HBRP PUBLICATION

Journal of Advances in Nanotechnology and its Applications
Volume 3 Issue 2

Bi-Layer Tablets: An Emerging State of Art Technology in Dosage Form Design

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ABSTRACT

Despite significant advancements in dosage form design, oral route still remains the most favoured route of drug administration. Even now-a-days tablets have got more attention compared to other dosage forms because of simple, inexpensive, greater stability and most suitable nature of tablets. More recently major considerations in tablet sector have been focused on development of controlled and immediate release drug delivery systems. Many pharmaceutical manufacturers are giving more emphasis to bi-layer tablet sector now a day, because of several advantages like extension of patent, improved therapeutic response, enhanced patient compliance etc. Bi-layer tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. These can release more than two drugs in combination chronologically. Two incompatible substances can be remaining separated from one another in a single tablet. They can provide a biphasic release with one immediate release layer to produce the loading dose and second layer is maintenance dose in order to achieve the immediate pharmacological response lasting for a prolonged period. Current review especially emphasizes on the rationale, various approaches for designing of the bi-layer tablets including patented techniques, types of tablet presses, quality and GMP considerations, advancement sin the field of bi-layer tablet technology, troubleshooting problems in the preparation of bi-layer tablets etc.

Keywords:-*Tablet; bi-layer; immediate release; sustained release, tablet press*

INTRODUCTION

Oral route is gaining much popularity day by day because of its easy administration, improved patient compliance, avoidance of sterility issues and flexibility in dosage form design. To provide a desired therapeutic response, ideally optimum quantity of drug should immediately reach and remain at the site of action for sufficient period. The ideal dosing regimen, which remains patient compliance and helps guard against over dosing and side effects, is made possible by controlled release delivery systems, which use a variety of mechanisms to deliver and maintain the drug at a certain level in the patient's blood stream[1].With advancement in technology and increase in awareness towards modification in standard tablet is done to achieve better acceptability as well as bioavailability because of which newer and more efficient tablet dosage forms are being developed. Combination therapy is the major benefit as it reduces the development of drug resistance and show synergistic effect. Dual release tablet is a unit compressed tablet dosage form intended for oral application [2]. Bi-layer tablet is a new era for the successful development of controlled release formulations along with various features to provide a way of

successful drug delivery systems. The preparations of bi-layer tablets were indeed due to incompatibility of active pharmaceutical ingredients (APIs) and to create a delivery system of relatively simple and inexpensive [3].

RATIONALE [4,5]

- To separate incompatible APIs from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property)
- Designing of buccal /muco-adhesive delivery systems, and floating tablets for gastro-retention
- To control the release rate of one or more drugs
- To achieve swell able/erodible barriers for modified release
- To get synergistic effect and maintain therapeutic justification

ADVANTAGES [6-8]

- Bi-layer execution with optimal single layer conversion kit
- Greater chemical and microbial stability
- Inexpensive and suitability for large scale production
- Reduced dosing frequency ultimately improves patient compliance
- Single unit can be used in combinational therapy containing two drugs in two layers
- Identification of product is easy

DISADVANTAGES [6-8]

- Difficult to gulp in case of children and unconscious patients
- Chances of cross contamination between the layers
- Adds complexity and bi-layer tablet presses are expensive
- Some drugs resist compression into dense compacts, owing to amorphous nature, lower density
- Inaccurate individual layer weight control
- If the compacted layers are too soft or too hard, they will not bind securely with each other which can lead to compromised mechanical integrity and the separation of the layers

TYPES OF BI-LAYER TABLETS

Bi-layer tablets may be either homogeneous or heterogeneous according to their release pattern. Homogenous bi-layer tablets are preferred when the release profiles of a same drug present in two different layers are different from one another. One layer is designed for immediate release while other layer designed to extend the release of drug as shown in Figure 1. Heterogeneous type bi-layer tablets are fabricated for sequential release of two incompatible drugs in combination [8, 9].

