

# An overview of layered tablets

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**ABSTRACT:** Tablets are age-old dose forms that are economical and easily accessible to everyone. They offer several benefits over other formulations, including the fact that they are largely stable, tamper-proof, and portable. There is a lot of research being done to create additional types. Layered tablets are one of the most recent. They are sometimes known as tablets inside tablets. The evaluation focuses on current trends and technology, as well as the benefits of multilayer tablets. It also defines the polymers utilized in tablet manufacturing. The newest technologies in the creation and assessment of multilayered tablets, such as DUROS, EROS, and GPT, are reviewed. The strategies and in-process control mechanisms for sustained and controlled release, as well as medication release methodology, and therefore address the shortcomings in the manufacturing process.

**KEYWORDS:** Immediate Release, Controlled Release, Gluing Agent, OROS, DUROS, Bilayer, Multilayer.

## I. INTRODUCTION:

Continuous scientific study into illness areas and multi-targeted techniques are opening up a wide variety of options in pharmaceutical development and manufacture in the current era. Bilayer tablet research and manufacture have been ongoing for many years. The matrix-type approach is typically used for stacked tablets. Polypharmacy benefits from multilayer tablet technology. Polypharmacy is a major topic of attention in the field of medicine. It discovers a successful solution in multilayer tablets by providing at least 5 medications at regular intervals. High-potency active pharmaceutical ingredients (HPAPI) with smaller but more potent concentrations of materials may be used in formulations developed for this purpose. These complicated formulations are used in multilayer tablet technology to provide more effective medicinal medicines. Specially formulated disintegrants have greater efficacy at lower concentrations. Croscarmellose sodium and sodium starch glycolate are the most common superdisintegrants.

### Classification of the layered tablets: <sup>[1]</sup>

1. Bilayered
2. Multilayered - trilayered and more than 3 layers.

**Double-layer tablets:** so-called bilayer tablets or multi Layered tablets are a tablet that has a combination of two or more 2 drugs in a single tablet and that is why they are also called controlled-release tablets. In double-layered tablets, 2 drugs are present out of which one layer is immediate release as a loading dose and the second layer is controlled release as a maintenance dose. Two drugs can be formulated into a bilayer directly by adding an insert intermediate layer. Tablets are formulated such that they overcome different disadvantages like expensive, layer combination, they have sufficient hardness.

In bilayer tablet is suitable for a sequential and simultaneous release of two different APIs. The layer is formulated to obtain the immediate release of the drug, to reach a high serum concentration in a short period. The second layer is a controlled release, sustained release as a maintenance dose or one layer acts as a loading dose, and the other layer releases the maintenance dose. A hydrophilic matrix is used to design and maintain an effective plasma level for a prolonged period. Drug release from fast releasing layer causes an immediate rise in blood concentration. However, the blood level is maintained at a steady state as the drug is released from the sustaining layer <sup>[2]</sup>. Bi-layer shows no dynamic and pharmacological interaction.

**Triple-Layer Tablet:** Triple-layer tablets consist of three layers the first layer is for the immediate release of drugs and the second layer is for sustained release. These two layers are separated by the middle barrier layer. This is more suitable for the delivery of two drugs that interact in them. <sup>[3]</sup> Bilayer tablet adds convenience for administration and provides brand recognition.

## II. ADVANTAGES OF BILAYER TABLETS <sup>[4, 5, 6]</sup>

1. The nonlinearity is associated with diffusion-controlled matrix devices by providing an additional release surface with time to compensate for the decreasing release rate.
2. Wide flexibility
3. The option of fine-tuning the availability of each API
4. Differentiation of their release times, being able to separate incompatible APIs,
5. Prolonging the medicine effect after administration
6. Reducing the dose frequency in elderly patients, and the number of tablets required each day impacts the quality of life.
7. Fewer medication errors.

