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A Review on Multi-layered Tablets: A way to control the drug release

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ABSTRACT

Due to necessities their affordable manufacturing costs and simplicity of administration, especially in controlled-release applications, tablet dosage forms have traditionally been chosen over other formulations for oral medication delivery. Over monotherapy, combination therapy has a number of benefits. The pharmaceutical industry has grown more interested in recent years in creating dosage forms (monolithic, bilayer, or multi-layered tablets) that combine two or more Active Pharmaceutical Ingredients (API), improving patient convenience and compliance. The active pharmaceutical ingredient (API) is delivered from controlled-release tablets over an intended or prolonged period of time after oral administration. This may allow for a reduction in peak plasma concentrations and dose frequency, which enhances patient compliance while lowering the likelihood of unfavorable side effects. To transfer APIs into the body, conventional single-layered matrix tablets have been widely used. These traditional single-layered matrix tablets, however, have less than ideal delivery characteristics, such as non-linear drug release profiles that could result in more side effects. A multi-layered technology has recently been created to expand upon or replace the single-layered tablet's constraints. With the use of this technology, pharmaceutical businesses may have a better chance of creating new medications and improving their life cycle management. An overview of multi-layered tablets is provided in this article, with particular attention paid to manufacturing challenges, different tablet designs, and drug release profiles. This article covers the necessity for quality Multi-layered Tablet development and production, as well as the present state of the market.

Keywords: Multi-layered Tablet, controlled-release tablets, monolithic, matrix tablets

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INTRODUCTION

The basic objective of oral controlled drug delivery systems is to keep therapeutic drug blood levels nearly constant after oral administration for a predetermined amount of time. The three main benefits of oral controlled release systems are reduced frequency of dose, reduced adverse effects related to high plasma drug concentrations, and higher patient compliance. Despite the large variety of oral controlled release products on the market, only three approaches-matrix, reservoir, osmotic, or ion exchange - are used. Geomatrix® and Smartrix®, multilayered tablets and technologies, are regarded as typical examples of coupling system dimensions with release behavior. These systems were able to produce release kinetic models that were nearly zero-order. The major objective of designing such systems is to keep the surface area open to medication delivery constant. As a helpful controlled release technique with numerous other applications, such as drug combinations with lower chances of interaction and/or producing different drug release profiles in one dose form, multi-layered tablets have drawn increasing attention. (1)

Combination therapy is currently being used in both developed and developing nations to treat a variety of illnesses and conditions that require long-term treatment, such as hypertension, diabetes, and cardiovascular diseases. Due to its stronger and broader therapeutic synergism and fewer adverse effects, combination preparation plays a significant role in clinical treatment. When available, combination pharmaceuticals (monolithic or bilayer dosage forms), which are dosage forms that contain more than one active ingredient, can be administered in place of individual medications to accomplish combination therapy. (2) There are a number of factors that have led to the development of drug combinations that combine two or more medications in a single dosage form in order to treat a variety of illnesses, including common conditions like Parkinsonism and allergic rhinitis. The original goal of creating such a formulation was to combine various APIs into a single dose for patients who couldn't take frequent doses for a variety of reasons. But nowadays, a doctor will typically prescribe two or more medicines individually for a single ailment if a patient has that disease. The development of FDCs is becoming increasingly important on a global scale since the human mind process is to receive relief in a single dose, to reach site therapeutic concentration immediately, and to retain the same dose over 12 h or more in the present rapid living. (3)

To induce a quick onset of action and maintain the therapeutic impact in specific pathological circumstances, fast release of the dose must be performed. One option for carrying out the dual drug release notion is a multi-layer tablet formulation.