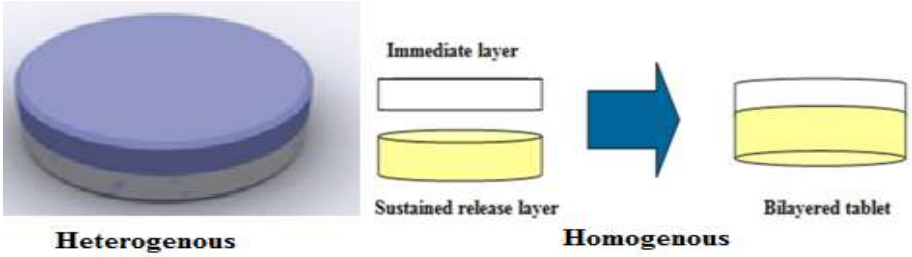

Fig.1:-*Heterogeneous and homogenous bi-layer tablets*

Various Approaches for Designing of Bi-layer Tablets

Floating drug delivery systems

These are designed to have a low density and a dual release pattern. These floats on gastric contents after oral administration

until the system either disintegrate or lose buoyancy. These bi-layer tablets are designed in such a manner that, one layer gives the immediate dosing of the drug to provide a faster onset of action while another layer gives a floating sustained action which lasts for many hours in the stomach[10]. Approaches followed for designing of floating bi-layer tablets are as follows [11].

Intra-gastric bi-layered floating tablets

These are also known as compressed tablets containing two different layers as shown in Figure 2 i.e.an immediate and a sustained layer.

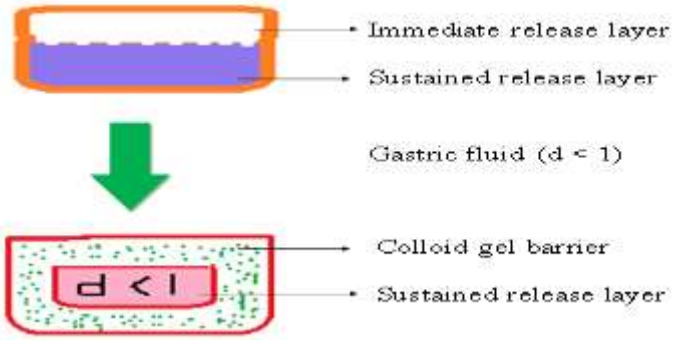

Fig.2:-*Intra-gastric bi-layer floating tablets after delivery of immediate release layer*

Multiple unit type floating pills

These consist of a total of three layers as shown in Figure 3 out of which sustained release pills at the core encircled by a bi-layer. An effervescent agent is provided as the inner layer and a swell able membrane layer as the outer layer. These systems initially sink and subsequently float as their density becomes lesser than that of gastric fluids because of the swelling of the outermost layer like balloons.

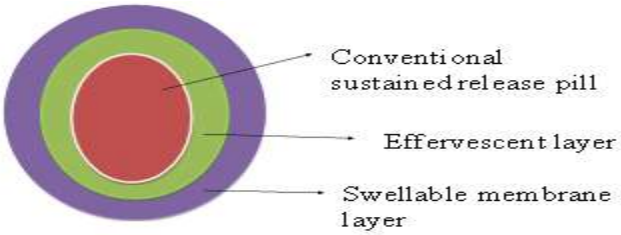

Fig.3:-*Multiple unit type of floating pills*

Though these types of floating dosage forms have several advantages but still they possess certain drawbacks. Higher dose levels of highly hydrophilic drugs are not suitable for design of floating tablets as large quantities of polymer are required to control their release. The performance of floating tablets may also be posture dependent. A patient sitting upright may ensure prolonged gastric residence of a buoyant dosage form, whereas a supine patient might allow ready presentation of the floating dosage form to the pylorus and thus allow rapid exit of the dosage form from the stomach. Hence, floating dosage forms might be expected to only have limited applications.

Polymeric bio-adhesive systems

These are designed as a bi-layer formulation with an immediate release layer and a bio-adhesive property layer. The outer layer becomes viscous, tacky in nature and sticks to the gastric mucosa after they come in contact with the bio fluids. This should encourage gastric

retention until the adhesive forces are weakened [11].

The results obtained in the animal models were not found to be similar in human volunteers. The system adheres to mucous not mucosa many times. In case of human beings the mucous layer blows off rapidly. Therefore, bio-adhesive dosage form would not appear to offer a solution for extended delivery of drug over a period of more than few hours [12].

Swelling systems

These systems are small in size for their ease in administration through oral route, but after ingestion, they swell rapidly and produce a size that can't pass through the pylorus. Thus they remain inside the stomach until the required amount of drug releases.