8. Avoid chemical incompatibilities of formulation components by physical separation.
9. Enables the development of controlled delivery of active pharmaceutical ingredient's
10. predetermined release profiles
11. Combination of different release patterns (combining slow-release with immediate-release layers)
12. to improve the effectiveness of therapy
13. patent extension for industries
14. Marketing purposes.

### III. KEY CONSIDERATIONS FOR MULTI-LAYER TABLETING:

The inherent complexities of producing good multi-layer tablets, at appreciable speeds, take many forms.

The following In process formulation problems of multilayered tablets :

1. Cross-contamination, or color "bleeding", between layers
2. Delamination (when the layers of the final tablet physically separate)
3. Poor load cell resolution, especially for very thin first layers requiring almost no force
4. Inefficient first-layer sampling processes, either in terms of speed, or transitional rejects
5. Off-target weights for individual layers
6. The lower output than single-layer tablet operations
7. weight control
8. tablet thickness
9. compression force
10. an elastic-modulus mismatch between the layers
11. improper layer weights or layer ratios
12. Relatively low production efficiencies
13. high rejection rates
14. the cross-contamination of incompatible APIs
15. missing a clear boundary layer

### IV. THE LATEST TECHNOLOGY OF MULTILAYERED TABLETS PREPARATION: [7,8,9,10]

1. OROS Technology
2. Compaction
3. EN SO TROL
4. L-OROS
5. Gluing
6. Giatti, compression technologies
7. Elan Drug Technology (DUREDASTM Technology)
8. Geminex
9. PRODAS or Programmable Oral Drug Absorption System Prodas
10. Erodible Molded Multilayer Tablet Egalet

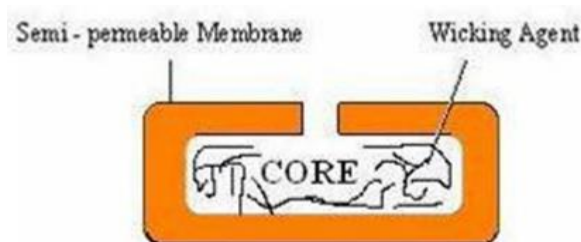
#### Production of Bi-Layer Tablets:

Step 1 Preparation of two different layers one layer of the drug for immediate release and a second layer designed to release the drug in extended form.

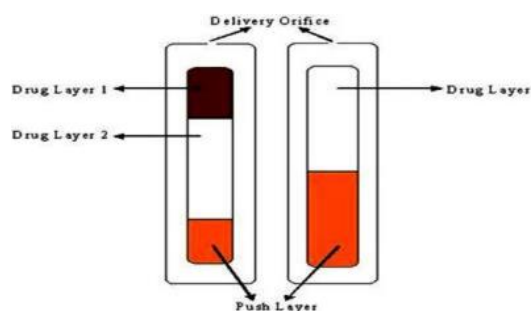
Step 2 separate layers of each incompatible drug are prepared to minimize the area of contact between layers.

Step 3 Additional intermediate layer of inert material may be included.

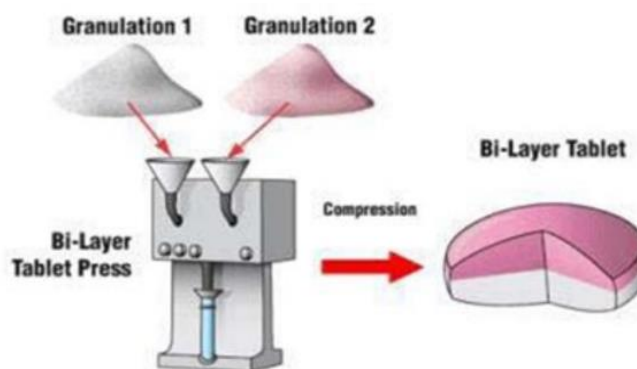
#### EN SO TROL Technology:[7]



Shire laboratory focussed on the enhancement of controlled-release of drugs by using enhancement technologies.

