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Multi-layered tablets: A comprehensive review on technologies and research

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Abstract

Multilayered tablets combine two or more active pharmaceutical ingredients for an improved therapeutic effect or to achieve a specific drug release profile. In multi-layered tablets two or more active pharmaceutical ingredients can be combined where one layer or one drug may be for immediate release and the other layer of the drug may be for sustained release of drug i.e., one layer is a loading dose and the other layer may be a maintenance dose. Multilayered tablets can help overcome the drug interactions and the disadvantages of non-linearity associated with diffusion-controlled matrix devices, providing an increased surface area and increasing drug release rate with time. This review article discusses different techniques involved in the preparation of multi-layered tablets along with research on multi-layered tablets.

Keywords: Multi-layered tablets; Immediate release; Sustained release; Tableting techniques

1. Introduction

The dissolution curve of drug release from a hydrophilic matrix shows a time-dependent profile. The release profile of the drug dissolved follows the first-order diffusion where the drug release is initially high due to the dissolution of the drug present at the surface of the matrix accompanied by a rapid decrease in the drug release rate [1]. An enhanced release rate is observed briefly at the beginning of the release process. This is known as the burst effect which is undesirable as it has negative therapeutic effects like toxicity due to an increase in the concentration of the drug or accumulation of the drug on repeated administration.

Later on, the erosion or swelling of the polymer occurs leading to the controlled release of the active principals. This leads to an increased diffusion path length and a saturation effect is attained resulting in a slow-release rate at the end of dissolution [2]. To achieve a zero-order or nearly zero-order drug release, multi-layered matrix tablets were developed as a drug delivery system.

Multi-layered matrix tablet compresses a matrix core of active principal and one or more barriers or modulating layers. The modulating barriers delay the interaction of the active principle with the dissolution medium by controlling the penetration rate of solvent and reducing the surface available for the release of solute. The protected core prevents the water penetration for some time and reduces hydration rate resulting in less or controlled release of active principal at the core. Thus, the bust effect can be controlled and the release rate can be constantly maintained [3]. A linear drug release profile can be achieved by combining a time-dependent control of hydration rate with a reduction of tablet surface exposed to the dissolution medium.

1.1. Advantages of multi-layered tablets [4]

- In the case of drugs having a low half-life, each of the two layers of the tablet contains a loading dose and maintenance dose of the same, thus increasing the bioavailability of the drug.

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- Immediate-release and sustained-release active principals are combined into a single pill in multi multi-layered tablet. The pharmacological effect can be short from the immediate release active and over a longer time from the sustained-release active when the actives are separated into two distinct layers.
- Incompatible active ingredients or excipients, which are harder to blend can be compressed into the same final formulation as a multi-layer tablet form since the effects of these incompatibilities can be mitigated.
- Reformulation of existing single-layer tablets into new multi-layered variations leading into a new product line, as a result, a new patent can be accepted for the revised form. They can extend the life of a product line
- Some powerful unintended ingredients in the drugs can be combatted adding an antagonistic layer to the tablet that stops people from extracting the desired ingredient (i.e. that which may be abused).

1.2. Disadvantages of multi-layered tablets [4]

- 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.
- Cross-contamination, or color "bleeding", between layers
- Delamination (when the layers of the final tablet physically separate)
- Poor load cell resolution, especially for very thin first layers requiring almost no force
- Inefficient first-layer sampling processes, either in terms of speed, or transitional rejects
- Off-target weights for individual layers
- Lower output than single-layer tablet operations.

2. Various kinetic models in multi-layered tablet design

Multi-layered tablets are designed on the following aspects [5,6,7] 1) Matrix hydration rate and subsequently decrease in the dissolution rate. 2) Modulation of the surface matrix through which the drug is delivered.

Different designs:

2.1. Zero-order sustained release

The tablet comprises a hydrophilic or hydrophobic active principal as an intermediate layer and one or two modulated layers which are coated on both sides leaving the sides of the core uncovered to dissolve the drug in the dissolution medium. A linear profile can be obtained by applying a hydrophilic modulated layer on both the sides of hydrophobic core of the active principal or by applying a hydrophilic modulated layer on one face and a hydrophobic modulated layer on the other face of the matrix tablet.

