodium	Bilayer tablet	Synergistic effect in pain	(Payghan et al.,2011)
Saxagliptin	Bilayer tablet	Synergistic effect in diabetes	(Mahata et al., 2022)
Baclofen	Bilayer tablet	Synergistic effect in muscle relaxant	(Makwana et al.,2015)
Allicin	Bilayer tablet	To treatment of Controlled antihypertensive effect	(Das et al., 2017)
Paracetamol, Ibuprofen	Bilayer tablet	Synergistic effect in pain	(Chauhan et al., 2019)
Metoprolol Succinate	Bilayer tablet	To Treatment of angina pectoris and Hypertension	(Nazim et al., 2015)
Granisetron HCL	Bilayer Buccal tablet	To overcome bioavailability problem, reducing side effects	(Shilpa et al., 2011)
Glimepiride, Metformin Hydrochloride	Bilayer tablet	Synergistic effect in diabetes	(Pattanayak et al., 2011)
Indomethacin	Bilayer Floating tablet	Biphasic drug release	(Jain et al., 2011)
Cefixime Trihydrate, dicloxacillin sodium	Bilayer tablet	Synergistic effect in bacterial infection	(Ramasanay et al.,2011)
Metformin Hydrochloride, Pioglitazone	Bilayer tablet	Synergistic effect in diabetes mellites	(Raghunandhan et al., 2011)
Propranolol HCL	Bilayer tablet	Bimodal drug release	(Patra et al.,2007)
Telmisartan, Simvastatin	Bilayer tablet	To minimize contact b/w Simvastatin and Telmisartan	(Kohlrausch et al.,2006)
Tramadol, Acetaminophen	Bilayer tablet	Synergistic effect in pain	(Naeem et al., 2010)
Atorvastatin, Atenolol	Bilayer Gastroretentive Matrix Tablet	Treatment of hypertension and hypercholesterolemia	(Chattopadhyay et al., 2014)
Pioglitazone HCL, Gliclazide	Bilayer tablet	Treatment of Type II diabetes mellitus	(Sharma et al., 2014)

Atenolol, Lovastatin	Bilayer floating tablet	Synergistic effect in hypertension and biphasic release profile	(Kulkarni et al., 2009)
Acetaminophen	Bilayer tablet	Synergistic effect in pain and Fever	(Banu et al., 2011)
Metformin Hydrochloride, Empagliflozin	Bilayer tablet	Synergistic effect in diabetes mellitus	(Chinta et al., 2021)

CONCLUSION:

Bi-layer tablets provide one of the most significant design strategies for combining incompatible drugs with different indications and the same drug with different release rates in a single unit. The bilayer tablet is an improved technology that overcomes the limitations of single-layered tablets. Bilayer and monolayer tablet manufacturing share several common features of technology as both of these pharmaceutical formulation are prepared by compacting powdered or granulated API with or without excipients.(Singh et al., 2021) Bi-layer tablet quality and GMP requirements can vary widely. This explains why a wide range of presses, from simple single-sided presses to highly sophisticated equipment, are utilized to manufacture bi-layer tablets. When producing a quality bi-layer tablet with exact weight control of both layers, compression force-controlled presses are clearly limited due to their poor sensitivity and hence lack of precision at low compression forces required to secure interlayer bonding. Such problems become even more apparent when the tablet compression speed is high or increased. Precise individual layer weight monitoring or control at high speed and in combination with reduced layer separation risk can be achieved with the displacement weight control system-based presses. (Ghosh et al., 2014)

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