**OROS Push Pulls Technology:<sup>[7]</sup>**

Uses an osmotic agent and a suspending agent. it has two or three layers among which one or more layers are essential to the drug, other layer consists of the push layer. Thus, this drug layer comprises drug which is in poorly soluble form. The Tablet core is surrounded by a semi-permeable membrane. The introduction of bi-layer tablets into the pharmaceutical industry has enabled the development of pre-determined release profiles of active ingredients. The incompatible active ingredients are incorporated into the single-unit dosage form.

**COMPACTION TECHNOLOGY: <sup>[7]</sup>****Gluing Pills Technology for the Production of Multi-Layer Tablets <sup>[11,12,13]</sup>**

[11]

Gluing agent: The agent used to join two separate layers of a multilayered tablet.

This gluing agent technology is a novel one and was developed to overcome challenges in multilayered tablet manufacturing like

- in-line control of tablet weight
- the tendency to delamination
- contact between the two tablet layers
- avoid cross-contamination
- real-time production
- promote individualized fixed-dose combinations
- help in translational pharmaceuticals
- personalized medicine
- offers flexible fixed-dose combinations (FDC)
- patient adherence (cost-saving)
- life-cycle management (LCM) of pharmaceutical products

**Gluing agent characteristics:**

- ✓ The tack (adhesive strength)
- ✓ viscoelastic properties of the gluing agent
- ✓ evaporation time of solvent,
- ✓ the thickness gluing layer.

- ✓ glass transition temperature
- ✓ concentration range

The interfacial bonding (Dipole-dipole / dipole-induced dipole interactions/hydrogen bond) By this gluing technology several challenges for bilayer manufacturing are overcome. Each layer is compacted separately, and tablets are attached in an automated process with a binding agent, which at the same time acts as a barrier against cross-contamination and interactions between the tablet layers.

#### The advantages of GPT :

- ✓ the flexibility of API combinations,
- ✓ reduced waste
- ✓ higher process efficiency
- ✓ different layers of different thicknesses combined in one dosage
- ✓ no redevelopment process
- ✓ fulfills the demands of individualized medicine

#### Methodology:

- Step 1 feeding of the first tablet layer
- Step 2 . application of gluing agent
- Step 3 . feeding of the second tablet layer
- Step 4 . hardening of the gluing agent between the two tablet layers
- Step 5 production of bilayer tablets
- Step 6 unloading
- Step 7 application of more layers

