International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 7 Issue 1, January-February 2023 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

A Review on Bilayer Tablet Dosage form Development and it's Various Advancement in Field of Bilayer Tablet

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ABSTRACT

Bilayer tablet dosage form is new concept for successful development of controlled or sustained release formulation and immediate release formulation. The bilayer tablets are specially design sequential release of two drugs. Bilayer tablet dosage form are design to achieve sustained and immediate delivery of different drugs with previously set release profile. This type of bilayer tablet dosage form are combination of different APIs in single dosage form has increased in pharmaceutical company to promoting patient convenience and improve patient compliance toward solid dosage form(Tablets). To manufacture good quality tablets various type of machinery or equipment used as per GMP requirement. Now a day various pharmaceutical companies manufacture bilayer tablet for the variety of reasons: improve therapeutic effect, patent extension, reduce dose, marketing and to reduce capital investment…etc. In this review summaries various aspects of bilayer tablets.

KEYWORDS: *Bilayer tablets, Combination drugs, Incompatibilities, Sustained release, Immediate release, GMP requirements, Bilayer tablet presses*

How to cite this paper: Amit Chaudhari | Sauravi Ghuge "A Review on Bilayer Tablet Dosage form Development and it's Various Advancement in Field of Bilayer Tablet" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-7 | Issue-1, February 2023, pp.622-636, URL: www.ijtsrd.com/papers/ijtsrd52733.pdf

IJTSRD52733

INTRODUCTION

The conventional dosage forms are unable to provide control on drug release. To maintain the drug concentration within the therapeutically effective range, it is necessary to take it several times a day which results in significant fluctuation in a drug levels [1]. The conventional dosage form produce wide-ranging fluctuation in drug concentration in the blood stream and tissues which may cause consequent undesirable toxicity and decrease therapeutic efficacy of drugs. To avoid this of factor such as repetitive dosing and unpredictable absorption. It is required to change the concept of controlled drug delivery systems. The main purpose in designing bilayer tablet dosage form is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, providing uniform drug delivery and reduce the dose [2]. The main objective of Bilayer drug delivery is to make sure safety and to improve effectiveness of drugs as well as patient compliance. Now a day most of the pharmaceutical companies are developing bi-layered tablets for a variety of reasons: Patient convenience, to reduce dose, patent extension, therapeutic, marketing to a name a few. Bi-layer tablet is suitable for two incompatible substances and sequential release of two drugs in combination in which one layer is immediate release as initial dose and second layer is maintenance dose [3].

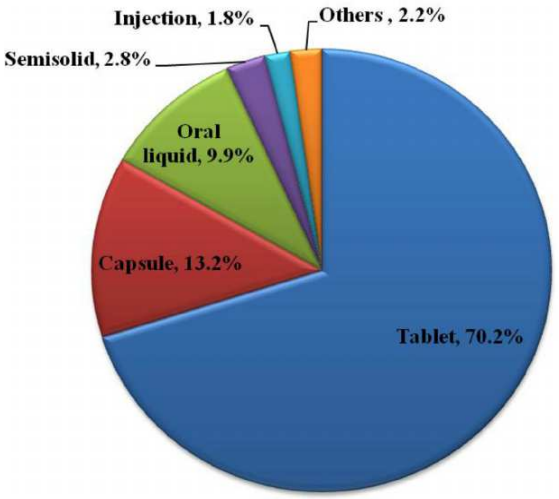

Figure 1 Share of different dosage forms in percentage.

Now a day most of the pharmaceutical industry show interest in manufacturing of combination of two or more Active Pharmaceutical Ingredients in a single dosage form has increased. The main objective of combination therapy is to encourage the utilization of lower doses of drugs to treat patients, to minimize dose dependent side effect and adverse reactions. To avoid the drawbacks of conventional dosage form this bilayer layer concept was came into force. Bilayer tablets can be a primary option to avoid chemical incompatibilities between APIs by physical separation, and to enable the development of different drug release profiles (immediate release with extended release) [4].

TERMINOLOGY [4,5,6,7]:

A. Immediate Release:- Tablets are those which disintegrate rapidly after administration orally and get dissolved to release the medicaments (Such as tablets containing a painkiller, Antacid tablet)

B. Controlled release:- It is one which delivers the drug at a predetermined rate, for locally or systematically for a specified period of time.

C. Sustained release: - Drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.

D. Extended release:- These release drug slowly so that plasma concentration are maintained at a therapeutic level for a prolonged period of time usually between 8-12 hours.

E. Delayed release:- These is designed to release the drug at a time other than promptly after administration. The delayed may be time based or based on the influence of environmental condition like Gastro-intestinal pH e.g. Enteric coated tablet.

F. Site specific targeting:- These system refer to targeting of a drug directly to a certain biological location.

G. Receptor targeting:- These system refer to targeting of a drug directly to a certain biological location. In these case the target is the particular receptor for a drug within an organ or tissue.

TYPE OF TABLETS & CLASS OF TABLETS [9]

1. Oral Tablets for Ingestion.
I. Standard compressed tablets
II. Multiple compressed tablets
a) Layered tablets
b) Compression coated tablets
c) Inlay tablets
III. Modified release tablets
IV. Delayed action tablets
V. Targeted tablets:
a) Floating tablets
b) Colon targeted tablets
VI. Chewable tablets

2. Tablets Used In the Oral Cavity.
I. Buccal tablets
II. Sublingual tablets
III. Troches and lozenges
IV. Dental cones

3. Tablets Administered By Other Routes.
I. Implantation tablets
II. Vaginal tablets

4. Tablets Used To Prepare Solution.
I. Effervescent tablets
II. Dispersible tablets
III. Hypodermic tablets

MULTIPLE COMPRESSED TABLETS [9]:

It consist of two or more drugs (API) in single tablet. It is the best option to administer two or more incompatible API's in same unit. In multilayer tablet dust extraction is essential during compression to avoid contamination.

