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MULTILAYERED TABLET: A NOVEL APPROACH FOR ORAL DRUG DELIVERY

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ABSTRACT: A new era in controlled release formulation and effective medication administration has dawned with the advent of the multi-layer tablet. One important solution for preventing chemical incompatibilities across APIs is the use of bi-layer tablets.in order to physically separate them and to make it easier to create various medication release patterns. A multi-layer tablet is ideal for the sequential release of many medications at once, as well as for sustained release tablets with a loading dosage that is released immediately and a maintenance dose that is released at regular intervals. Therefore, anti-hypertensive, diabetic, anti-inflammatory, and analgesic medications often use combination treatment, which is a distinct feature of bi-layer tablets. There are a number of reasons why pharmaceutical firms are actively working on bi-layer tablets. Some of these reasons include marketing, therapeutic, and patent extension. Even though the fundamentals of tablet production are the same, there is a great deal more to think about when producing multi-layer tablets due to the many formulation and operational issues, incompatible goods, and extra equipment required. Introduction to bi-layer tablet technology, difficulties in producing multi-layer tablets, different tablet presses, quality and GMP standards for their manufacture, bi-layer tableting techniques, and recent advances in the field are all covered in this object.By gradually increasing the surface area available for release to offset the slowing rate of release, the multi-layered matrix system circumvents the non-linearity that is a fundamental drawback of diffusion-controlled matrix devices.

This technology is quite versatile and may be used for a variety of purposes. An integral part of these systems' operation is polymeric materials. One common use for hydrophilic polymers is in the development of matrix-type controlled delivery systems. 1.

For many reasons, including medicinal, patent extension, and marketing, several pharmaceutical firms are now developing bi-layer tablets. In order to save down on capital expenditure, it is common practice to create and manufacture these tablets using preexisting tablet presses that have been adapted.

Keywords: Multi layer tablet, Loading dose Maintenance dose, Bi-layer technology

INTRODUCTION: History: Among various drug delivery systems, oral drug delivery is the most preferred route for administration for various drugs. Recently, pharmaceutical research has focused on controlled drug delivery which offers definite advantages over conventional release formulation of the same drug. Controlled delivery systems that can provide zero-order drug delivery have the potential for maximizing efficacy while minimizing dose frequency and toxicity.

Using a modified tablet press may therefore not be your best approach in producing a quality bi-layer tablet under GMP-conditions, especially when high production output is required. Over the past 30 years as the expense and complications involved in marketing new drug entities have increased, greater attention has been focused on development of sustained or controlled release drug delivery systems. Bi-layer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. This review focuses on the controlled drug release of multilayer tablets, drug release mechanism, system design, and different process and formulationparameters.

Multilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and

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tissues with undesirable toxicity and poor efficiency. Therefore the factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems.

The aim of designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose frequency or providing uniform drug delivery.

The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles.

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. [3]

Problems Related with Conventional Drug Delivery System: [7]

- Poor patient compliance.
- Improved chances of missing the dose of a drugwith short half-life for which repeated administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index wheneverover medication occur.
- However, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Thus, these shortcomings have been circumvented with the introduction of controlled release dosage forms.

Basic Terminology: [4]

- **Sustained Release Dosage Form:** Drug delivery system that is designed to achieve prolonged therapeutic effect by continuously releasing the medicament over an extended period of time.
- **Zero Order Drug Delivery:** It is a process thattake place at constant rate independent of drug concentration involve in a process.

Advantages of Multilayered Tablet:

- Cost is lower compared to all other oral dosageform.
- Greatest chemical and microbial stability overall oral dosage form.
- Unpleasant odor and bitter taste can be maskedby coating technique.
- Flexible Concept.
- They are unit dosage form and offer the greatestcapabilities 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 pilot plant scale up technology.

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- The tablet can be easily used for combination therapy.
- In case of drugs having a low half-life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of thedrug.
- Improved patient compliance.
- Bi-layer execution with optional single-layer conversion kit.