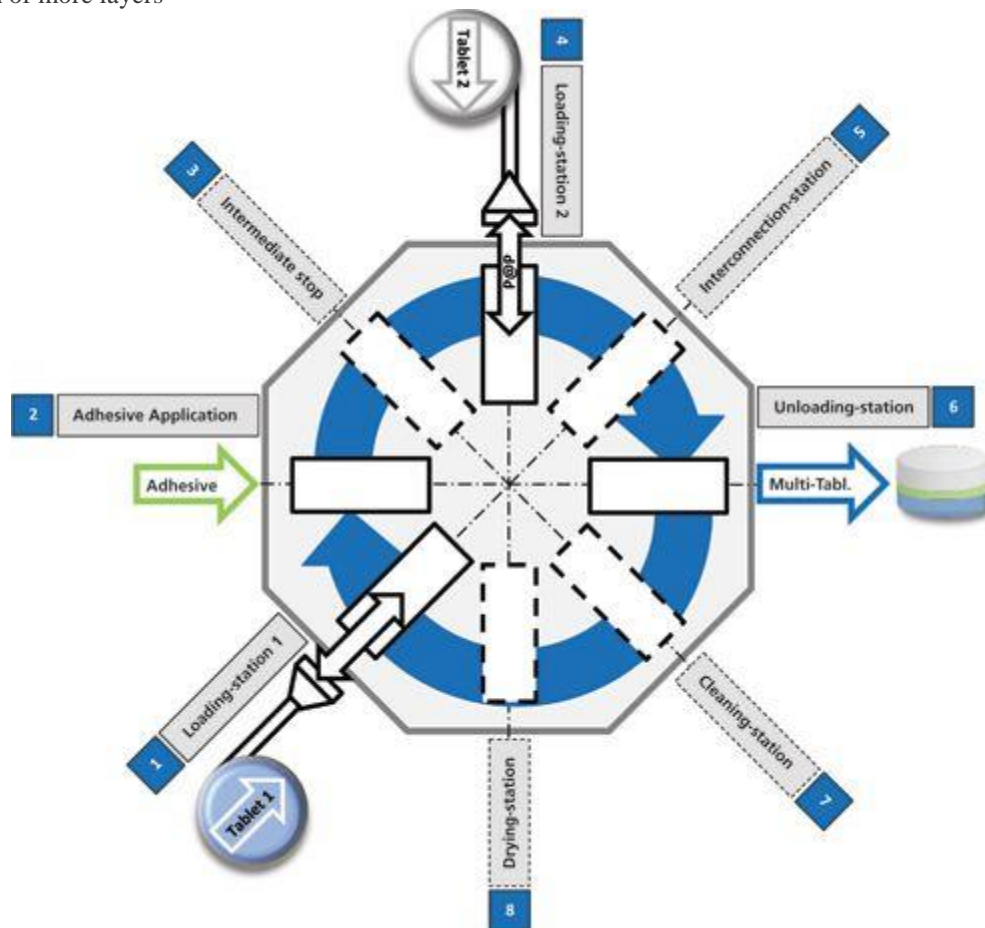
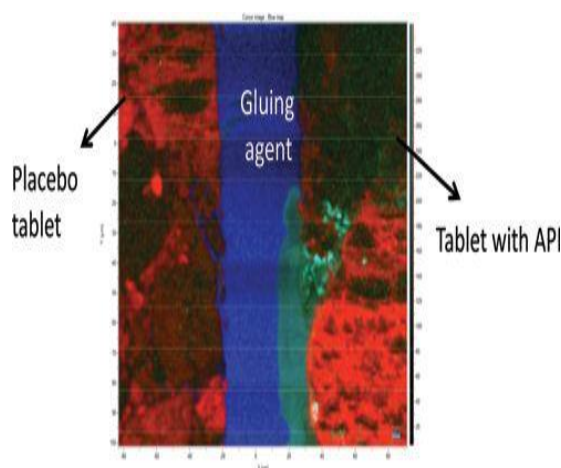


Fig: Schematic diagram of automated gluing pills technology [11]

The GPT follows quality-by-design principles, applying analytical technology (PAT) tools for in-line monitoring. This system ensures thickness, continuity of binding layer, amount of gluing agent, and adjustment of this layer on the tablet. the process.



[11]

There is a nozzle system for glue application. it is based on piezo technology. The gluing material is melted and applied with the binding agents are both aqueous and organic. The polymers are melted and spread with the nozzle. The solvent can be aqueous to protect the environment. Studies different gluing agents are used ie organic and inorganic solvents.



ML7, ML 240 equipment, GPT <sup>[11]</sup>

#### **DUREDASTM:** <sup>[14]</sup>

Dual Release Drug Absorption System is by the Elan Corporation

Used for dual release of a drug from the tablet prepared by two separate direct-compression. It has 1. An immediate-release granulate (for rapid onset of action) and 2. a controlled-release hydrophilic matrix complex within one tablet. The controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, and the drug released from the immediate granulate dissolves. The matrix expands and transforms the becomes a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid.

Fluid penetrates deeper into the dosage form as the gel expands, dissolving the medicine and allowing the resultant solution to diffuse out in a regulated manner. The manufacture of controlled-release combination dosage forms, in which two separate medications are included in the various layers and the drug release of each is regulated to maximize the therapeutic benefit of the combination, is another extension of the DUREDASTM technology. Immediate and controlled release combinations are prepared using DUREDASTM. Initially, the DUREDASTM technology was used in OTC controlled-release analgesics.