They leave the stomach after a significant period because of their continuous erosion and disintegration in to small particles. The swell able bi-layer tablet may be designed as an immediate-extended release composite as shown in Figure 4 or as conventional release or both layer as controlled release in Figure 5 [12,13].

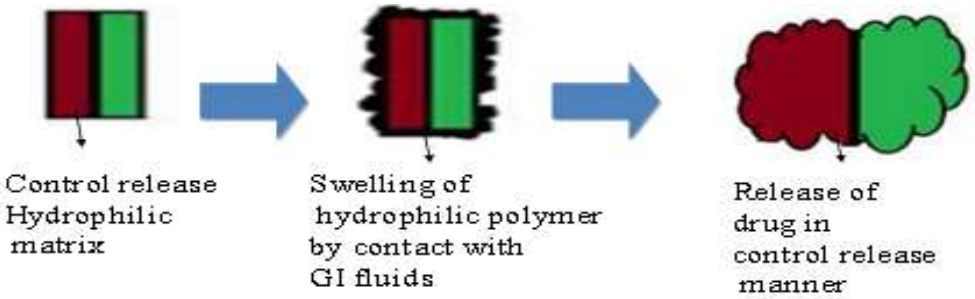

Fig.4:-*Bi-layer tablet consisting of two swellable controlled release layers*

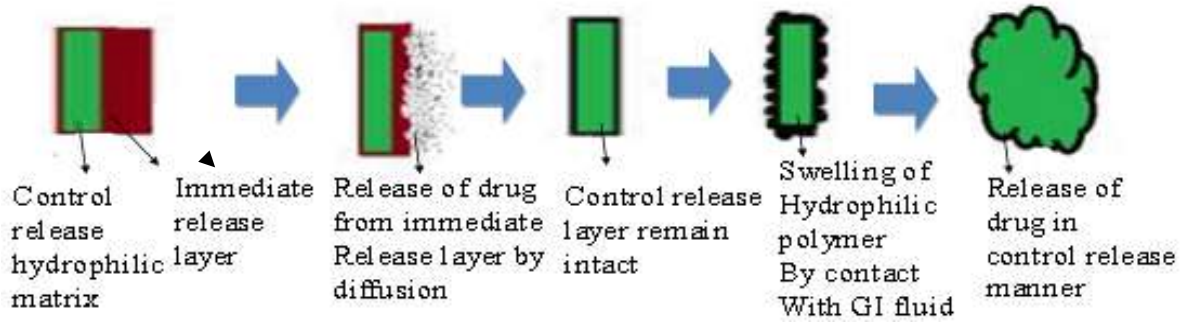

Fig.5:-*Bi-layer tablet consisting of immediate release and controlled release layers*

Preparation of Bi-Layer Tablets

Bi-layer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form. The bi-layer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug to minimize area of contact between two layers [14].

The compaction process of bi-layer tablets are shown in the Figure 6 below.

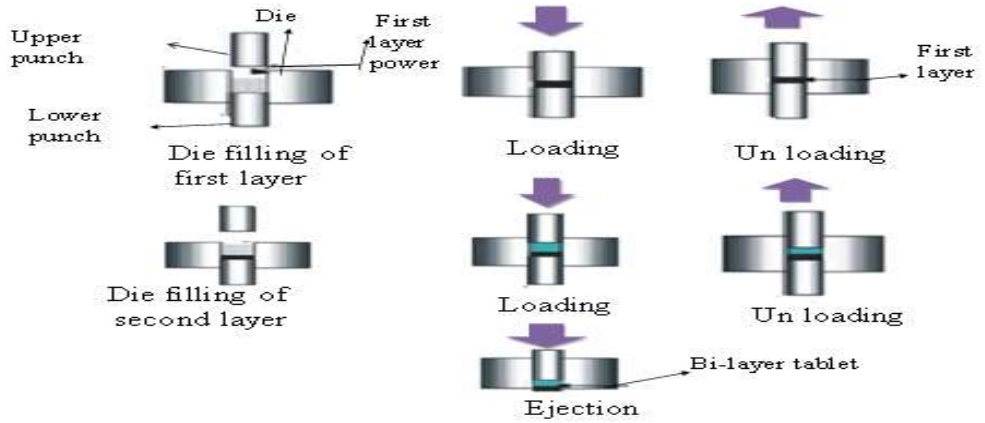

Fig.6:-*Bi-layer tablet compaction process*

To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be difficult task for the formulator to achieve these conditions especially in bi-layer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination.