Disadvantage of Multilayered Tablet:

- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Bitter testing drugs, drugs with an objection able odor 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 regimens.

Objective of Preparing Multilayer Tablets: [6, 20, 21, 22]

- To use different APIs in combination having proven advantages over single compounds Administered separately for therapeutic effect.
- To overcome the limitations in case of a single drug which is unable to treat or avoid adverse drug effect, if any.
- To get dual release profile so as to reduce dosing frequency and thereby increasing patientCompliance.
- To combine compatible or incompatible drugs with different release characteristic in same dosage form and enhancing the stability of dosage form as compared to its dosage form.
- To treat critical disease condition when single active unable to produce complete therapeutic action and to maintain over a period 12 h or more.

Steps Involved in Formation of Multilayer Tablet: Various steps involved in the tablet manufacturing is shown in **Fig. 1**.

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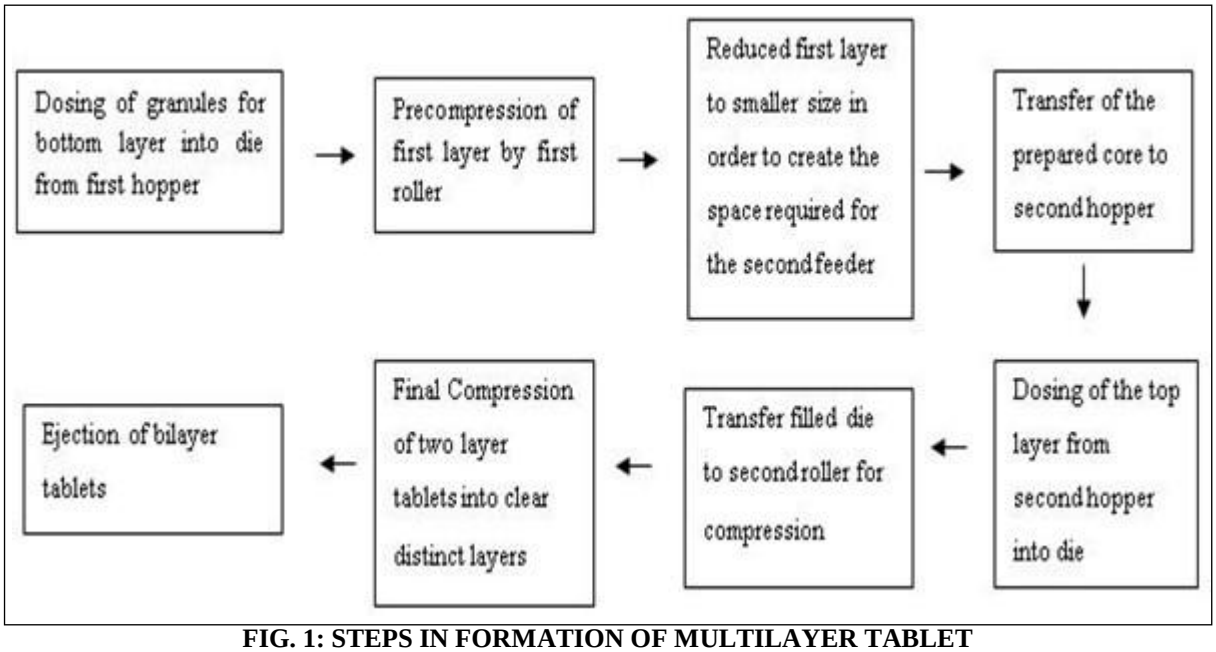

FIG. 1: STEPS IN FORMATION OF MULTILAYER TABLET

Various Kinetic Models in Development of Multi-layered Tablets: [1, 5, 23, 24, 25] The design of multi- layer through varying the geometry of the devices or modulating layers which allows 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 been discussed below:

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

Zero Order Sustained Release: System compriseshydrophilic 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.