2.2. Quick or slow delivery system

An initial rapid-release phase followed by a constant slow-released phase is characteristic of this system. So, the tablet is designed by application of an immediate release layer to the conventional layered matrix tablet. A prompt therapeutic effect followed by an extended-release phase at a constant rate can be achieved for the drug.

2.3. Time-programmed delivery system

Immediate release of the drug followed by time-controlled release is a time-programmed delivery system. The drug release is required in the gut in a time-controlled fashion rather than the release of the drug in a continuous manner according to circadian rhythm. The system consists of a core which is coated with different polymeric barriers. The drug shows a pulsatile release from the core after the eroding of a hydrophilic or hydrophobic module.

2.4. Bimodal release profile

An initial rapid release followed by a period of constant and slow release is characteristic of a bimodal release system. It has the advantage that 1) It produces rapid drug release during the initial and later phases to compensate for the relatively slow absorption in the stomach and intestine. 2) It can be used to design programmed pulse-release oral drug delivery systems for therapeutic agents that perform more effectively when the drug level at the site of action undergoes periodic changes.

3. Latest preparation technologies in multi-layered drug preparation

3.1. OROS push-pull technique

Here the tablet consists of two or three layers of which one or two consist of the drug while the other is a push layer. The drug layer consists of osmotic and suspending agents as it is poorly soluble. Moreover, the core is surrounded by a semipermeable membrane. The bilayer and trilayer OROS push-pull technique is illustrated in Figure 1.

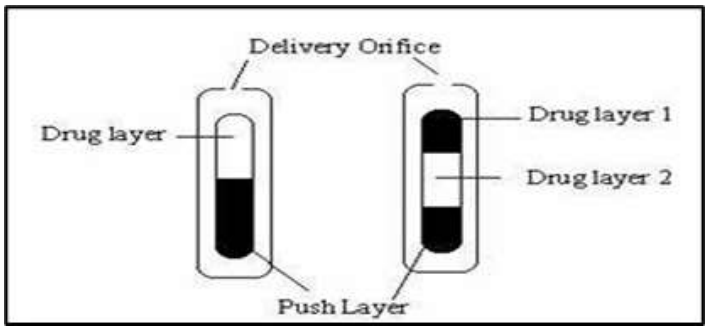

Figure 1 Bilayer and trilayer OROS push-pull technique [7]

3.2. Compaction

Initially, the die is filled with the required amount of sustained released drug portion and is lightly compressed. The rapid-release drug portion is placed over this compressed layer and pressed hard to get a bilayered compressed tablet. The compaction technique is illustrated in Figure 2.

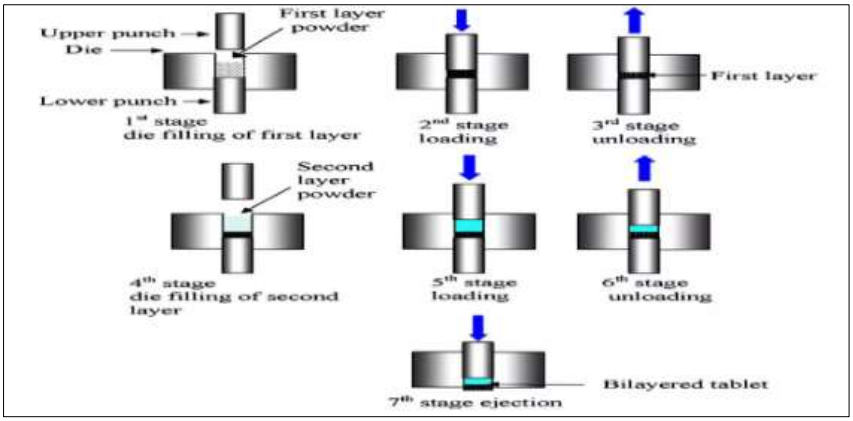

Figure 2 Compaction technique [8]

3.3. EN SO TROL technique

Multi-layered tablets consist of different layers of drugs, one layer of the drug for immediate release and a second layer designed to release the drug in extended form. Shire laboratory developed this enhancement technique by introducing a wicking agent into the core to increase the controlled release of the drug. EN SO TROL technique is illustrated in Figure 3.