The multi-layer tablet is a drug delivery method designed to simultaneously release two or more medications at the appropriate release rate or to administer two or more pharmaceuticals at separate rates. Furthermore, a multi-layer tablet that contains two or more incompatible medications may be created. Due to the regulated release profiles of the active components, multi-layer tablets are used. When using the same active ingredient, modified/controlled release dosage forms have more advantages over immediate release dosage forms. Products with modified or regulated drug release are created to enhance patient comfort and compliance while optimizing treatment regimens. Controlled release systems' primary goal is to keep the rate of drug delivery consistent. Numerous oral dosage forms have been developed over the years as a result of research aiming at creating new dosage forms with zero order or nearly zero order kinetics. These have changed release qualities, and examples include dosage forms created employing three-dimensional (3D) printing technology, electrostatic deposition, osmotic or ion control, and film-coated capsules, pellets, or tablets. Changes in the composition, arrangement of layers, or geometry of multi-layer tablets can be used to achieve different release profiles, such as delayed release, pulsatile release, or multimodal delivery profiles. (4)

Advantages of bilayer tablet:

1. Better chemical and microbiological stability than other oral dose forms, according to this. (5)
2. Separating the incompatible parts reduces their potential for physical and chemical incompatibilities. (6)
3. Coating technology can hide offensive odours and tastes. (7)
4. It can be made to have a modified discharge, keeping one layer's release as extensive and the other as instantaneous. (7)
5. It is less expensive than other dose types. (8)
6. Well suited for industrial production. (7)
7. It is simple to swallow and has a low tendency to hang up. (7)
8. The capacity to combine various release rates. For chronic conditions that need for repeated dosing, IR and SR are combined in one tablet. (2)
9. Patient comfort and compliance are encouraged because fewer daily doses are needed than with a conventional administration system. (5,9)
10. Fix the degradation issue. (2)
11. Lighten the patient's pill load. (10)
12. Maintain a stable chemical and physical environment. (6)

13. Maintain potency and guarantee correct dosage. (2)
14. Smaller and lighter. (6)
15. The simplest and least expensive to package and strip. (11)
16. When using an embossed and/or monogrammed punch face, product identification is simple, quick, and requires no additional processes. (12)
17. Low compression force is used to prevent capping and separating the two layers. (12)
18. This system may give various drug release kinetics of the same or different medications, such as extended and immediate release, so that drug release behaviour is not limited to one kind. (13)

Difficulties and challenges in making of Multi-layered Tablets

1. Dose dumping-related toxicity. (7)
2. Incorrect weight management for each individual layer. (2)
3. Intermingling of contaminants between the layers. (8)
4. Inadequate hardness. (2)
5. A decreased production. (6)
6. Increases complexity and the cost of bilayer rotary presses. (8)
7. Because some drugs are amorphous and low density, they defy compression into impenetrable compacts. (7)
8. Poisonous medicines, offensive-smelling medicines, or oxygen-sensitive medicines. (14)
9. Could need coating or encapsulation. (7)
10. Low yield due to layer separation and insufficient hardness. (6)
11. Since they are difficult to create and make, production may encounter a number of issues that alter the dosage form's characteristics. Principal challenges include insufficient hardness, inaccurate layer and tablet weight management, elastic mismatch between conterminous layers, and susceptibility to delaminate throughout various manufacturing phases. (2)
12. Delamination (distinct separation of layers along the interface). The delamination could take place between neighbouring layers (interlayer delamination) or within one of the layers and could happen right away after compression, at a later stage of the technical process, or during storage (interlayer delamination). (5,15,16)
13. Inadequate bonding and adhesion between neighbouring compacted layers, which is frequently caused by an interfacial fissure and layer separation. (6).

14. It is necessary to develop two compatible granulations, which means that formulation, analysis, and validation will take more time. (16)

Objective of making multilayer tablets:

1. To treat fundamental disease circumstance when single active unable to produce whole therapeutic action and to hold over a length 12 h or more. E.g. telmisartan/amlodipine tablet. (17)
2. To use combination having tested advantages over single compounds administered one after the other for therapeutic effect. (7)
3. To mix different capsules for synergistic therapeutic impact or distinctive capsules in order to gain a unique launch profile. E.g. efavirenz, emtricitabine, and tenofovir disoproxil fumigate in multilayer pill for the treatment anti-HIV-1 infection. (18)
4. To overcome the boundaries in case of a single drug which is unable to deal with or keep away from adverse drug effect, if any. (11)
5. Incidence of each local and systemic negative side consequences can be reduced in sensitive patient. To set up a manufacturer identity, as they are sincerely exclusive from other products from common opponents and also from affected man or woman identification over routine white pills and when affected person is unable to take traditional dosing of identical drug. (4)
6. To get twin release profile so as to minimize drugs consumption and thereby growing affected person compliance. (10)
7. To combine nicely applicable or incompatible drugs with one-of-a-kind launch characteristic in identical dosage structure and improving the steadiness of dosage structure as in contrast to its conventional monolith counterpart. Steps worried in schooling of bilayer capsules Parameters to be considered at some component of Multilayer tableting. (17)