Quick / Slow Delivery System: Quick / slow delivery system which is characterized by initial rapid release followed by extended/ prolonged release of the drug to achieved immediately a therapeutic effect and to sustain a constant release of drug to maintain plasma level concentration. This concept applied on where doses regimen not satisfies simple release of the drug.

Time Programmed Delivery System: Time programmed delivery system provide immediate release of the drug followed by time controlled release, when the delivery of 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/eroding of hydrophobic or hydrophilic barrier of coating that show pulsatile release of the drug.

Bimodal Release Profile: Bimodal release profile show 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

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releases that perform more effectively at the site of action to undertake periodic changes.

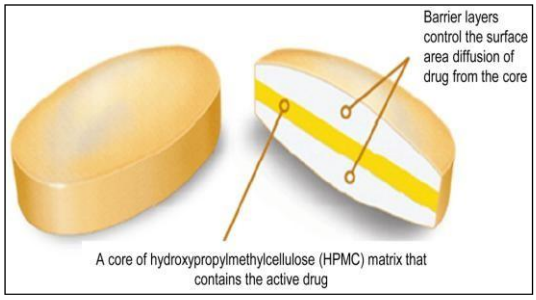
Types of Multilayer Tablets: [7] Bi-layer tablets to quadruple layered tablets are available.

Bilayer Tablet: Bi-layer tablets are suitable forsequential 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. Bi-layer tablet is suitable to deliver two drugs at one time without any dynamic and pharmacological interaction. Bilayer tablets areshown in **Fig. 2**.

FIG. 2: BILAYER TABLET

Triple Layer Tablet: Triple layer tablet consist of three layer of which first layer is for immediate release of drug and the second layer is for sustained release. These two layers are separated with themiddle barrier layer. This is more suitable for the delivery of two drugs which have interactions in them. Triple layer tablets are shown in **Fig. 3**.

FIG. 3: TRIPLE LAYER TABLET



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Surrounding Coated Cora Tablet:

Multilayer Tablet and Controlled Release: Multilayer tablet consists of layers of drug with different release rate, having ability to prevent drug- excipient incompatibility. It provides multiple release kinetics profile in single delivery system of one or more drugs. In this immediate release and then sustained release of drug is designed as control system. Immediate release layer is designed with disintegrating monolithic matrix in order to achieveinitial peak and sustained release layer is designed with erodible monolithic matrix to deliver the drug as later part to maintain the drug plasma concentration. The mechanism of drug release frommulti layer tablets is shown in **Fig. 4**.

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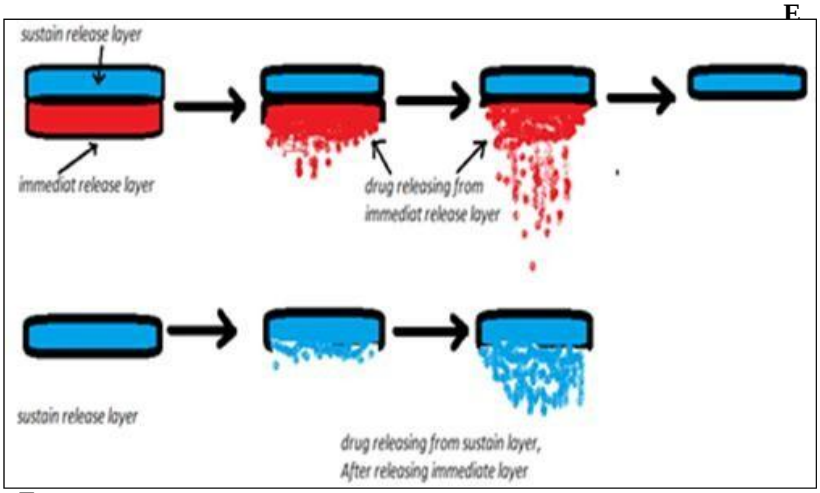