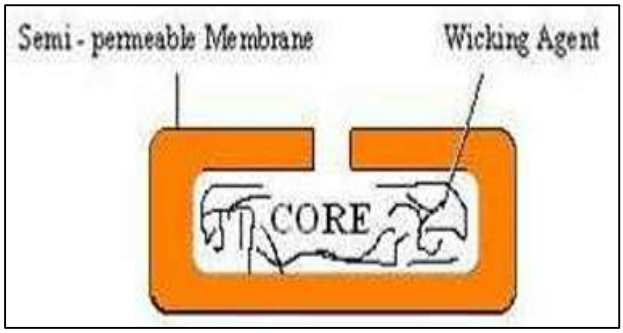

Figure 3 EN SO TROL technique [8]

3.4. Gluing pill technique

A gluing agent is used to join two separate layers of multilayered tablets. this technique has been designed to overrule complications like cross-contamination, contact between the two layers of the tablet, and delamination, which allows flexibility in fixing dose combinations, and is cost-effective. The first tablet layer is filled into the tablet mold then the gluing agent is melted and applied with binding agents using a nozzle system. The second tablet layer is then filled and pressed to harden the gluing agent between the two tablet layers. More tablet layers are produced by this process. A schematic diagram of the automated gluing pills technique is illustrated in Figure 4

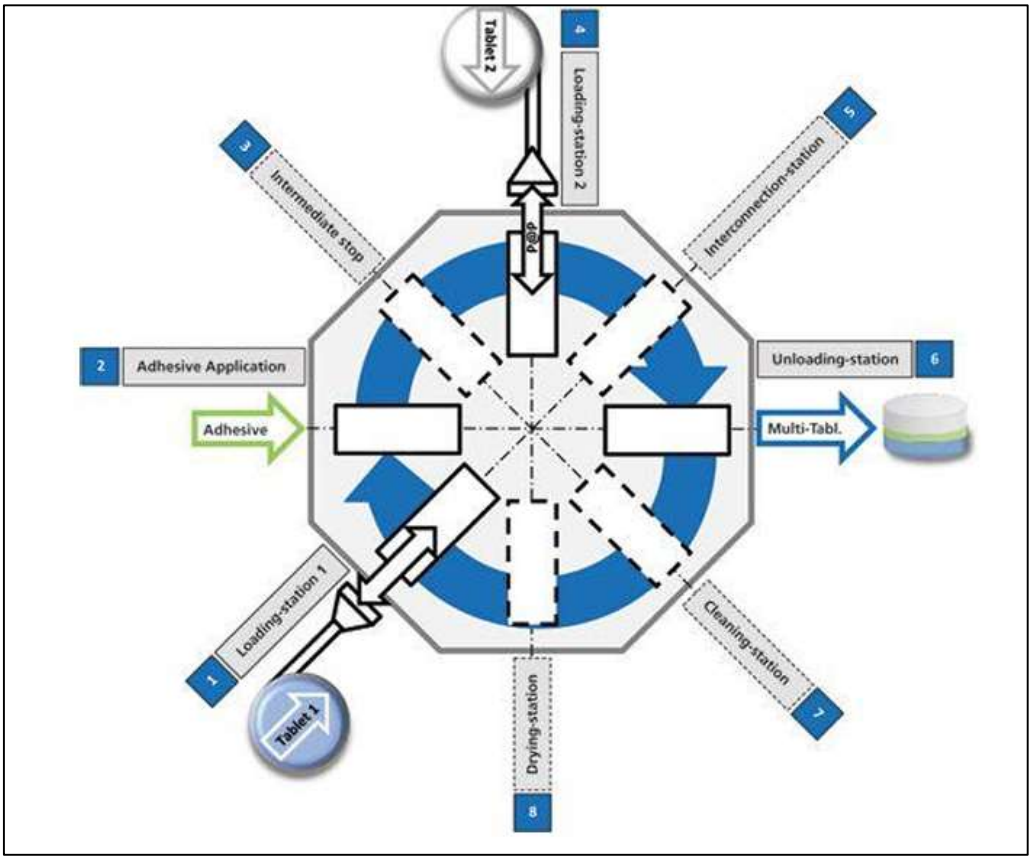

Figure 4 Schematic diagram of automated gluing pills technique [8]