The compressibility and consolidation are the two major steps of compaction. Compression is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts. Consolidation is the property of the material in which there is increased mechanical strength due to inter particulate interaction (bonding). The key factor governing tablet de-lamination is the compression force on first layer
[15].

Compression Force for Bi-Layer Tablets

A bi-layer tablet is produced by compressing the materials twice in the die cavity. To achieve a good adhesion and interfacial interaction between the two layers, compression force acts as the key determinant. To have good particle interlocking and adhesion between both the layers, a certain amount of surface roughness of the initial layer is essential. As the surface roughness of the first layer is reduced, the contact area for the second layer is significantly reduced at the interface and makes the adhesion weaker. Sometimes the elastic energy stored unevenly in the second layer after compaction may create fracture on the first layer resulting a weaker tablet structure. Capping or de-lamination may be a result thereof. The surface roughness of the first layer is inversely proportional to the compression force and influences highly the interaction between two adjacent layers.

Therefore, the level of plastic/elastic deformation of the initial layer has profound effects on the strength of the interface [15]. Thus, to understand the failure mechanisms of bi-layer tablets, it is essential to study the interaction and adhesion activities between different layers consisting of different ingredients of physico-chemical diversities. Also to predict the interaction, understanding of material attributes of the ingredients undergoing compression and compaction is desired [16]. The whole process of bi-layer tablet compression is given below in Figure 7 in a cyclic manner.

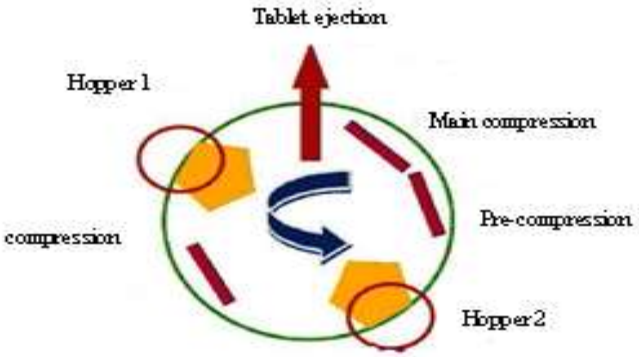

Fig.7:-*Bi-layer compression process in a cyclic manner*

Types of Bi-Layer Tablet Press

Single sided tablet press

Single sided press as shown in Figure 8 consists of two different chambers separated from each other and connected with two different feeders on each side. Two individual layers of the tablets are produced as each chamber have gravity or forced fed with different powders. When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second-layer powder. Then the entire tablet is compressed in one or two (pre-and main-compression) steps. The two layers in the die mix slightly at their interface and in most cases bond sufficiently[4,17].

Fig.8:-*Single sided bi-layer tablet press*

Though the machine has a very simplest design but also it possess certain drawbacks as follows [17]

- No weight control/monitoring of the individual layer
- Visual separation of both layers is not distinct
- Because of small compression roller and lesser dwell time, it may result in poor de-aeration, capping, hardness etc.
- For in-line quality control and weight variations tests it is very difficult to have the first-layer sampling

Double sided tablet press

These presses consist of individual fill station, pre-compression and main compression facilities for each of the layer as shown in the Figure 9. Most of the 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 that layer. Measured peak compression force (under constant thickness) is the signal used by the control

system to reject out-of-tolerance tablets and correct the die fills depth when required[7,17].

Fig.9:*-Double sided bi-layer tablet press*

Apart from the advancements and automation in the design the machine possess certain limitations. A compression force-controlled system requires a minimal compression force of several hundreds of daN(Dalton Newtons), but many bi-layer formulations require less than 100 daN to compress the first layer in order to retain the ability for bonding with the second layer. Bonding between two adjacent layers may not be sufficient above 100 daN. This may result in low hardness, weaker mechanical strength and separation of the two layers. Risk of separation and capping increases at higher production speeds, due to insufficient dwell time [17].