Necessities and reasons for preparing multilayer tablets:

- For the administration of constant dose combination of one of a range energetic pharmaceutical ingredient, lengthen the drug product existence cycle, buccal transport system; fabricate novel drug transport computing system such as chewing desktop and floating pill for gastro-retentive drug delivery.(7)
- For reason of administration of twin launch constant dose combos of extraordinary APIs. (11)
- For the motive of growing novel drug transport pc such as buccal/Mucoadhesive transport machine and floating capsules for gastro retentive drug transport system. (5)

- To alter bilayer capsule in such way that floor location reachable for lively ingredient layer with the aid of capacity of way of placing between one or two in lively layers for carrying out swell able/erodible barrier for modified release. (5)

Formulation and training of Multi-layered Tablet:

Three-layered pills have been equipped with the resource of a single step direct compression technique through manual feeding of a hydrophobic barrier layer in the bottom followed by way of Ind core layer and any other hydrophobic barrier layer at the top. Two spherical compression sets; 6mm and 12 mm had been used. Both the upper and bottom layers had been composed of EC containing 1 % of magnesium stearate. Four batches have been equipped differing fully in each thickness of the drug layer or the capsule diameter. Table 1 indicates the proper composition of each batch. Number of elements used to be once studied including, pill thickness to diameter ratio and the drug layer floor area. (1)

Steps in formation of multilayer tablet: (3, 19)

1. Dosing of granules for bottom layer into die from first layer two
2. Pre-compression of first layer by way of first roller
3. Reduce first layer to smaller measurement in order to create the space required for 2d layer
4. Transfer of first layer to 2nd hopper
5. Dosing of the pinnacle layer from 2d hopper into die
6. Transfer the fill to second curler for compression ground area. (1)
7. . Final compression of two-layer tablet into clear wonderful layers.
8. Ejection of bilayer tablet.

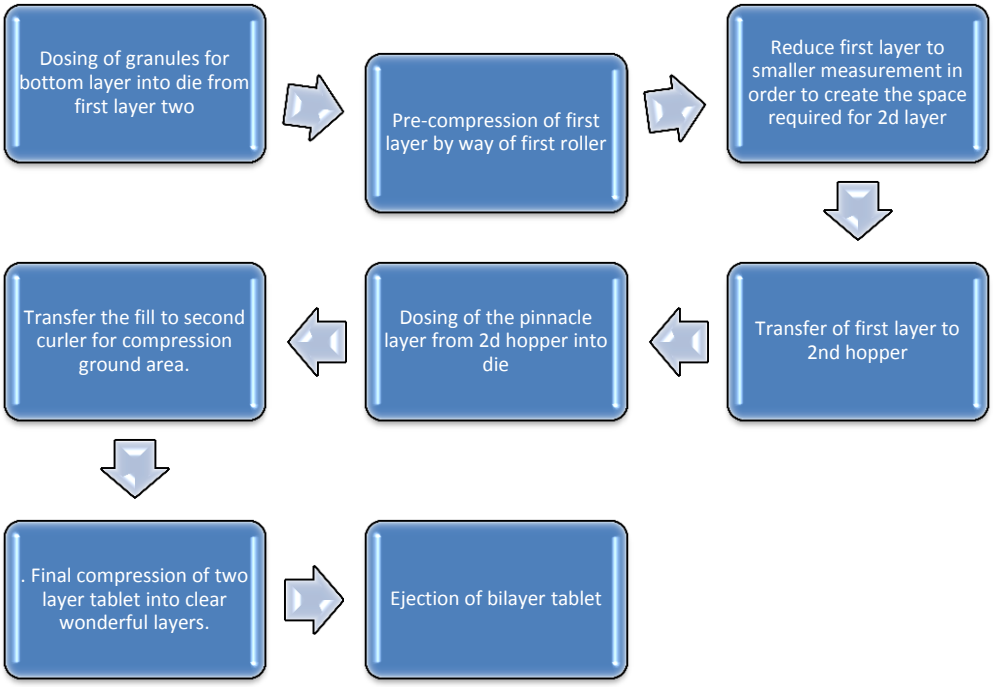

Figure 1: Steps in formation of multilayer tablet

Various techniques for bilayer tablet:

1. PUSH PULL OROS® Technology:

It consists of two or three layers, one of which is the push layer and the other of which is the layer that is necessary for the medicine. The drug layer is made up of the drug and two or more different agents. As a result, the medication in this layer is in a poorly soluble form. Osmotic and suspending agents can also be included. The core of the tablet is encased in a semi-permeable membrane. (11, 20)

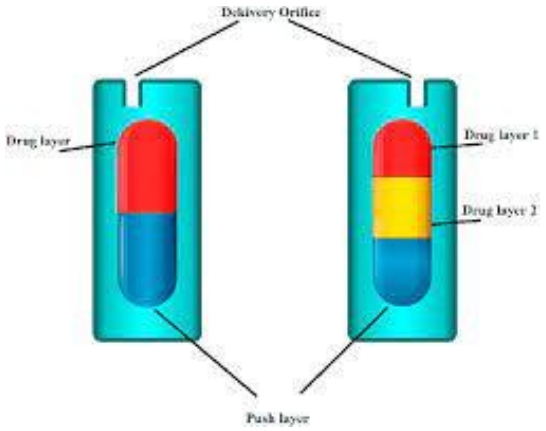

Figure 2: PUSH PULL OROS® Technology

2. L-OROS Technology:

The solubility problem was handled by this system. Alza created the L-OROS system, which involves manufacturing a lipid soft gel product that contains a drug in a dissolved state and

coating it with a barrier membrane, an osmotic push layer, a semi-permeable membrane, and drilling an exit core. (14, 20)

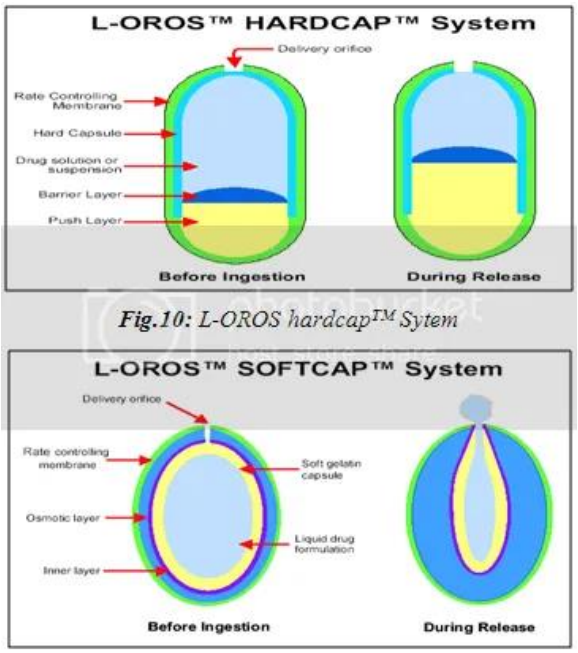

Fig.10: L-OROS hardcap™ Sytem

Figure 3: L-OROS Technology

3. EN SO TROL technology:

A method to drug delivery that emphasizes identification and implementation of the identified enhancer into controlled release technologies is used to increase solubility or to develop optimum dose forms. (11, 20)

Figure 4: L-OROS Technology

4. Elan Drug Technologies':

Dual release drug delivery system is another name for this system, which is called DUREDAS technology. A bilayer tablet with DUREDAS TM Technology allows for the immediate or sustained release of two drugs or various release rates of the same drug in a single dosage form. A modified release hydrophilic matrix complex and an immediate release granulate can be provided by the tableting process as separate layers within a single tablet. Several hydrophilic polymers work together to give the dosage form its modified-release properties. (5, 20)