3.5. L OROS TM technique

Alza developed the L-OROS system for poorly soluble and insoluble drugs. The core here is a lipid soft gel product in a dissolved state containing the drug coated with a soft gelatine capsule acting as a barrier membrane followed by an osmotic push layer and semipermeable membrane, at the end an exit orifice is drilled. L OROS TM technique is illustrated in Figure 5.

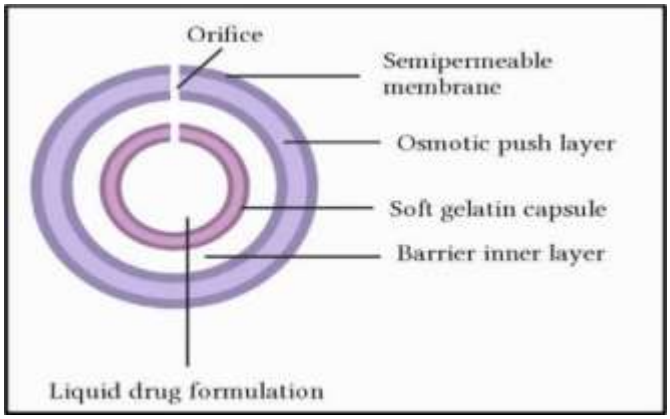

Figure 5 L OROS TM technique [9]

3.6. Elan Drug Technique (DUREDASTM Technique)

The Elan Corporation developed the Dual Release Drug Absorption System of bi-layered tablets by direct compression where one is an immediate release layer for the immediate onset of drug action while the other layer is composed of a sustained release hydrophobic matrix within the same tablet, which remains intact and slowly absorbs fluid from the GI tract. The matrix expands and becomes a viscous porous gel acting as a barrier between the surrounding fluid and the drug. As the gel expands the fluid surrounding it penetrates the drug and dissolves it. The dual Release Drug Absorption technique is illustrated in Figure 6.

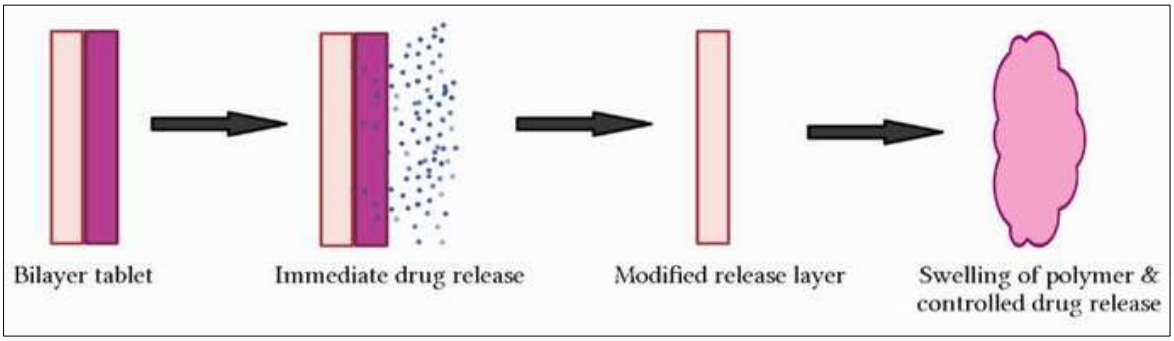

Figure 6 DUREDASTM technique [9]

3.7. Geminex

One or more drugs can be administered at various times by this dual medication delivery technique by adjusting the respective release rates to get the optimum therapeutic efficacy.

3.8. PRODAS or Programmable Oral Drug Absorption System

It is a multi-particulate drug delivery system developed by the Elan Corporation where the mini tablets of diameter from 1.5 to 4 mm with various drug release profiles are combined and blended into a single tablet. Immediate-release, delayed-release, and/or controlled-release micro tablet combinations are possible.