Bi-layer tablet press with displacement monitoring

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre-compression force [7, 17]. This double-sided tablet press produces high class bi-layer tablets as shown in Figure 10 and offers [17]:

Fig.10:*-Bi-layer tablet press with displacement monitoring*

- Accurate and independent weight control of the individual layers by 'Displacement' weight monitoring/control.
- Low compression force exerted on the first-layer to avoid capping and separation of the two individual layers

- Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed
- Reduced cross- contamination
- Visual separation between both the layers are clear
- Maximum yield

Quality and GMP-Requirements

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press must be capable of the followings [7,18]

- Avoiding capping and de-lamination
- Providing sufficient tablet hardness
- Preventing cross-contamination between the two layers
- Producing a clear visual separation between the two layers
- High yield
- Individual weight control of both the layers must be accurate

Various Patented Techniques for Bi-Layer Tablets

OROS® push pull technology

This system consists of mainly two or three layers among which the one or more layer is essential of the drug and other layer consists of a push layer as shown in the Figure 11. The drug layer mainly consists of poorly soluble drugs. It also consists of suspending and osmotic agents. All the layers after forming a single unit being coated with a semi permeable membrane as shown below [1,4].

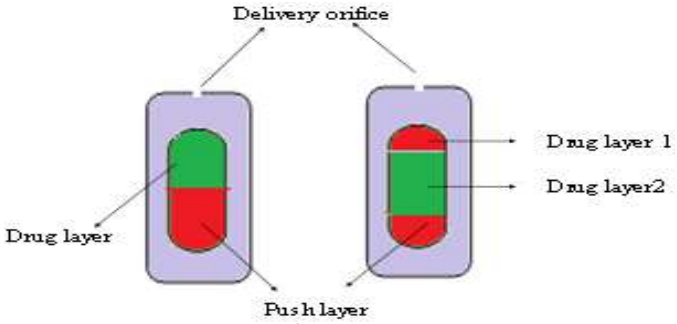

Fig.11:-OROS® push pull technology

L -OROS™Technology

This system was developed by Alza corporation, where a lipid soft gel product containing drug in a dissolved state is initially manufactured. Then it was coated with a barrier membrane followed by a osmotic push layer and a semi permeable membrane respectively. An exit orifice was made for drug release as shown in the Figure 12 below [4,8].

Fig.12:-L -OROS™ Technology

EN SO TROL technology

Shire laboratory use an integrated approach to enhance the magnitude of drug delivery focusing on identification and incorporation of certain release enhancers into controlled release technologies. The final formulation was in the form of a bi-layer tablet as shown in the Figure 13 below [8].

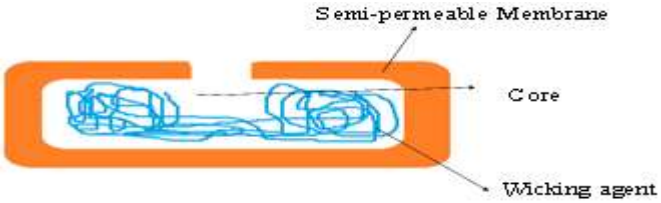

Fig.13:-*EN SO TROL technology*

PRODAS technology

Programmable Oral Drug Absorption System (PRODAS by Elan Corporation) is a multi-particulate system. This technology involves the encapsulation of controlled release mini tablets having size in the range of 1.5 to 4 mm in diameter [15]. This technology represents a combination of multi-particulate and hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in a single dosage form. A single unit dosage form of these mini-tablets with different release rates (like immediate release, delayed release, and/or controlled release rates) can be merged together to achieve a desired release pattern. PRODAS technology also facilitates the targeting of specific areas in GI tract in a controlled manner for a specified period [19].

GEMINEX technology

This is a novel bi-layer technology that delivers one or more drugs at various predetermined time intervals in order to enhance their individual therapeutic efficacy with reduced side effects [15]. The benefit of Geminex to the pharmaceutical industry, and ultimately to patients, is that two different actives or the same active can be delivered at differing rates from a single tablet. Penwest is actively applying its Geminex technology to the therapeutic areas like cardiovascular disorders, diabetes, cancer and disorders of the central nervous systems etc[15, 19].