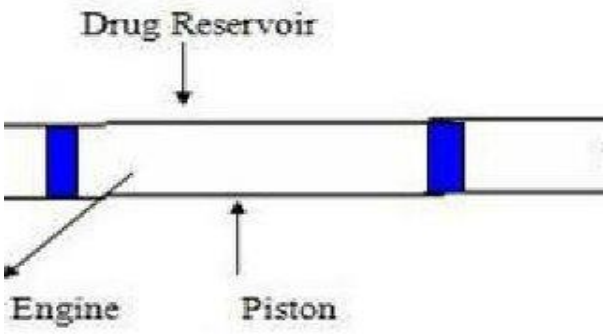

Figure 5: DUREDAS technology

***Benefits of DUREDAS technology*: (21)**

- Bilayer Tableting Technology is one of the advantages provided by DUREDASTM technology.
- Tailayred Two medication component release rates.
- Two different CR formulas' capacity.
- The ability to combine components with modified release and immediate release in a single tablet.
- A tablet of one dose.

5. DUROS Technology:

The system is also referred to as "Miniature Drug Dispensing Technology" by DUROS Technology. A titanium alloy reservoir is the main component of the system. The drug molecules are shielded from enzymes by this reservoir, which has high impact resistance. The DUROS technology is a tiny drug dispensing system that functions similarly to a miniature syringe and continuously dispenses a tiny amount of concentrated medication over the course of months or years. (14)

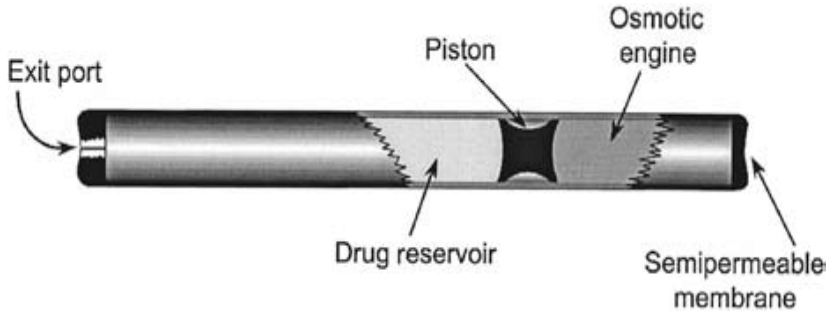

Figure 6: DUROS Technology

6. Geminex Technology:

This is helpful in reducing side effects and considerably increasing the therapeutic efficacy of medications. This method provides one or more medications in a single dose form at various

release rates. Both industry and patients find it to be very helpful. Pen west actively uses Gemini Technology in the following conditions: diabetes, cardiovascular disease, cancer, and CNS illnesses. (11)

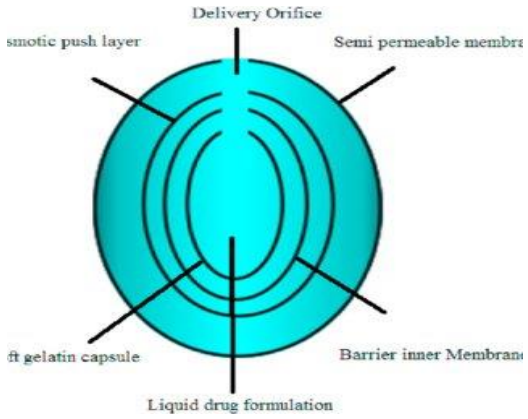

Figure 7: Geminex Technology

VARIOUS KINETIC MODELS IN DEVELOPMENT OF MULTI-LAYER TABLETS (4, 17)

Tablets having a particular release profile, such as pulsed, bimodal, delayed, and multimodal, can be made by altering the geometry of the drug form or the makeup of individual layers. The various drug delivery systems include time-programmed delivery, quick/slow delivery, sustained zero order release, and bimodal release profile