FIG. 4: MULTILAYER TABLETAND CONTROLLED RE

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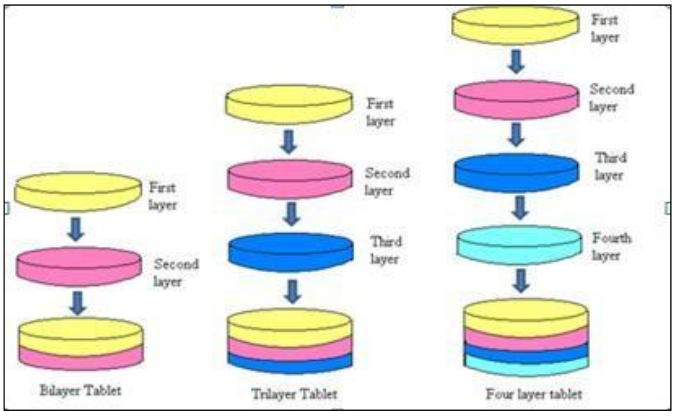
THERAPEUTIC ADVANTAGES: [7]

Better Execution Of Release Profile: Layering onthe tablet revealed better execution on release profile and it is one of the most important possible alternatives to conventional matrix tablets to avoid the initial burst release and to achieve zero-order release profile, which maintain availability of drug over 12 h or more. *e.g.* Venlafaxine hydrochloride.

Decrease Burst Effect and Fast Initial Release Rate: On placement of controlled release formulation in release medium or in dissolution medium, there is an immediate release of an initial large bolus of drug, before the release rate reaches a stable profile (stable matrix formation). This phenomenon is typically referred to as 'burst release' which is controlled using multilayer tableting. *e.g*. Terazosin HCl.

Multiple Release Profiles: Two or more layers in tablets are able to provide multiple release kinetics of same or different drugs of same or different physicochemical properties and it is possible to formulate each layer in order to parcel out the delivery of drug dose by means of different release control mechanisms. *e.g.* Naproxen, Loratadine andPseudoephedrine.



Synergistic Effects: It is well known that presenceof one drug enhances the effects of the second and formulation of two or more drugs together in singletablets offer therapeutic effect of these drugs that isgreater than the sum of the individual effects.

Reduction In Dosing Frequency: Formulate one layer in the form of immediate release disintegrating layer that deliver the initial quick release required to achieve peak plasma concentration and then sustaining the same drug over the period of time more than 12 hr so the multiple intake dosing frequency is reduced and thus get programmable drug delivery system of same or different active in single dose and thus reduction in dosing frequency.

Delayed Release: Application of erodible monolith for immediate and delayed release pattern is possible, which deliver the second installment of drugs in the latter part of GIT. *e.g*. Naproxen and Esomeprazole magnesium.

Controlled Release: Swelling monolith carry out by both swelling as well as eroding mechanism in which drug was continuously released throughout the GIT. *e.g*. Trimetazidinedihydrochloride.

Patient Compliance: Improved patient complianceby reducing tablet intake, "Layers" in tablets represented by two clearly different colors and produces a product that looked more attractive than a standard white "pill". Some double-layer productsare coated and appearing to be comprised of one uniform substance. This allows a decrease in the dosing frequency and a reduction in peak plasma concentrations, thereby improving patient compliance. Multilayered systems which contains bi-layered, triple-layered, quadruple-layered, *etc* are becoming increasingly recognized as controlled-release drug delivery systems. Stepwise diagrammatic preparation of various tablets is as shown in **Fig. 5**.

FIG. 5: FORMATION OF MULTILAYER TABLET

Characterization of Multilayer Tablets:Micromeritic Properties:

- **Particle Size Distribution:** The particle size distribution was measured using sieving method.

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- **Photo-Microscope Study:** Photo-microscope image of TGG and GG was taken (X450 magnifications) by photomicroscope.

- **Angle of Repose:** The diameter of the powder cone was measured and the angle of repose was calculated using the following equation. Tan Ø=h/r where h and r are the height and radius ofthe 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.

- **Density:** The loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated.

Dwell Time: It is the contact between punch head and compression roller. If shorter the first layer- dwell time, which results into pours, aeration, capping and hardness problems. It may be removedthe mistakes by reducing the turret-rotation speedor by extending the dwell time.