A. Layer Tablets:

Layer tablets are composed of two or three layers of different API's compressed together. Final layer tablet have the look like a sandwich. It is the combined preparation of sustained release and immediate release in one layer.

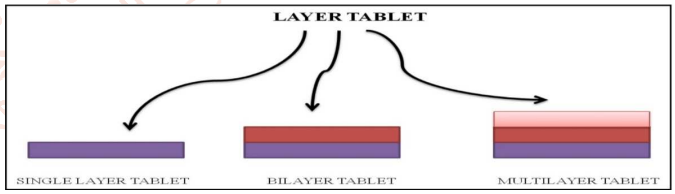

Figure 2: Layer Tablet.

B. Inlay Tablets

It is the type of layered tablet in which the core tablet being not completely surrounded by coating instead that only top surface is expose.

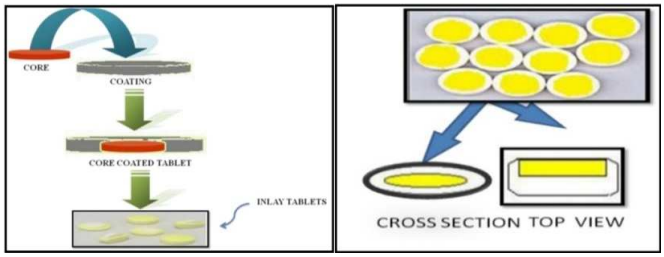

Figure 3: Inlay Tablets.

C. Compression Coated Tablets

In this type of tablet consist of two parts internal core and surrounding coat in which core is small porous tablet and prepared on one turret.

BILAYER TABLETS:

New oral delivery device was proposed, in the form of a double-component tablet, one portion is formulated to obtain a prompt release of the drug with the aim to achieve high serum concentration in a short period of time. The second portion is a prolonged release layer which is designed to maintain an effective plasma level for a prolonged period of time. The drug release from fast releasing component leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer.

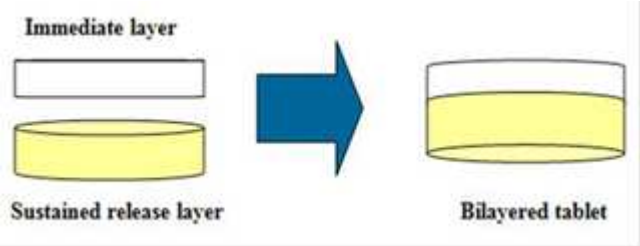

Figure 4: Bilayer tablets (different drug with different release pattern)

➢ **Need of developing bi-layer tablets [9,10,14] :**

1. For the supervision of fixed dose combinations of drugs, prolong the drug product life cycle, manufacture novel drug delivery systems such as floating or mucoadhesive bilayer tablets for gastro - retentive drug delivery systems.
2. Controlling the delivery rate of either single or two different active pharmaceutical ingredients (API'S).
3. To available total surface area for API layer either by sandwiching in order to achieve swell able / erodible barriers for sustained release.
4. To separate incompatible API's with each other [15].

➢ **Advantages of bi-layer tablets [9,10,11,12] :**

a) Bi-layer execution with optional single layer conversion kit.
b) Low cost compared to other dosage forms.
c) Greatest chemical and microbial stability compared to other oral dosage forms.
d) Objectionable odor and taste can be masked by coating technologies.
e) Flexible concept.
f) Offer greatest precision and the least content uniformity.
g) Easy to swallow with least hang up problems.
h) Fit for large scale production.
i) Bi-layer tablet is suitable for incompatible two drugs and thus to maximize the efficacy of combination of two drugs [14].
j) Expansion of a conventional technology.
k) Prospective use of single entity feed granules.
l) Separation of incompatible components.
m) Patient compliance is improved leading to improve drug regimen efficiency [13,14].
n) Patient compliance is improved because fewer daily dosages are required compared to traditional delivery system [16].
o) Maintain physical and chemical stability.
p) Product identification is easy.
q) Easiest and cheapest to package and strip.

➢ **Disadvantages of bi-layer tablets [9,10]:**

a) Complexity and bi-layer rotary presses are expensive.
b) Insufficient hardness, layer separation, reduced yield.
c) Imprecise individual layer weight control.
d) Cross contamination between the layers.
e) Difficult to swallow in case of children and unconscious patients.
f) Some drugs resist compression into dense compacts, due to amorphous nature, low density nature.
g) Drugs with poor wetting, slow dissolution properties, optimal absorption high in GIT may difficult to manufacture as a tablet that will still provide ample drug bio availability [12,15].

➢ **General properties of bilayer tablet dosage forms [8,10]:**

a) A bilayer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
b) Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
c) Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.
d) Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents [16].

➢ **Quality and GMP Requirements for bilayer tablets [10,16]:**

1. Preventing capping and separation of the two individual layers that constitute the bilayer tablet.
2. Providing sufficient tablet hardness.
3. Preventing cross-contamination between the two layers.
4. Producing a clear visual separation between the two layers by addiction of coloring agent.
5. High yield.
6. Accurate and individual weight control of the two layers.

➢ **Types of Bilayer Tablets [9,17]:**

a) Homogeneous Type: Bilayer tablet is consists of same drug with different release pattern from one another. In this type tablet one layer being immediate release and second layer is extended release.

b) Heterogeneous Type: Bilayer tablet is designed for sequential release of two drugs different in combination, with same or different release pattern.

IMMEDIATE RELEASE LAYER:

Immediate release tablets are disintegrate rapidly in stomach and get dissolved to release the medicaments from dosage form. Most of the patients require quick onset of action in particular therapeutic condition like acidity, pain. Immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs and high molecular weight protein and peptide. The oral therapeutic effect of drug dependent on disintegration, dissolution and various physiological factors. Recently mostly patient prefer immediate release tablets because they are easy to administer, has quick onset of action is economical and better patient compliance [18].