3.9. Erodible Moulded Multilayer Tablet

The tablet consists of a coat and a matrix. The matrix erodes when exposed to water whereas, the coat is biodegradable and prevents the penetration of water as it has a low water permeability. The drug release follows the zero-order release kinetics.

4. Marketed products of multilayered tablets

Multilayered tablets enabled the development of pre-determined release profiles of active ingredients and the incorporation of incompatible active ingredients into the single-unit dosage form. Some of the marketed products are illustrated in Table 1.

Table 1 Marketed products of multilayered tablets

Drugs	Product name	Manufactured by	Uses	Image
Pioglitazone, Metformin, Gliclazide	Glycinorm Total	Ipca Laboratories Ltd	It is an anti-diabetic medicine that treats type 2 diabetes mellitus. It helps control blood sugar levels in adults with diabetes.	
Alprazolam, Sertraline	Alprax Plus	Torrent Pharmaceuticals Ltd	To treat depression. By decreasing the abnormal and excessive activity of the nerve cells it calms the brain	
Metformin hydrochloride, Glimepiride	Glycomet-GP2Forte	USV Ltd	An anti-diabetic drug, to treat type 2 diabetes mellitus in adult	
Metoprolol succinate, Hydrochloro thiazide	Tolol-H 50	Unichem	To treat Pulmonary arterial hypertension.	
Desloratadine, Pseudoephedrine sulfate	Clarinex-D	Merck Sharp and Dhome Corp	To treat sneezing, runny or stuffy nose, itchy or watery eyes, hives, skin rash, itching, and other symptoms of allergies and the common cold.	
Guaifenesin, Pseudoephedrine HCl	Mucinex D	RB Health LLC	To treat nasal and sinus congestion. also to reduce chest congestion caused by the common cold, infections, or allergies	
Dextromethorphan Hydrobromide, Guaifenesin	Mucinex DM	RB Health LLC	It relieves coughs, common colds, bronchitis, and other breathing illnesses	
Desloratadine, pseudoephedrine	Clarinex-D 12h	Merck Sharp and Dhome Corp	To treat sneezing, runny or stuffy nose, itchy or watery eyes, hives, skin rash, itching, and other symptoms of allergies and the common cold.	

Glimepiride Pioglitazone HCl	Glujey-PM2	Ellanjey Lifesciences	To control high blood sugar in patients with type 2 diabetes.	
Cetirizine hydrochloride, Pseudoephedrine hydrochloride	Zyrtec-D 12h	Johnson and Johnson Consumer Inc	It is a decongestant used to provide relief from nasal congestion, sinus pressure, and allergy symptoms.	
Sitagliptin, Metformin	DIASIT-M	Omnica Laboratories	It controls high blood sugar in patients with type 2 diabetes.	
Levetiracetam	Elepsia XR	Tripoint Therapeutics	It is an antiepileptic drug used as adjunctive therapy in the treatment of partial-onset seizures.	
Diclofenac Sodium, Paracetamol	Diclo + plus	Origin Pharmaids	To reduce pain and inflammation in conditions like rheumatoid arthritis.	
Tramadol, Diclofenac Sodium	Tromacure-D	Adwin	It relieves severe acute pain and inflammation (redness and swelling).	
Metoprolol Succinate, Amlodipine Bisaltae	Supermet-AM	Abbott	It helps to control high blood pressure and heart rate. Also, for heart-related chest pain (angina), abnormal heart rhythms, and chronic (long-term) heart failure.	
Lamivudine, Stavudine, Nevirapine	Triomune	Cipla Ltd.	In the treatment of HIV infection.	
Telmisartan, amlodipine.	Twynsta	Boehringer Ingelheim	To treat high blood pressure, lowering the risk of a stroke or heart attack.	

5. Various works in the field of Multilayered Tablets

A large number of research works have been carried out in this field. Some of the recent work in this field are illustrated in Table 2.