1. Zero order sustained release: A hydrophilic or hydrophobic polymer acting as a matrix or a protective layer is present in a formulation for zero order sustained release. By polymer covering the matrix on two sides and leaving the other sides unprotected, the release control is obtained, allowing the drug to dissolve through the medium.
2. Quick/slow drug delivery system: The drug releases quickly at first, then more slowly, according to the quick/slow drug delivery system-type formulation. A constant drug release is then maintained to guarantee a constant plasma concentration, giving the drug immediate action.
3. A time-programmed delivery system: offers both instant drug release and regulated drug release over time, such as timed release in the intestines. This system is made up of a tablet core that has been coated in various polymers. After the hydrophobic or hydrophilic coating surrounding the core swells or erodes, the medicine is released from the tablet core in a pulsatile manner.
4. A bimodal release system formulation is characterized by initial rapid release, followed by slow and quick release once more. This release profile has a sigmoidal shape. In order to

make up for the stomach and large intestine's relatively slow absorption, this system offers quick action.

Types of Multi-layered Tablet

1. Bilayer Tablets
2. Triple layer Tablets
3. Surrounding blanketed Cora tablet (19)

Table 1: Examples of Multi-layered Tablets and their composition (3, 11)

Sr. no	Drug Combination	Therapeutic uses
1	Paracetamol and diclofenac sod.	Synergistic effect in pain
2	Atorvastatin and atenolol	Treatment of hypertension and hypercholesteremia
3	Aspirin and isosorbide 5–mono nitrate	Treatment of pain, fever and other inflammatory conditions
4	Pioglitazone HCl and Glicazide	Type 2nd diabetes
5	Losartan potassium	Treatment of hypertension
6	Diclofenac and cyclobenzaprine	Synergistic effect in pain
7	Metformin and glimepiride	Synergistic effect in diabetes
8	Metformin HCl and Atorvastatin Ca.	To develop polytherapy for treatment of NIDDS and hyperlipidemia
9	Piracetam and vinpocetine	Synergistic effect in Alzheimer's disease
10	Cefuroxime axetil potassium clavulanate	Synergistic effect against microbial infection
11	Amlodipine besylate and metoprolol succinate	Synergistic effect in hypertension
12	Ibuprofen and methocarbamol	Synergistic effect in back pain
13	Atorvastatin and nicotinic acid	Synergistic effect in Treatment of hypercholesteremia
14	Salbutamol and Theophylline	Synergistic effect in treatment of asthma
15	Tramadol and acetaminophen	Synergistic effect in pain

Evaluation of Multi-layered Tablets:

General Appearance:

It consists of its visible identity; "elegance" is required for patient acceptance. Other parameters are tablet's size, colour, shape, presence or absence of an odour, taste, ground texture, bodily flaws and consistency and legibility of any figuring out marking. (11)(15)

Transmission Raman Spectroscopy (TRS):

has come to be an increasing number of greater applied science in the analysis of pharmaceutical drugs for great control purposes, developing aspects and gadget understanding. Bilayer tablet represents an unusually challenging state of affairs based totally absolutely on its complicated composition. This quantitative mannequin of evaluation aimed for the prediction of API content cloth in multi-layered tablets. (22)

Powder particle properties:

Particle size distribution of powder combinations is evaluated with a laser diffractometer. The particle shape is estimated by using particle roundness. Images of particles are taken with an optical microscope and digitally processed in order to calculate the particle roundness in accordance to the following.

$$R = \frac{4A}{\pi lmax2}$$

Where, A represents the projected region and

⌊max represents the most measurement of the single-particle. (22)

Powder flow characteristics:

Calculating the Hausner ratio and Carr's compressibility yields information on the flow properties of powder mixtures. Hausner ratio is calculated as: Tapped Density/Bulk Density.

Carr's compressibility index $= \frac{\text{(Tapped density–Bulk density)}}{\text{Tapped density}} \times 100$. (22)

The moisture content of powder mixtures:

A thermal balance uses gravimetric measurement to determine the moisture content of powder mixtures. (22)

Weight uniformity

The tablets comply with the test if not more than 1 individual mass is outside the limits of 85–115% of the average mass. The tablets fail to comply with the test if more than 1 individual mass is outside these limits, or if 1 individual mass is outside the limits of 75–125% of the average mass. (23)

Table 2: Limits of Weight Variation According to Pharmacopoeias.