A. Advantages of Immediate Release Drug Delivery System [18,19]:

a) Improved compliance/added convenience.
b) Improved stability, bioavailability.
c) Allows high drug loading.
d) Ability to provide advantages of liquid medication in the form of solid preparation.
e) Adaptable and amenable to existing processing and packaging machinery.
f) Cost- effective.
g) vii) Improved solubility of the pharmaceutical composition.
h) Decreased disintegration and dissolution times for immediate release oral dosage forms.

B. Disadvantage of Immediate Release Drug Delivery System [19]:

a) Possess swallowing difficulty.
b) Chance of GI irritation caused by locally high concentrations medicaments.

C. Desired Criteria for Immediate Release Drug Delivery System [19,20,21]:

a) In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.
b) In the case of liquid dosage form it should be compatible with taste masking.
c) Be portable without fragility concern.
d) Have a pleasing mouth feel.
e) It should not leave minimal or no residue in the mouth after oral administration.
f) Exhibit low sensitivity to environmental condition as humidity and temperature.
g) Be manufactured using conventional processing and packaging equipment at low cost.
h) Rapid dissolution and absorption of drug, which may produce rapid onset of action.

D. Salient Features of Immediate Release Drug Delivery System [19]:

a) Drug should possessing long biological half-life for immediate release drug delivery.
b) The drug is released quickly and completely in one shot.
c) High bioavailability expected with immediate release dosage form.
d) Rapid drug therapy intervention is possible.
e) But main criterion for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat unwanted defect or disease.

E. Excipients Used In Immediate Release Tablets [18,19]:

a) Bulking agents: It enhance the textural characteristics that in turn improve the disintegration in the mouth, other than; adding bulk also lessen the concentration of the active in the composition. The suggested bulking agents for this delivery system should be more sugar-based, e.g. mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch for higher aqueous solubility and good sensory perception.

b) Lubricants: It remove grittiness and help the drug transport mechanism from the mouth down into the stomach. E.g. Magnesium stearate, Stearic acid.

c) Super disintegrants [20]: A disintegrant is an Excipients, which is included to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment e.g. cross carmallose sodium, sodium starch glycolate, ludiflash.

➢ **Advantages**

- Effective in lower concentrations.
- Less effect on compressibility and flow ability.
- More effective intragranularly.

➢ **Some super disintegrants [19,20]:**

1. Sodium Starch Glycolate (Explotab, primogel): Utilized in concentration of 2-8% & optimum is 4%.
2. Cross-linked Povidone (crospovidone) (Kollidone): Utilized in concentration of 2-5% of weight of tablet, that completely insoluble in water.
3. Low-substituted hydroxyl propyl cellulose: Which is insoluble in water. Quickly swells in water. Grades LH-11 and LH-21 shows the greatest degree of swelling.
4. Cross linked carboxy methyl cellulose sodium (i.e. Ac-Di-sol) Croscarmellose sodium.

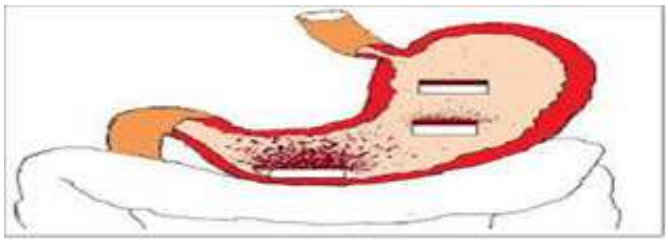

Figure 5: Immediate drug release from IR layer in stomach.

SUSTAINED RELEASE LAYER:

Sustained release dosage forms are mainly developed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. The main purpose was intended to modify and improve the drug performance by increasing the duration of drug action, reduces the frequency of dosing, decreasing dose quantity and to improve patient compliance [22]. SR tablet are prepared by coating the tablets so that the rate of solubility is controlled and it reduced the toxicity by slowing drug absorption, improved palatability and availability of formulation in liquid and solid, SRDDS increased stability by protecting the drug from hydrolysis in the GI tract [23].

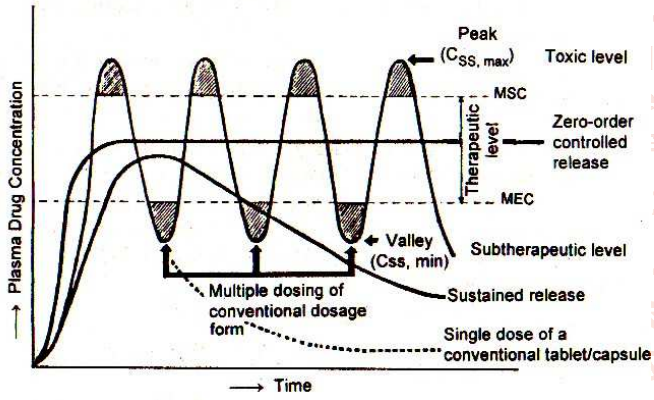

Figure 6: A Hypothetical Plasma Concentration Vs Time Profile.

It is designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. The basic rationale of SRDDS is optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized, side-effects are reduced and treatment of the disease is achieved more effectively [24].

Principle of Sustained Release Drug Delivery [4,24,25]:

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme in figure.

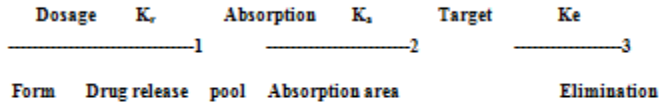

Figure 7: Schematic representation of the kinetics of sustained release DDS.