Table 2 Various works in the field of multilayered tablets

Drugs	Dosage form	Method of preparation	Uses	Reference
Atorvastatin immediate-release layer, Ezetimibe sustained-release layer.	Modified-Release Bilayer Tablets	Compaction	Used in preventing and curing hyperlipidemia	12
Atorvastatin calcium immediate release layer, Metformin hydrochloride sustained release layer.	Bilayered tablet	Compaction	Used as an anti-hyperglycaemic agent in patients with type 2 diabetes.	13
Aspirin immediate release layer, Isosorbide 5-mononitrate sustained release layer.	Sustained bilayer tablets	wet granulation and compression technique	Used for prevention of angina and heart disease II	14
Cyclobenzaprine hydrochloride sustained release layer, Diclofenac potassium immediate release layer.	Bilayered tablet	wet granulation method	Used for the effective treatment of severe pain due to inflammation and muscle spasms.	15
Cefixime trihydrate immediate release layer, Dicloxacillin sodium sustained release layer.	Bilayered tablet	wet granulation process	used to treat infections caused by bacteria such as pneumonia, bronchitis, gonorrhea, and ear, lung, throat, and urinary tract infections.	16
Cefuroxime and clavulanic acid are both fast-release layers.	Bilayered tablet	Dry Granulation and Compression	It is an antibiotic used to cure uncomplicated urinary tract infections and reproductive tract infections, pharyngitis and tonsillitis, gonorrhea and chronic bronchitis, and skin infections.	17
Amoxycillin immediate release layer, Potassium Clavulanate sustained release layer.	Bilayered Tablets	Dry granulation method and compression	Used to treat bacterial infections.	18
Rifampicin and pyrazinamide are both immediate-release layers, Isoniazid sustained release layer.	Fixed-Dose Combination Bilayer Tablets	wet granulation method and direct compression	Used for the treatment of Tuberculosis.	19
Tramadol 35% immediate-release layer and a 65% sustained-release layer.	Bilayered sustained-release tablet	Compaction	Used in patients with cancer pain.	20
Salbutamol and theophylline both sustained release layers.	Bilayer sustained release tablets	wet granulation and direct	Used in asthma for prolonged bronchodilation	21

		compression method		
Atorvastatin calcium, immediate release layer, and Nicotinic acid sustained release layer.	Bilayered tablets	Aqueous and non-aqueous granulation method.	Used to reduce the low-density lipoprotein cholesterol.	22
Metoclopramide hydrochloride immediate release layer and Ibuprofen sustained release layer.	Bilayered tablets	Direct compression	Effectively used in the treatment of migraine.	23
Atenolol immediate release layer and Amlodipine sustained release layer.	Bilayered tablets	Dry granulation technique	Used as an antihypertensive drug.	24
Glipizide immediate release layer and Metformin hydrochloride sustained release layer.	Bilayer matrix tablet	Direct compression technique	Used in Type 2 diabetes.	25
Atenolol sustained release layer and Lovastatin immediate release layer.	Bilayer floating tablets	Direct compression method	Used for the treatment of hypertension and hypercholesterolemia.	26
Montelukast sustained release layer and levocetirizine immediate release layer.	Bilayered tablets	wet granulation method	Used in the treatment of allergic rhinitis and bronchial asthma.	27
Simvastatin Immediate release layer and Atenolol sustained release layer.	Gastro-bilayer Floating Tablets	Direct compression method	Used as a combination therapy for hypertension and dyslipidaemia	28
Aspirin and isosorbide 5-mononitrate are both sustained release layers.	Sustained bilayer tablet	wet granulation and compression technique	Used for the prevention of angina and heart disease	29
Ziprasidone HCl and trihexyphenidyl HCl both sustained release layers.	Bi-layer floating tablets	Direct compression method	Used to treat Schizophrenia.	30
Metformin HCl sustained release layer and Evogliptin tartrate immediate release layer.	Bilayer tablet	Direct compression method	Used in Type 2 diabetes.	31

6. Conclusion

Multilayered tableting is an inexpensive and simple method of combining incompatible active ingredients into two or multiple layers of which one layer is an immediate-release initial dose and the second layer is a maintenance dose. Several pharmaceutical industries and formulating scientists across the globe are working on this technique of multilayered tableting with the ultimate aim of a better health care system.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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