Elan drug technologies's dual release drug delivery system

An immediate or sustained release of two different drugs or different release rates of a single drug in one dosage form can be possible by DUREDAS™Technology. This is a bi-layer tablet technology consisting of an immediate release and a modified-release hydrophilic matrix composite, as two different laminates within a single structure. They also can be modified to allow incorporation of two controlled release layers. In this way, greater prolongation of sustained release can be achieved. Typically, an immediate release granulate is first compressed followed by the addition of a controlled release element which is compressed onto the initial tablet. This gives the characteristic bi-layer effect to the final dosage form. An advancement in the DUREDAS™ technology consists of two different drugs in two different layers, from which the release of each drug is controlled to produce maximum therapeutic response. Several combination products utilizing this technology approach have been evaluated. The DUREDAS™ technology was initially employed in the development of many OTC controlled release analgesics. But to achieve a fast onset of action, one layer is

fabricated as immediate releases granulate. By the use of hydrophilic polymers, the second layer releases drug in a controlled manner due to a combined diffusion or erosion mechanism within the hydrophilic polymer matrix [19].

GEOMATRIX Technology

It is a multilayer tablet technology with a matrix core containing the active drug. The core is coated with several barrier layers. These barrier layers delay the dissolution of core, thus extending the drug release. The technology favors control release of both poorly and highly soluble drugs. It provides an almost zero-order, biphasic release of the drug in certain cases. Simultaneous or phased release of several drugs at individualized release rates from a single tablet was made possible by this technology [19].

Marketed Bi-layer Tablets and its advancements are shown in Table 1 and 2 below. While troubleshooting of processing problems in bi-layer tablet compression is shown in Table 3.

Table 1:-*Marketed Bi-layer Tablets[20,21]*

Product Name	Active Pharmaceutical Ingredients	Manufacturer
Pioglu	Pioglitazone	Emcure Pharmaceutical Ltd.
Xilla M- Forte	Metformin hydrochloride	Emcure Pharmaceutical Ltd.
Gluconorm	Glimepride, Metformin hydrochloride	Lupin Pharmaceuticals
Volise-M	Glimepride, Metformin hydrochloride	Ranbaxy Laboratories Ltd.
Glimeto- MP	Voglibose, Metformin hydrochloride	RPG Life Sciences Ltd.
Istamet	Glimepride, Pioglitazone	Ranbaxy Laboratories Ltd.
Glyrep	Sitagliptin, Metformin hydrochloride	Emcure Pharmaceutical Ltd.
Unistar	Glyclizide, Metformin hydrochloride	Unichem Laboratories Ltd.
Clarinex – D	Rosuvastatin, Aspirin	Merck & Co.
Alprax Plus	Desloratadine/Pseudoephedrine Sulphate	Torrent Pharmaceuticals Ltd.

Table2:-*Various advancements in the field of bi-layer tablets[22- 45]*

S. No.	Drugs	Dosage forms	Rationale	References
1	Sitagliptin phosphate, Simvastatin	Bi-layer tablets	Treatment of diabetes and hyper lipidemia	22
2	Nifedipine	Bi-layer tablets	Treatment of hypertension and angina pectoris	23
3	Aspirin, Isosorbide5-mono-nitrate	Bi-layer tablets	Treatment of pain, fever and other inflammatory conditions	24
4	Pioglitazone HCl, Gliclazide	Bi-layer tablets	Treatment of type II diabetes	25
5	Losartan potassium	Bi-layer tablets	Cytoprotective anti-ischemic, platelet inhibitor in acute coronary Syndromes	26
6	Clopidogrel bisulphate, Trimetazidine HCl	Bi-layer tablets	Synergistic effect in pain	27
7	Diclofenacpotassium, Cyclobenzaprine HCl	Bi-layer tablets	To overcome bioavailability problems, reducing side effects	28
8	Granisetron HCl	Bi-layer Buccal tablets	Biphasic drug release	29
9	Metformin HCl, Glimepiride	Bi-layer tablets	Synergistic effect in diabetes	30
10	Indomethacin	Bi-layer floating tablets	To overcome bioavailability	31
11	Cefixime trihydrate, Dicloxacilline sodium	Bi-layer tablets	Synergistic effect in bacterial infections	32
12	Piracetam, Vinpocetin	Bi-layer tablets	Synergistic effect in Alzheimer disease	33