The absorption pool represents a solution of the drug at the site of absorption, Kr , Ka and Ke - first order rate constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. For non-immediate release dosage forms Kr<< Ke i.e. the release of drug from the dosage form is the rate limiting step. The drug release from the dosage form should follows zero-order kinetics, as by the following equation:

Kro = Rate In = Rate Out = Ke CdVd

Where,

Kro: Zero-order rate constant for drug release Amount/time, Ke: First-order rate constant for overall drug elimination-time, Cd: Desired drug level in the d body Amount/volume and Vd: Volume space in which the drug is distributed in litre.

A. Advantages of Sustained Release Matrix Tablets:

Patient compliance: Lack of compliance in patient with chronic disease which required long term treatment with different type of medications. Patient compliance is affected by so many reasons like patient confidence in treatments, lack of knowledge of ailment process, repetition of same medicine and disease related strict treatment plan. To avoid this type of issue the administration of sustained release drug delivery system [26,27].

1. Reduced 'see-saw' fluctuation:

Drug concentration in the systemic circulation and tissue compartments show „see saw" pattern frequently when the drug administration in conventional dosage form. The 'see-saw' pattern is more prominent just in case of drugs with biological half-life less than 4 hrs. since recommended dosing intervals are rarely less than 4 hrs. A Sustained release drug delivery system can widely reduce the frequency of drug dosing and also maintain a steady drug concentration in blood circulation [6, 26].

2. Total dose reduction:

To treat an ailing condition less measure of aggregate drug is used in Sustained release drug delivery systems. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

3. Improvement of deficiency in treatment:
To improvement in treatment of disease requires an effective transfer of active drugs to the targeted tissues/organs that need treatment. Required quantity of dose to be administered in order to achieve the necessary therapeutically effective concentration for this purpose a sustained release dosage form is the better choice for management of the acute or chronic disease condition.

4. Economy:
The average cost of treatment over the prolong period of time may be less for sustained release dosage form.

B. Disadvantages of Sustained Release System [25,27]:

1. Inhibition of prompt termination of therapy: Administration of sustained release medication does not permit the prompt termination of therapy such as might be encountered if significant adverse effects are noted, cannot be accommodated.
2. Dosage form design: The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form design.
3. Patient variation: Sustained release forms are designed for the normal population i.e. on the basis of average drug biologic half-lives and disease states that alter drug disposition, significant patient variation.
4. Economic factors: Economic factor must also be assessed since more costly processes & equipment are involved in manufacturing many sustained release forms.
5. Poor In-Vivo and In-Vitro correlations: In sustained release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. It may give rise to unsatisfactory drug absorption in vivo despite excellent in-vitro release characteristics.
6. Dose dumping: Dose dumping is a phenomenon where by relatively large quantities of drug in sustained release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. This can lead to fatalities in case of potent drug e.g. Phenobarbital [6].

C. Criteria of drug to be met to formulate sustained release dosage forms [6,25,28]:

1. Desirable half-life.
2. High therapeutic index.
3. Small dose.
4. Desirable absorption and solubility characteristics.
5. Desirable absorption window.
6. First past clearance.

1. Desirable half-life:
The drug should have half-life of 3 to 4 hrs. for design of sustained release tablet. If the drug has a short half-life, the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half-life of 8 hours or more are sufficiently sustained in the body.

2. High therapeutic index:
Drugs with low therapeutic index are unsuitable for incorporation in SR formulation. If the sustained release system fails in the body, dose dumping may occur and it may leading to fatalities e.g. Digitoxin.

3. Small dose:
The dose of drug in sustained release formulation is consider while developing of SRDDS, because the size of dose in SR formulation would become too large and It is too difficult for administration.

4. Desirable absorption and solubility characteristic:
Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into SR formulations may reduce absorption efficiency.

5. Desirable absorption window:
The drugs which exhibited an "Absorption window", such as fluorouracil, thiazide diuretics, if formulated as SRDDS are unsuitable.

6. First pass clearance:
Delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism when administered in sustained release forms.

MATRIX TABLET:
It is defined as "Oral solid dosage form in which API (Active Pharmaceutical Ingredients) is uniformly dispersed throughout polymeric matrices (hydrophilic or hydrophobic) which retards the drug release rate. It is widely used in design of SR formulation.

1. Advantages of matrix system [29]:

- Easy to manufacture.
- Cost effective.
- Improved patient compliance.
- Sustained release formulations avoid the high blood concentration.
- Reduce drug toxicity by controlling drug absorption.
- Enhanced drug stability in GI milieu.
- Minimize the local and systemic side effects.

- No see-saw fluctuations in plasma drug concentration profile.
- Less amount of drug is required.

2. Disadvantages of matrix tablets:

- Matrix needs to be removed after drug release.
- It is very costly in comparison with conventional dosage form.
- Presence of food and gut transition time can affect the release rate.

3. Classification of Matrix Tablets [25,30]:

- On the basis of retardant material used matrix can be divided into 5 types:

a) Hydrophobic matrices (plastic matrices):
E.g. polyethylene, poly vinyl chloride, ethyl cellulose.

b) Lipid matrices:
E.g. carnauba wax in combination with stearyl alcohol

c) Hydrophilic matrices:
In this type of system a variety of hydrophilic polymers can be used, such systems are also known as swell able matrices. These polymers are more preferred than former ones as they are cost effective and a desirable drug profile can be easily obtained.
Classification of hydrophilic polymer matrices:

a) Cellulose derivatives [31]: Methyl cellulose 400 and 4000cPs; Hydroxyl ethyl cellulose, Hydroxyl propyl methyl cellulose (HPMC) 25, 100, 4000 and 15000cPs and Sodium carboxyl methyl cellulose.

b) Non cellulose natural and semi-synthetic polymers: Agar-Agar; alginates; carob gum; molasses; polysaccharides of galactose and mannose; chitosan and modified starches.

c) Polymer of acrylic acid: carbopol-934.

4. Biodegradable polymers [32]:
E.g. Polyanhydrides, proteins, polysaccharides.

Mineral matrices: Species of sea weeds like alginic acid are used as release retardants.