Cohesiveness: When the first layer is compressed at a very high compression force, bonding between layers is severely controlled. Various bi-layerformulations necessitate a first layer compression force NMT 3 Kpor 30 N to maintain the ability of first layer to bond with the second layer. Thus at elevated manufacturing speed, the jeopardy of separation and capping increases which can be minimized by adjusting adequate dwell time at all compression stages.

Risk of Separation and Capping: It is necessary to avoid risk of separation and capping, by forming correct bonding which can be attained by the first layer formation at low compression force. Therefore this first layer can still interact with the second layer during final compression of the tablet.

Cross-contamination: Multilayer tablet machines are equipped with suction nozzles or dust extractor to remove fine powder or granules to eliminate cross-contamination between the two layers and getting a clear visual separation between layers. It is very important to remove any powder residue from the die plate and for this purpose dedicated scraper plate are located before and after each die fill, to remove residual powder dust to the of the die table, where the high efficiency suction nozzles are located.

Desertion: If dwell time increases, it increases the desertion of the powder and the re-arrangement of the granules in the die. So, these two factors increase the hardness of the tablets significantly and avert potential capping problems.

Final Compression Force: This force is appliedon the final bi-layer tablet is always more than the compression force on first layer, which results in suitable bonding of both the layers.

Weight Variation: Weight variation occurs some time due to non-uniform flow of granules, incomplete die filling and lower punch jamming due to excessive fines in final blend and thus these parameters should be controlled carefully during tableting.

First Layer Weight Layer Measurement: When producing multilayer tablets, this stage is challenging for different reasons because sampling of first layer for weight check at the start and in- between compression cycle is difficult. For this reason, first weight layer is compressed at high hardness to make sampling and easy separation and weighing is possible because first layer hardness is generally low and difficult to handle. Once the target weight of first layer achieves, reduce pressure as much as 20 to 30 N. Many modified tablet press has push button which automatically separate layered tablet due to pressure difference.

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Weight Adjustment: First layer pressure is useful for weight adjustment of second layer. Many formulators use such technique to achieve desired weight instead of using weight adjustment knobthat totally depends on handling experience of suchdouble rotary press.

Layer Weight Ratio: Generally layer weight ratios 50:50, 60:40 and 25:75 are used for formulation of such tablets, provided that granules are having good binding property

Hardness and Thickness: This parameters need to be tightly controlled during final compression because it directly affect the release of active drug. Many times due to high hardness disintegrating matrix may take time more than limits.

Segregation: Sometimes segregation occurs in out coming granules in most machines and therefore it is better to blend granules before putting into hopper for reuse to minimize the contentuniformity in finished products.

Multilayer Tablet Presses: Many companies having leadership in Pharma machinery supply machines from single layer to two to three layered tableting for lab scale such as Cadmach, Karnavati, Elizabeth-Hata, KG pharma, Fette, GEA Process Engineering, Korsch *etc*. It has D or B or both types of tooling with additional facility for manufacturing in various sizes and shape with maximum output with advanced facilities

Tablet Thickness and Size: Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using venire caliper.

Tablet Hardness: The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured 1 kg/cm^2

Friability: Friability is the measure of tablet strength. Electrolab EF- 2 friabilator (USP) was used for testing the friability using the following procedure. 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.

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

Percentage friability of tablets less than 1% is considered acceptable.

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

Dissolution Studies: Bi-layer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37° ± 0.5°C, and pH 1.2 buffer (900 ml) (*i.e*. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) and experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectro- photometer using multi component mode of analysis.

FT-IR Compatibility Study: FT-IR spectroscopy can be used for the structural analysis. Using the potassium bromide sample disk method, the core as well as the coated core can be analyzed by recording their IR spectra in the wave number range 4000 - 400 cm^{-1}; the characteristic peaks observed are then matched with reference peaks. Identification of drug and drug excipients and physical mixture can also be confirmed by FT-IR analysis of the sample to reveal that there is no interaction between the drug and other excipients.