#### **Geminex :** <sup>[15,16]</sup>

Geminex is a dual medication delivery feature tool that allows one or more pharmaceuticals to be administered at various times. It adjusts the release rate of the two medications to optimize therapeutic efficacy. In a single tablet, two separate active ingredients might be supplied at various speeds. Is used to treat cardiovascular disease, diabetes, cancer, and central nervous system diseases.

#### **Programmable Oral Drug Absorption System:** <sup>[16]</sup>

The Elan Corporation's Programmable Oral Drug Absorption System is a multi-particulate drug delivery system based on the embedding of controlled-release micro tablets varying in diameter from 1.5 to 4 mm. The technique is a hybrid of multi-particulate and hydrophilic matrix tablet technologies, combining the advantages of both drug delivery systems into a single dosage form. To achieve the necessary release rates, mini tablets with the varying release of drugs can be blended and combined into one dose form.

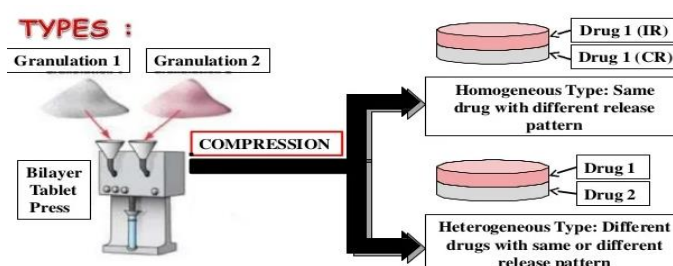


Combinations of immediate-release, delayed-release, and/or controlled-release micro tablets are possible. In addition to regulated absorption over a predetermined period, PRODAS technology allows for targeted medication administration to a specific site of absorption across the GI tract. Combination goods too are achievable through the use of mini tabs.

### Egalet erodible molded tablets <sup>[16]</sup>

Egalet erodible molded tablets are based on erosion. It has the virtue of providing zero-order or extended-release with minimal gastrointestinal effect. The manufacturing process is used to create Egalet erodible molded multilayered tablets. Egalet technology uses a coat and a matrix. The drug is slowly released on disintegration. The mode and rate of release are modified by the matrix, coat, and geometry to produce either zero-order or delayed release. The coat is biodegradable, with low water permeability which, prevents it from penetrating. When exposed to accessible water, the matrix erodes. Egalet is developed based on standard plastic injection molding to ensure reproducibility and is economic

### Various Approaches used in the Bi-Layer Tablet <sup>[17,18]</sup>



### BILAYER Floating Drug Delivery System

1. BILAYER Floating Drug Delivery System BILAYER <sup>[17]</sup>
2. Polymeric Bio adhesive System
3. Swelling System

### Problems in bi-layer tablet compression and possible remedies to be followed

#### Tablet weight variation

- a) Poor flow characteristics of the material
  1. Wrong setting of the hopper.
  2. Material bridging in the hopper
  3. Too much recirculation
- b) Dies not filling
  1. Press running too fast
  2. Wrong feeder paddle speed or shape
- c) Loss of Material
  1. Recirculation band leaking
  2. Excessive vacuum or nozzle improperly located

#### Product yield:

- a) Incorrect feeder fit to die table
- b) Incorrect action on the recirculation band
  1. Gap between the bottom edge and die table
  2. Binding in mounting screw
  3. Too little hold down spring pressure
- c) Die table scraper action insufficient
  1. Scraper blade is worn or binding
  2. Outboard edge permitting the material to escape
- d) Loss at compression point
  1. Compressing too high in the die
  2. Excessive or misdirected suction on the exhaust nozzle

#### Low hardness:

- a) Factors related to machine
- b) Lubricant level
  1. Press speed is reduced to increase total compression time
  2. Over-mixing can reduce tablet hardness