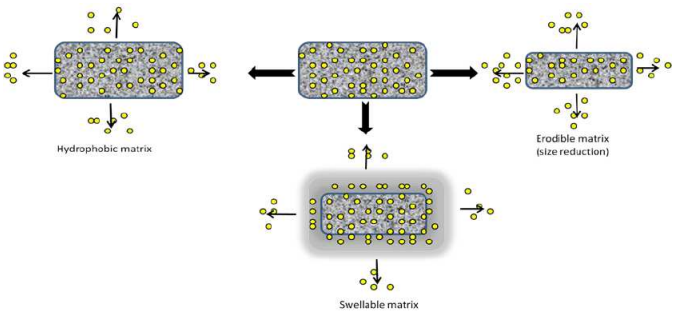

Figure 08. Schematic representation of drug release from different type of matrix tablet

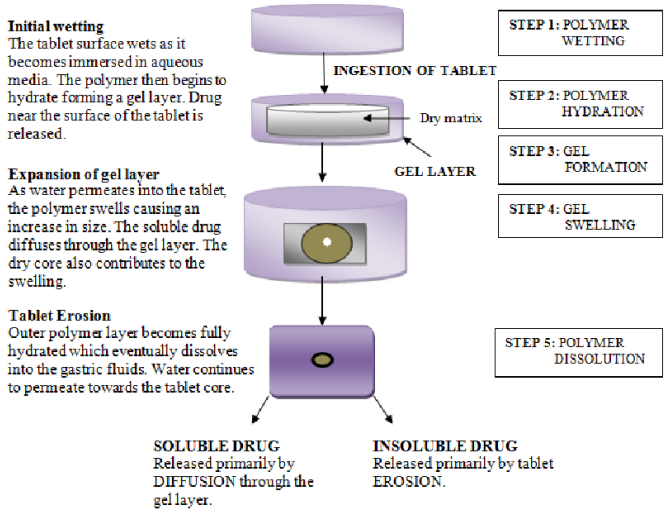

Figure 09. Mechanism of drug release from hydrophilic matrix tablet.

5. Characteristics of an ideal polymer [23]:

- It should be possess a wide range of mechanical, physical, chemical properties and should be versatile in nature.
- It should have good mechanical strength and should be non-toxic and should easily administered.
- It should be easy to fabricate and inexpensive.
- It should be compatible with environment.
- Criteria followed in polymer selection [22,23]:
- The polymer should be easy to synthesis and Soluble.
- It should have finite molecular weight.
- It should be compatible with biological environment.
- It should be biodegradable.
- It should provide good drug polymer linkage.

6. Polymers Used In The Matrix [23,26]:

a) Hydrophilic Polymers:
Hydroxyl propyl methylcellulose (HPMC), hydroxyl propyl cellulose(HPC),hydroxyl ethyl cellulose (HEC), Xanthan gum, Sodium alginate, poly(ethylene oxide), and cross linked homopolymers and co-polymers of acrylic acid.

b) Hydrophobic Polymers:
This usually includes waxes and water insoluble polymers in their formulation.

c) Waxes:
Carnauba wax, bees wax, candelilla wax, micro crystalline wax, ozokerite wax, paraffin waxes and low molecular weight polyethylene.

d) Insoluble polymers:
Ammoniomethacrylate copolymers (Eudragit RL100, PO, RS100, PO), ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate and latex dispersion of meth acrylic ester copolymers.

7. General mechanism of drug release from polymer:

The mechanism of drug release from polymers are three primary type by which active agents can be released as follow:

➢ **Diffusion:**

The diffusion mechanism occurs when the drug releases from the polymer matrix into the external environment. In this type of system since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release. In these type of mechanism the combinations of polymer matrices and bioactive agents are used for the drug to diffuse through the pores or macromolecular structure of the polymer into the biological environment [23].

➢ **Degradation:**

Biodegradable polymer are used in this mechanism to degrade within the body by natural biological processes. Biodegradable polymer need to remove from drug delivery system after release of the active agent has been completed. Most of the biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains and progressively smaller compounds.

➢ **Swelling:**

The polymers are initially dry and when placed in the body will absorb water or other body fluids and swell. The swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen 16net work into the external environment [30].

1. Drug release mechanism of sustained release drug delivery systems [27]:

a. Zero Order Kinetics:

$Qt - Qo = Ko\ t$

Where,
Qt = Amount of drug release dissolved in time't'.
Qo = Initial amount of drug concentration in solution.
Kot = Zero order rate constant.

When the data was plotted as cumulative % drug release verses time, if the plot is linear then data obeys zero order kinetics with slope equal to Ko. This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

b. First Order Kinetics:

A first order release would be predicted by the following equation:

$$\text{Log } Qt = \log Qo\ K1 \frac{t}{2.303} \ldots\ldots\ldots\ldots\ldots\ldots$$

Where,
Qt = Amount of drug released in time't'.
Qo = Initial amount of drug concentration in solution.
K1t = First order rate constant.

When data was plotted as log cumulative % drug remaining verses time yields a straight line indicating that the release follows first order kinetics. The constant K can be obtained multiplying slope values.

c. Higuchi's Model [33]:

Drug release from the matrix device by diffusion has been described by Higuchi's Diffusion equation

$ft = Q = A\sqrt{(D\ (2C - Cs)\ Cst)}$

Where,
Q = Amount of drug released in time't'.
D = Diffusion coefficient of the drug in the matrix.
Cs = Solubility of the drug in the matrix.
A= Porosity of matrix.
t= Tortuosity.
t = Time (h).

d. Peppas Korsmeyer Equation [23,32]:

$Mt / M\infty = Ktn$

Where,
K = Constant.
n = Release.
t = Time.
Mt and = Absolute cumulative amount of drug t released at time't'.