ISSN: 0976-0172
Journal of Bioscience AndTechnology
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Stability Study: Stability studies were carried out a per ICH guidelines by storing the prepared multilayered tablet at various temperature conditions like room temperature (25°C ± 2°C) andelevated temperature of 40°C ± 2°C) from a period of one month to three months. Drug content and variation in the dissolution data were periodically monitored.

Various Techniques for Bilayer Tablet: [4]

OROS® Push Pulls Technology: This system consist of mainly two or three layer among whichthe one or more layer are essential of the drug andother layer are consist of push layer. The drug layermainly consists of drug along with two or moredifferent agents. So this drug layer comprises ofdrug which is in poorly soluble form. There isfurther addition of suspending agent and osmoticagent. A semi permeable membrane surrounds thetablet core. OROS Push Pull technical presentationis shown in **Fig. 6**.

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. L-OROSTM technical presentation is shown in **Fig. 7**

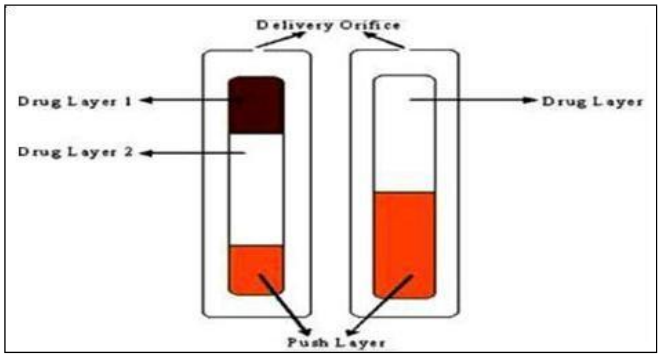

FIG. 6: OROS® PUSH PULLS TECHNOLOGY DIAGRAM

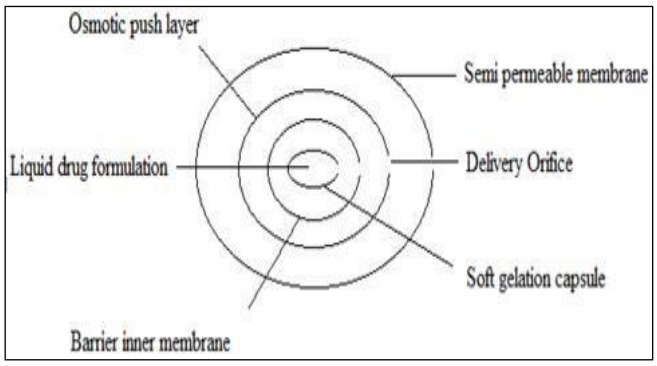

FIG. 7: L-OROSTM TECHNOLOGY DIAGRAM

EN SO TROL Technology: Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies. EN SO TROL technology diagram is shown in **Fig. 8**.

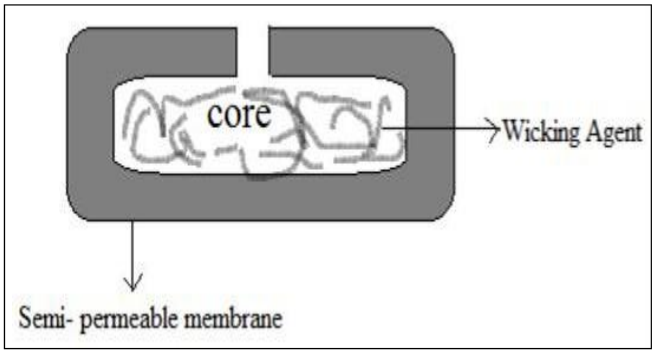

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FIG. 8: EN SO TROL TECHNOLOGY DIAGRAM

ISSN: 0976-0172
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DUROS Technology: The system consists from anouter 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 minute quantity of concentrated form in continues and consistent from over months or year. DUROS technical working is shown in **Fig. 9**.