**Capping and lamination:**

- a) Non-optimized formulation
  1. Incorporate plastically deforming matrix
- b) High compression force
  1. Reduced compression force
  2. Reduced press speed
- c) Ratio of pre-compression to main
- d) Compression is insufficient
  1. Pre-compression force high can be harmful
  2. Use a large compression roller diameter
- e) Curled or damaged punches
  1. Tools should be rewashed or replaced Picking and sticking
- f) Excessive heat generation during compression
  1. Use of a cooling system for the compression section
  2. Lower mechanism section may be helpful
- g) Fouling the punch faces
  1. The startup should always be close to optimum conditions
 Separation of two individual layers
- h) Insufficient bonding between the two layers during the final compression of the bi-layer tablet
  1. The First layer should be compressed at a low compression force

**Mottling:**

- a) Improper setting of both feed frame
  1. Both feed frames should be set properly.
- b) Due to weak suction
  1. Suction capacity should be such that, all waste material is sucked.

**The bi-layer tablet presses:** <sup>[19]</sup> are single sided press and double-sided tablet press and bi-layer tablet press with displacement monitoring

**V. SELECTION OF EXCIPIENTS:** <sup>[20,21,22,23]</sup>

The problem to be eliminated while compression is delamination. Reasons for delamination:

- Inadequate manufacturing process
- Delamination may occur during storage
- interlayer delamination

(Interlayer delamination) As a consequence, the patient cannot receive one of the intentional substances or receives an improper dosage.

- Improper dosage
- applied substances properties
- Formulation process parameters.
- tools and materials which may be incorporated into the design
- mechanical strength of the tablet and each layer
- the interphase adhesion of the layers

Excipient selection, speed of tablet press, the degree of suction, and uniform flow of the blend of excipients help in achieving uniform die filling and ultimately consistent tablet weight uniformity.

The flow of the blend should be uniform in all the layers. the first layer's surface should have a rough enough porosity resulting in complete adhesion of the second layer. If the first layer is too smooth subsequent layer will not adhere well and layers may separate with minimal agitation during ejection, discharge, packaging, or over the shelf-life of the product. the tablet shouldn't be fragile.

**VI. MULTILAYERED DESIGN AND Q/D DESIGN:**

In several studies, quality-by-design was applied to evaluate the range and cause of risks for a single-layered tablet in the formulation design research, The stabilizer and disintegrate were taken as factors and the critical process parameters were the wet granulation and tableting process. After deciding on the design. The single-layered tablets were formulated, and their dissolution patterns were compared with that of the double-layered tablet. The selected quality-by-design (QbD) approach single-layered tablet formulated using design space was found to be bioequivalent to the Twynstar® double-layered tablets. Hence, the development of single-layered tablets with two APIs using the Q/D approach could improve the medication compliance of patients and could be used as a platform to overcome time-consuming and excessive costs and eliminate technical commercial limitations.

**VII. EVALUATION OF LAYERED TABLETS:** [24, 25, 26, 27, 28].

Pre-compression evaluations	Post compression evaluations
powder characteristics and micromeritics	Weight uniformity- ensure intra and inter-batch uniformity data. Done using 20 tablets Calculating individual and average weight and deviations.
powder particle size analyzed by laser diffractometer.	Thickness- <ul style="list-style-type: none"> <li>• Vernier caliper</li> <li>• Enable swallowing</li> </ul>
Hausner's ratio, Carr's index, and angle of repose	Friability- friability apparatus Hardness- Pfizer/Monsanto hardness tester
moisture content-TGA	Content uniformity - UV Visible spectrophotometer
	Disintegration time In-vitro drug release Drug release kinetic-based on layers (release rate )
<ul style="list-style-type: none"> <li>✓ Stability studies of the layers, degradation, and shelf life.</li> <li>✓ Morphology analysis-Scanning Electron Microscopy (SEM) using cross-section samples</li> <li>✓ Thermal analysis-drug-excipient, drug-drug, and excipient-excipient interactions Differential Scanning Calorimetry (DSC)</li> <li>✓ Crystallinity-affects stability, and solubility. Using X-Ray Diffractometer (XRD). vice</li> </ul>	