This is used when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

e. Hixon-Crowell Equation:

Drug released from the matrix device by diffusion has been described by Hixon-Crowell diffusion equation;

$Wo1/3 - Wt1/3\ Kt$

Where,
Wo = Initial amount of drug.
Wt = Remaining amount of drug.
t = Time.
K = Constant (Kappa).

This expression applies to pharmaceutical dosage form such as tablets where the dissolution occurs in planes that are parallel to drug surface if tablet dimensions diminish proportionally in such manner that the initial geometrical form keeps constant all the time.

TYPES OF BILAYER TABLET PRESS [33]:

a. Single sided tablet press.
b. Double sided tablet press.
c. Bilayer tablet press with displacement monitoring.

a. Single sided press:

In this single press both chambers of the doublet feeder separated from each other. Each chamber is gravity with different power, producing the two different individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

Limitations of the single sided press:

- No weight monitoring / control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor deration, capping and hardness problems.
- This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

b. Double sided tablet press:

In most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

c. Bilayer tablet press with displacement monitoring [9,33]:

The displacement tablet weight control principle is different from the principle based upon compression force. When measuring displacement the control system sensitivity depends on the applied pre-compression force.

- **Advantages:**

a) Weight monitoring/ control for accurate and independent weight control of the individual layer.

b) Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.

c) Independence from the machine stiffens.

d) Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed.

e) Maximum prevention of cross-contamination between the two layers.

f) Clear visual separation between the two layer and maximized yield.

PREPARATION OF BILAYER TABLETS [9,13,33]:

Bilayer tablets are designed with one layer of drug for immediate release and the second layer designed to sustained release drug. The bilayer tablets contained two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers and in this additional intermediate layer of inert material may also be included. To produce adequate tablet formulation, certain requirements such as sufficient tablet hardness and desired drug release profile. But this may be difficult task for formulator to achieve these conditions especially in bilayer tablet formulation. This is difficult task in which double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and lamination.

a) **Compression:** it is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

b) **Consolidation:** it is the property of the material in which there is increased mechanical strength due to inter-particulate interaction (bonding). The compression force on first layer was found to be major factor influencing tablet delamination

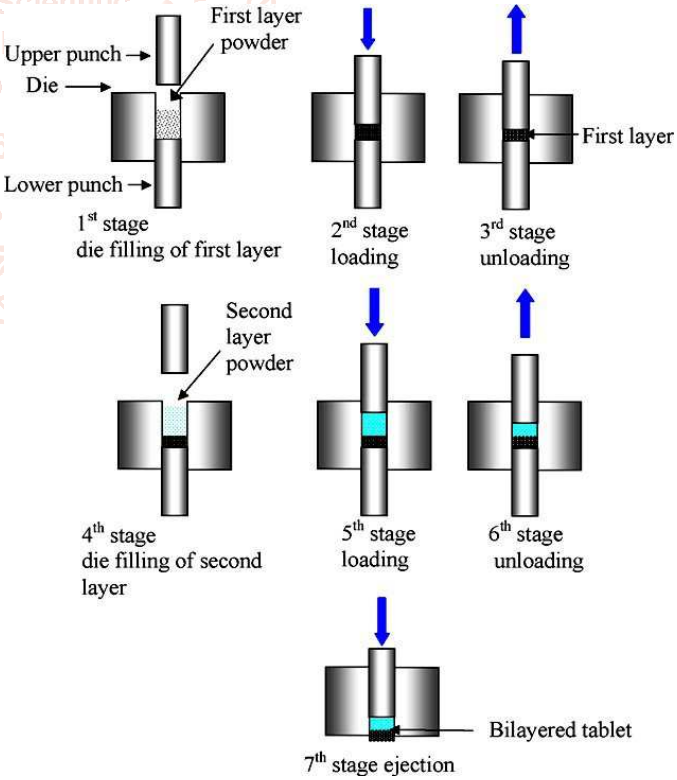

Figure 10: Preparation of bilayer tablet Compaction.

1. **Challenges in formulation of Bilayer tablet [8,10]:**

a) Lamination i.e. Layer separation is major problem in production of layered tablet.

b) Mixing of both the layer i.e. Cross-contamination.

c) Lack of sufficient bonding and adhesion at adjacent layers.
d) Difficult to maintain integrity of final Tablet.
e) Individual layer weight control is difficult.
f) Insufficient hardness.
g) Production yield of Bilayer tablet is very low compared to single layer tablet.
h) Bilayer tab letting is more expensive than single layer tab letting.

2. Problems occur in developing bilayer tablets [8,10]:

a) Layer separation.
b) Order of layer sequence.
c) Layer weight ratio.
d) Elastic mismatch of the adjacent layers.

DRUG RELEASE MECHANISM

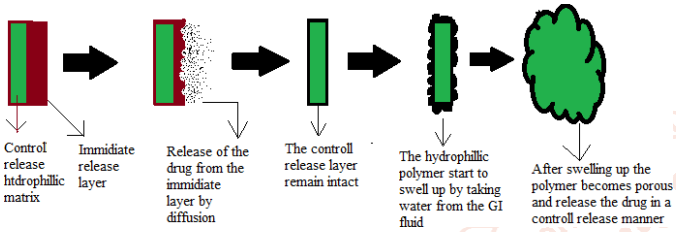

Figure 11: Drug Release Mechanism.