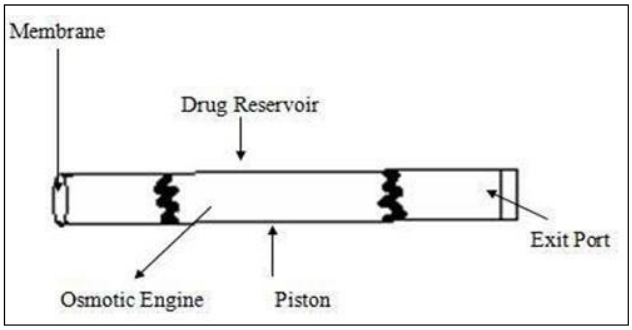

FIG. 9: DUROS TECHNOLOGY

Elan Drug Technologies's 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 tab letting 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.

Benefits offered by the DUREDAS™ technologyinclude:

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

Applications: [9 - 19]

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bi-layer. Two different release rates can be achieved from each side. In this way greater prolongation of sustained release can be achieved. Typically an immediate release granulate is first compressed followed bythe addition of a controlled release element whichis compressed onto the initial tablet. This gives the characteristic bi-layer effect to the final dosage form. 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 maximize 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 utilizing this technology approach have been evaluated. The DUREDAS™ technology was initially employed in the development of a number of OTC controlled release analgesics. In this case a rapid release of analgesic is necessary for a fast onset of therapeuticeffect. Hence one layer of the tablets is formulated as immediate releases 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.

ISSN: 0976-0172
Journal of Bioscience AndTechnology
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TABLE 1: APPLICATIONS FOR MULTILAYER TABLETS

S. No	Drug	Immediate release / sustain release	Treatment	Year	Reference
1	Nebivolol and Nateglinide	Immediate release – Nebivolol Extended release – Nateglinide	Diabetes and hypertension	2015	[9, 17]
2	Pioglitazone HCl and Glicazide	Pioglitazone HCl –as immediate release Glicazide- as controlled release	Type-2 diabetes mellitus	2014	[11]
3	Metoprolol and Amlodipine	Metoprolol- as sustained release Amlodipine- as immediate release	Hypertension	2014	[15]
4	Pioglitazone hydrochloride and Metformin hydrochloride	Pioglitazone HCl –as immediate release Metformin HCl- as controlled release	Type-2 diabetes mellitus	2013	[10, 12]
5	Levofloxacin and Ambroxol hydrochloride	Levofloxacin- as immediate release Amoxol HCl- as sustained release	Respiratory tract infections	2013	[19]
6	Metformin HCl and Atorvastatin Calcium	MetforminHCl- sustained release Atorvastatin calcium- immediate release	Hyperlipidemia	2011	[13]
7	Piracetam and Vinpocetin	Piracetam-immediate release Vinpocetin- sustained release	Alzheimer's disease	2011	[16]
8	Atorvastatin and Nicotinic acid	Immediate release-Atorvatstatin Extended release– Nicotinic acid	Hyperlipideima and prevention of cardiovascular disease.	2008	[18]

Future Prospective: [8]

Floating Drug Delivery Systems: From the formulation and technological point of view, the floating drug delivery systems are significantly easy and consistent approach in the development ofGastro retentive dosage forms (GRDFs)

Approaches to Design Floating Drug Delivery System: The following approaches have been used for the design of floating dosage forms of single- 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 releaselayer.

Multiple Unit Type Floating Pills: These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density.

Due to limitation of time, various studies have not been completed which may be left for future study.

- 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: Bi-layer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet

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Journal of Bioscience AndTechnology
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in which one layer is immediate release as initial dose and second layer is maintenance dose. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. Bi-layer tablet quality and GMP- requirements can vary widely.

This explains why many different types of presses are being used to produce bi-layer tablets, ranging from simple single sided presses to highly sophisticated machines such as the Courtoy-R292F. Whenever high quality bi-layer tablets need to be produced at high speed, the use of an 'air compensator' in combination with displacement control appears to be the best solution.

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