Sr no	IP/BP	USP	Limits
1	80mg or less	130 mg or less	10%
2	More than 80mg or less than 250mg	130mg to 324mg	7.5%
3	250mg or more	More than 324mg	5%

Hardness test:

The crushing strength of 10 pills was assessed using the hardness tester. (22)

Test for friability:

Both single- and multi-layered tablets are subjected to friability testing. A friability test is employed to examine the propensity of stacked tablets to delaminate. The number of delaminated tablets is counted in accordance with the following after 100 rotations per minute. Where W0 is

the initial weight of the tablets and Wf: is their final weight, friability is equal to (W0– Wf) /W0 x 100. (22)

Uniformity of thickness:

The thickness of each barrier layer in each of the 10 three-layered tablets was measured using a micrometre, and the thickness of each tablet was also calculated. (1)

In vitro disintegration time:

Utilizing the USP tablet disintegration tester apparatus type I, in vitro disintegration time is measured (basket mode). 900 cc of filtered water heated to 37 ±0.5 °C is frequently used as the disintegration medium. The amount of time in minutes needed for full disintegration is calculated. (22)

Study of in vitro dissolution:

The following operating factors were used to conduct the study of in vitro dissolution. The dissolving rate test device was used to conduct the in vitro release research for all formulations.

Apparatus: Type 2 USP dissolving apparatus (paddle type) I.P 75 rpm is the paddle's speed.

Temperature: 37.5°C plus 0.5°C

Medium of dissolution: Acid stage: 1 hour of 900 cc of 0.1 N hydrochloric acid. Stage of the buffer: 900 ml of pH 6.8 phosphate buffer over the following hours.

The dissolution medium included one pill that had previously been weighed. At half-hour intervals, 10 ml samples were taken, filtered, diluted to 10 ml, and then examined using a UV spectrophotometer at a specific wavelength (nm). Fresh dissolving media was used to replace aliquots of the sample that was withdrawn. Each aliquot's absorbances were recorded. Using the PCP Disso v2.08 programme, the concentration was estimated. (24, 25)

Stability Study (Temperature Dependent):

The bilayer tablets are packaged appropriately and kept in the following circumstances for the duration of the accelerated study period as specified by ICH rules. (11)

Table 3: Accelerated study period data

Sr no	Study	Storage conditions	Duration
1	Long term	25°C±2°C / 60% RH ± 5%RH 30°C±2°C / 65% RH ± 5%RH	12months
2	Intermediate	30°C±2°C / 65% RH ± 5% RH	6months
3	Accelerated studies	40°C±2°C / 75% RH ± 5% RH	6months

SEM studies:

Using a gold sputter module in a high vacuum evaporator, the three-layered matrix tablet was cut in half using a sharp razor and coated with gold palladium under an argon atmosphere. Then, a scanning electron microscope was used to look at the gold-palladium coated tablets. (26)

Study using FT-IR:

The material was placed inside potassium bromide discs, and the infrared spectrum was captured. In order to identify the common bands of the vibrational spectra of each individual medicine and its formulations as well as any variations in the formulation's vibrational spectrum, the samples of pure drug and granules comprising various polymers were individually scanned. (27)

DTA/TG Study:

A thermogravimetry/differential thermal analysis (TG/DTA) thermogram of pure drug and formulation AN2 was recorded in a TG/DTA analyzer (STA 1500, PL Thermal Sciences, India) at a heating rate of 20 °C/min from 0 to 600 °C in an air atmosphere to characterize drug-excipient interactions. (28)

Market trend and current scenario: (9)

Multi-layered tablet market trends Due to its advantages, multi-layered matrix dosage forms have received a lot of attention recently from both industry and academics. They can modify the total surface area available for API layer by sandwiching with one or two inactive layers to achieve swellable/erodible barr, separate APIs that are incompatible from one another, control the release of an API from one layer by utilizing the functional property of the other layer, and control the delivery rate of either a single active pharmaceutical ingredient (API) or two different APIs (Bogan, 2008; Kulkarni and Bhatia, 2009; Nirmal et al (Efentakis and Peponaki, 2008; Phaechamud, 2008). Due to these distinct qualities, multi-layered matrix tablets are frequently used to deliver a combination of an immediate release dose for quick relief and a dose of controlled release to keep the therapeutic impact. The multi-layered products on the market with active components and applied disorders are shown in Table I. Multilayered tablets' current problems and difficulties Despite significant advancements in multi-layered matrix tablet formulations, a number of problems still exist, including layer separation, insufficient hardness, incorrect individual layer weight management, and contamination between the layers. These issues could be extremely important for the product’s quality and safety. They mostly happen in manufacturing and occasionally in in vitro research. The physicochemical properties of the APIs and excipients must be carefully considered by pharmaceutical scientists and engineers in order to resolve or avert the problems. A multi-layered tablet’s quality and effectiveness are greatly