VARIOUS TECHNIQUES FOR BILAYER TABLET:

A. OROS ® push pull technology [10]:

This technology consist of mainly two or three layer among which the one or more layer are necessary for the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprise of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

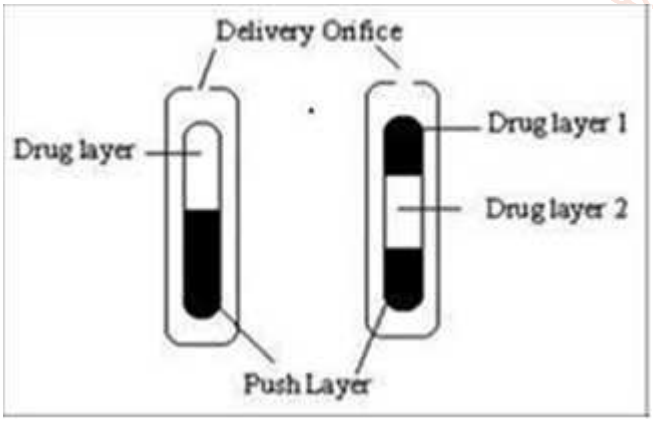

Figure 12: OROS ® push pull technology.

B. L-OROS ® tm technology [10,12]:

This system used for the solubility concern 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.

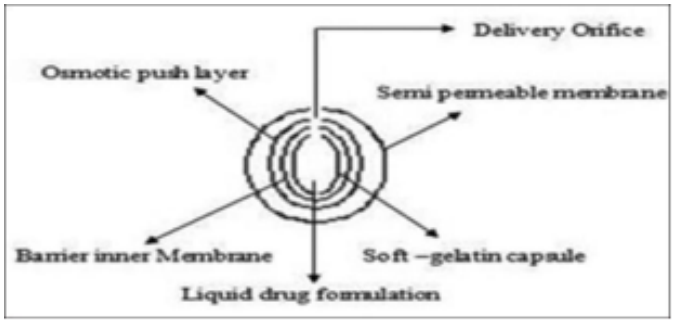

Figure 13: L-OROS ® tm technology.

C. DUROS ® technology [14,16,35]:

The system consists from an outer cylindrical titanium alloy reservoir .This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the minuscule drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form

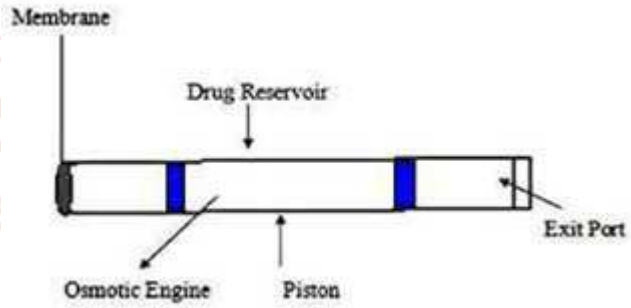

Figure 14: DUROS ® technology.

D. ENSOTROL® 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.

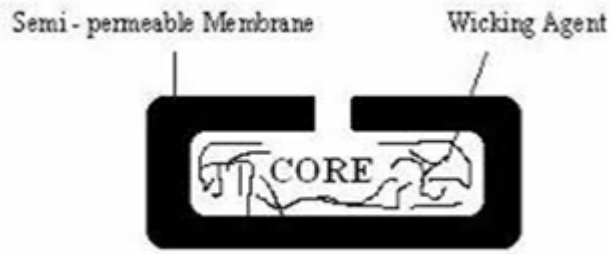

Figure 15: ENSOTROL® technology.

E. Duredas Technology [10,16,35]:

Duredas or Dual release drug absorption system (Élan Corporation) utilizes bilayer tableting technology. Which is specifically developed to provide two different release rates or dual release of drug from single dosage form as immediate release layer and controlled release layer within signal tablet? Controlled release matrix remains intact and slowly absorbs fluid from GI tract, which causes matrix to expand and transform hydrophilic matrix into porous

viscous gel which acts as barrier releases drug in controlled manner.

Benefits offered by the DUREDAS technology:

a) Bilayer tab letting technology.
b) Tailored release rate of two drug components.
c) Capability of two different CR formulation combined.
d) Capability for immediate release and modified release component in one tablet.
e) Unit dose tablet presentation.

F. Geminex Technology:

This technology controls the release rate of two drug to maximize their individual therapeutics effect and minimize side-effect. The benefits of this technique are that two different actives can be delivered at different rate in a single tablet.

➢ EVALUATION OF PRE-FORMULATION PARAMETERS

A. Flow properties (Angle of Repose):

The angle of repose of granules was determined by funnel method. The funnel was fixed at a particular height (2.5 cm) on a burette stand. The powder sample was passed through the funnel until it forms a pile. Further adding of granule was stopped as soon as the pile touches the tip of the funnel. A circle was drawn across it without disturbing the pile. The radius of the pile was noted down. The same procedure was repeated for three times and the average value was taken. The angle of repose was calculated by using equation:

$\tan \theta = h/r$ (or) $\theta = \tan^{-1}(h/r)$

Where, h and r are the height and radius of the powder cone.

Table 1: Angle of repose as an indication of granule flow properties

Angle of repose (°)	Type of flow
<25	Excellent
25 – 30	Good
30 – 40	Poor
>40	Very poor

B. Bulk density: (Db)

Procedure: Weighed quantity of drugs were transferred into a 50ml measuring cylinder without tapping during transfer the volume occupied by granules was measured. Bulk density (Db) was measured by using formula.

$$Db = m/Vo$$

Where,
m: Mass of the blend.
Vo: Untapped Volume.