The formulations of every layer should be compressible and compactable. During compaction, the interface between the layers should weld, and strong adhesion forces should keep the layers together following tablet ejection. To provide adequate surface roughness for the particles to nest and connect between the layers, the compaction pressure used to form the first tablet layer should be reduced to a minimum. The increased surface roughness creates a wider contact area between the layers, increasing the interlayer. The necessity for developing an experimental procedure that could be applied to bilayer tablets to detect lamination tendencies that are no longer obvious when the tablet is ejected but become apparent after storage and handling of the compacts were highlighted.

The main issue that must be resolved, is to understand in detail the sources of these problems in micro- and macro scales and to develop remedies to solve them during solid dosage delivery design. The mechanical properties should be comparable with the standard. The relative densities are changing according to the compositions that were used. The tablets can be formulated into both sustained and zero-order kinetics.

**VIII. MARKETED FORMULATIONS OF MULTILAYERED TABLETS FDA- AND EMA-APPROVED FDC PRODUCTS WITH MULTILAYER TECHNOLOGY.**<sup>[28]</sup>

Product Name	Chemical Name
Alprax Plus	Sertraline/ Alprazolam
Glycomet-GP2Forte	Metformin hydrochloride/Glimepiride
Lopressor HCT	Metoprolol/Hydrochlorothiazide



Diovan HCT	Valsartan/ Hydrochlorothiazide
Lotensin HCT	Benazepril/Hydrochlorothiazide
Clarinox-D	Desloratadine/Pseudoephedrine sulfate
Treximet	Sumatriptan/Naproxen sodium
Atripla	Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate
Under -In clinical development EP 2 682 112 A1 trials/Patent	Flurbiprofen 100 mg Famotidine 20 mg

## CONCLUSION:

Using contemporary advanced and up-to-date technology, the quality of multilayer tablets may be increased, and GMP criteria. Layered tablets can provide several benefits such as immediate-release and controlled-release in a single dosage form and avoid incompatibility between two or more active medicinal ingredients, cost savings, and improved stability. The characteristic of multi-layered tablets gives unique product performance targets that traditional tablets cannot achieve, but it also introduces additional obstacles for formulation design, manufacturing process, controls, and product life performance needs. They must also add hurdles in creating applicable regulatory controls to achieve product performance standards during the drug's life cycle.

To achieve these objectives, a deeper understanding of the ingredients and production factors is required to control the risks associated with product acceptability throughout the product life cycle to avoid batch failures and batch recall. To address production difficulties such as correctness in weight control of each layer, delamination / layer-separation during manufacturing and storage, insufficient tablet breaking force, and cross-contamination between the layers, the development, and production of quality bi-layer tablets necessitates a thorough understanding of the product and process in case of incompatible APIs).

The dosage form's goal is to guarantee that the pharmaceuticals supplied to patients are not only safe and effective but that they are also correctly made and packed to match the defined quality and target product profile during their shelf-life. A well-designed product will handle these difficulties successfully by including suitable control measures and defining the functional linkages of the material qualities and process parameters necessary to layer tablet quality. As a result, layered tablets may be regarded as an upgraded helpful technology capable of overcoming the shortcomings of other tablets. In some studies when single-layer and double-layer tablets were compared percentage yield was found to be almost similar. The problems relating to the quality, impurities, and manufacturing methods were solved without using a double-layer tablet press. This confirmed that irrespective of the manufacturing costs, there are possible high-quality improvements for manufacturing processes.

The different technologies mentioned in the article are aimed at increasing the production value of multilayer tablets and also, we can apply Q/D designs for optimization and research of the formulations.

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