impacted by the separation of each individual layer, which is a common issue. It might happen throughout the process of compression or disintegration. Inadequate bonding between neighboring layers while compressing the tablet may be the primary cause of the separation. The force needed to separate the layers of a multi-layered tablet can be measured, though, to alleviate this problem. By understanding the causes of each layer's separation, one may be better able to take effective corrective action. The development of a significant swelling pressure associated with the disappearance of the glassy core is possible when two symmetrical moving swelling fronts collide in a multi-layered matrix tablet made of a swellable hydrophilic polymer. The tablet may get laminated as a result, and a hydrated matrix in the shape of "the butterfly" may develop. The margins of the matrix would curl outward under the impact of swelling pressure and the varying levels of hydration in the split zone, resulting in the formation of "the butterfly shaped" matrix. The pressures of compaction and the ratios of the matrix's constituents may have an impact on this occurrence. The butterfly effect was only really noticeable when very thin tablets were squeezed with adequate power. The multi-layered matrix tablet's unfavorable release qualities may be impacted by this phenomenon.

Table 4: Commercially available bilayer tablets in U. S. market according to the FDA orange book (22)

Sr No.	Active ingredient	Strength	Proprietary name	Approval date	Mfg. by
1	Guaifenesin	1.2mg	Mucinex	Dec18,2002	RB Health US LLC
2	Dextromethorphan hydrobromide	60 mg	Mucinex DM	Apr29,2004	RB Health US LLC
3	Pseudoephedrine hydrochloride	120mg	Mucinex D	Jun22,2004	RB Health US LLC
4	Doxazosin mesylate	8mg	Cardura XL	Feb1,2006	Upjohn US 1 LLC
5	Desloratadine	2.5mg	Clarinex - D12h		Merck Sharp and Dohme Corp
6	Pseudoephedrine sulphate	120 mg			
7	Efavirenz	600mg	Atripia	Jul12,2006	Gilead Sciences LLC
8	Emtricitabine	200 mg			
9	Tenofovir diisoproxil fumarate	300mg			
10	Glimepiride	2 mg	Duetact	Jul28,2006	Takeda Pharmaceuticals USA Inc
11	Pioglitazone HCL	30mg			
12	Cetrizine HCL	5 mg	Zyretac-D12 h	Nov 9,2007	Johnson and Johnson consumer Inc Mcneil consumer healthcare division
13	Naproxen sodium	500mg	Treximet	Apr 15,2008	Currax Pharmaceuticals LLC

14	Sumatriptan Succinate	85 mg			
15	Metformine HCL	1mg	Janumet XR	Feb 2,2012	Merck Sharp and Dohme Corp
16	Sitagliptin Phosphate	100 mg			

CONCLUSION

Oral controlled drug delivery systems aim to keep therapeutic drug levels nearly constant after oral administration for a predetermined amount of time. The three main benefits of oral controlled release systems are reduced frequency of dose, reduced adverse effects related to high plasma drug concentrations, and higher patient compliance. A multi-layer tablet is a drug delivery method designed to simultaneously release two or more medications at the appropriate release rate. Due to the regulated release profiles of the active components, multilayer tablets are used. Products with modified or regulated drug release are created to enhance patient comfort and compliance while optimizing treatment regimens. Traditional single-layered matrix tablets have less than ideal delivery characteristics, such as non-linear drug release profiles that could result in more side effects. Multi-layer tablets combine two or more Active Pharmaceutical Ingredients (API), improving patient convenience and compliance.

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