C. Tapped density: (Dt)

Procedure: Weighed quantity of drug was taken into a graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500/ 750 and 1250 taps in tapped density tester (Electro Lab USPII) According to USP , the blend was subjected for 500 taps the % Volume variation was calculated by following formula

$$Dt = m/Vi$$

Where,
m: Mass of the blend
Vi: Tapped Volume

D. Compressibility Index:

The compressibility index of the granules was determined by the Carr's compressibility index

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{poured density}}{\text{Tapped density}} \times 100$$

Table 2: Carr's index as an indication of granule flow properties

Carr's index (%)	Type of flow
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
33 – 38	Very poor

E. Determination of Hausner ratio:

It is measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.

$$\text{Hausner Ratio} = Vo/Vi$$

Where,
Vo: Tapped density
Vi: Untapped density

Table 3: Hausner's ratio as an indication of granule flow properties

Flow character	Hausner's ratio
Excellent	1.00 – 1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 –1.45
Very Poor	1.46 – 1.59
Very Very Poor	> 1.60

➢ EVALUATION OF PREPARED FORMULATIONS:

Evaluation of IRL, SRL and bi-layered tablet [10,49]

The tablets prepared were evaluated for the following parameters:

a) Hardness

b) Thickness
c) Weight variation
d) Friability
e) Drug content
f) In-vitro Dissolution Studies
g) Stability Studies

a. Hardness:

The resistance of tablets to shipping or breakage under condition of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in the terms of kg/cm2 .5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

b. Tablet thickness:

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation. Vernier caliper consists of metric and imperial scales. The main matric scale is read first then read "hundredths of mm" of imperial scale (count the number of division until the lines concedes with the main metric scale. The imperial scale number is multiply with 0.02. Then that number obtained from imperial scale added with main metric scale to get final measurement

c. Weight Variation Test:

To study weight variation, 20 tablets of each formulation were weighted using electronic balance and the test was performed according to the official method.

Table 4: IP standards of Uniformity of weight

S.N.	Avg. Wt of Tablet (mg)	% of Deviation
1	≤80 mg	10
2	>80 mg – 250 mg	7.5
3	≥250 mg	5

d. Friability:

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. 10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded. Percentage friability was calculated by using the formula.

$$\% \text{ Friability} = \frac{\text{Initial weight-final weight}}{\text{Initial weight}} \times 100$$

e. In-vitro dissolution studies of immediate release layer:

The in-vitro dissolution studies were performed using USP-II (paddle) dissolution apparatus at 100 rpm. Phosphate buffer pH 6.8 dissolution media is maintained at 37±0.500C. A 5 ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 210 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

f. In vitro dissolution studies of sustained release layer:87

The in vitro release of sustained release layer was carried out for 18 hours using USP type-II apparatus (DT-1200) at 100 rpm for the first 45 minute in 900 ml 0.1N HCL maintaining at 37 ±0.50C and then at phosphate buffer pH 6.8 in 900ml for another 18 hour. A 5 ml was withdrawn at different time intervals and replaced with an equal volume of fresh medium. The samples were suitably diluted with blank dissolution medium, filtered and analyzed on UV spectrophotometer at 210nm.

g. Drug Content for IRF, SRF and Bi-layered tablet:

Ten tablets were weight and average weight is calculated. All tablets were crushed and powder equivalent to 100 mg drug was dissolved in pH 6.8 phosphate buffer and the volume was made up to 100 ml with pH 6.8 phosphate buffer. The solution was kept in sonicator for 1 hr. From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with pH6.8 phosphate buffer. Solution was filtered and absorbance was measured spectrophotometrically at 210 nm against pH6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

h. Stability Studies:

The optimized formulation was subjected for two month stability study according to standard guidelines. The selected formulations were packed in aluminum foils, which were in wide mouth bottles closed tightly. They were stored at 400C / 75% RH for 3 months and evaluated periodically.

Table 05: Various advancements in the field of bilayer tablets [13,33].

Drug(s)	Dosage Form	Rationale
Atorvastatin, Atenolol	Bilayer gastro retentive matrix Table	Treatment of hypertension and hypercholesterolemia.
Nifedipine	Gastro retentive floating bilayer tablets	Treatment of hypertension and angina pectoris.
Aspirin, Isosorbide 5-mono-nitrate	Sustained bilayer tablets	Treatment of pain, fever and other inflammatory Conditions.
Pioglitazone HCl, Gliclazide	Bilayer Tablets	Treatment of Type II Diabetes.
Losartan potassium	Bilayer tablet	Treatment of hypertension
Trimetazidine HCl, Clopidogrel bisulphate	Bilayer tablets	Cytoprotective anti-ischemic, platelet inhibitor in acute coronary syndromes.
Diclofenac, Cyclobenza-prine	Bilayer tablets	Synergistic effect in pain.
Granisetron HC1	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects.
Metformin HC1, Glimipiride	Bilayer tablets	Synergistic effect in diabetes.
Indomethacin	Bilayer floating tablets	Biphasic drug release.
Metformin HC1, Atorvastatin Calcium	Bilayer tablets	To develop polytherapy for the treatment of NIDDS & hyperlipidemia.
Cefixime Trihydrate, Dicloxacilline Na	Bilayer tablets	Synergistic effect in bacterial infections.
Piracetam, Vinpocetin	Bilayer tablets	Synergistic effect in Alzheimer disease.
Metformin HCl, Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus.
Atenolol	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration.

CONCLUSION

Bi-layer tablets offer an excellent opportunity for manufacturers to separate themselves from their Competitor, improve their products efficacy and protect against impersonator products. Bilayer layer tablets have been consist of two layers which is slow release and immediate release layer proposed a bilayer tablet, in which the one layer is formulating to achieve immediate release of the drug, with the aim of reaching a high serum concentration in a very short period of time. The second layer is a controlling release hydrophilic matrix, which is designing to maintain an effective plasma level for a prolonged period of time. By designed of bi-layer tablet dosage form we can administer incompatible drugs in combination as well as same drug with different release rate. This technology avoids repetition of drug administration of dosage form. Now a day such technology is used for administration of drugs like-diabetic, anti-hypertensive, anti-inflammatory, antipyretic, anti-asthmatic to the patients. Mostly conventional solid oral dosage forms are previously used for many disease treatment, but bi-layer tablet is a novel approach. This novel approach requires new type of tablet press machinery for manufacturing bilayer dosage form. In this article explains different types of presses used to produce bi-layer tablet by using various technology from simple single sided machines to highly sophisticated machines. For good quality bi-layer tablet the machines should be inherently built as per GMP requirement. This technique is cost effective, safe and reproducible.

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