13	Metformin HCl, Pioglitazone	Bi-layer buccal tablets	Synergistic effect in diabetes mellitus	34
14	Atenolol	Bi-layer tablets	To overcome bioavailability problem, reducing side effects and frequency of administration	35
15	Cefuroxime axetil Potassium clavulanate	Bi-layer tablets	Synergistic effect against microbial infections and to minimize dose dependent side effects	36
16	Atorvastatin calcium	Bi-layer buccoadhesive tablets	To overcome bioavailability	37
17	Paracetamol, Diclofenac	Bi-layer tablets	Synergistic effect of drugs in back pain	38
18	Losartan potassium	Bi-layer tablets	To overcome bioavailability	39
19	Metformin HCl, Pioglitazone	Bi-layer tablets	To overcome bioavailability	40
20	Guaifenesin	Bi-layer floating tablets	To reduce side effects and frequency of administration	41
21	Tramadol, Acetaminophen	Bi-layer tablets	Synergistic effect of drugs in pain	42
22	Montelukast, Levocetrizine	Bi-layer tablets	Biphasic release profile	43
23	Salbutamol, Theophylline	Bi-layer sustained release tablets	Synergistic effect of drugs in asthma	44
24	Telmisartan Hydrochlor- thiazide	Bi-layer tablets	To minimize contact b/w Hydrochlorothiazide & basic component of Telmisartan	45

Table 3:-*Troubleshooting of processing problems in bi-layer tablet compression[12]*

Trouble	**Possible causes**	**Remedies**
Tablet weight variation	1. Poor flow	a. Hopper wrong setting b. Material bridging in hopper c. Too much recirculation
	2. Dies not filling	a. Too fast press running b. Wrong feeder paddle speed or space
	3. Material loss or gain after proper die fill	a. Recirculation band leaking b. Excessive vacuum or nozzle improperly located
Product yield	1. Incorrect feeder fit to die table	a. Feeder bases incorrectly set
	2. Incorrect action on recirculation band	a. Gap between bottom edge and die table b. Binding in mounting screw too little hold down spring pressure
	3. Die table scraper action insufficient	a. Scraper blade worn or binding b. Outboard edge permitting material to escape
	4. Loss at compression point	a. Compressing too high in the Die b. Excessive or misdirected suction on exhaust nozzle
Low hardness	1. Factors related to machine	a. Tablet press having pre-compression and main compression facilities b. Press speed is reduced to increase total compression time
	2. Lubricant level	a. Over mixing can reduce tablet hardness
Capping & Lamination	1. Non-optimized formulation	a. Incorporate plastically deforming matrix
	2. High compression force	a. Reduced compression force b. Reduced press speed
	3. Ratio of pre-compression to main compression is insufficient	a. Pre-compression force high can be harmful b. Use large compression roller diameter

	4. Curled or damaged punches	a. Tools should be rewashed or Replaced
Picking & Sticking	1. Excessive heat generation during Compression	a. Use of cooling system for the compression section b. Lower mechanism section may be helpful
	2. Fouling the punch faces	a. Startup should always be close to optimum conditions
Layer separation	1. Insufficient bonding between the two layers during final compression of bi-layer tablet	a. First layer should be compressed at a low compression force so that this layer can still interact with second layer during final compression the tablet
	2. Improper setting of both feed frame	a. Both feed frame should set properly
	3. Due to weak suction	a. Suction capacity should be such that, all waste material is sucked

CONCLUSION

Bi-layer tablet is an improved beneficial technology to overcome the short coming of the single layered tablets. Fixed dose combination therapy is important in the modern era for various diseases and disorders such as hyper tension, diabetes, inflammatory and asthmatics. These can release more than two drugs in combination chronologically. Two incompatible substances can be remaining separated from one another in a single tablet. They can provide a biphasic release with one immediate release layer to produce the loading dose and second layer is maintenance dose in order to achieve the immediate pharmacological response lasting for a prolonged period. Bi-layer tablet consisting various combinations is useful for different ailments with a single intake. Thus bi-layer formulation is a safe, convenient dosage form and provides a better patient compliance. It provides greater advantages to both patient and clinician as it can be administered as a single tablet in once a day. Therefore in this modern era most of the pharmaceutical industries are focusing on the bi-layer tablet technology.

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