1) INTRODUCTION:

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration. It is well known that modified release dosage forms may offer one or more advantages over immediate release formulations of the same drug. There are many ways to design modified release dosage forms for oral administration; from film coated pellets, tablets or capsules to more sophisticated and complicated delivery systems such as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology. The design of modified release drug product is usually intended to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval whilst also providing greater patient compliance and convenience \(^1-3\). The most common controlled delivery system has been the matrix type such as tablets and granules where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period \(^4,5\). Bilayer tablets have some key advantages compared to conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with pre-determined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers. However, these drug delivery devices are mechanically complicated to design/manufacture and harder to predict their long term mechanical properties due to the poor mechanical and compression characteristics of the constituent materials in the compacted adjacent layers, elastic mismatch of the layers, insufficient hardness, inaccurate individual mass control, cross contamination between the layers, reduced yield, and their tendency to delaminate at the interface between the adjacent compacted layers during and after the various stages of production downstream of the compaction process. Therefore, the major problem, that has to be overcome, 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.

One of the major challenges is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack driven by residual stresses in the tablet propagating a finite distance within the tablet and leads to delamination
(layer-separation) which may not always be apparent immediately after compaction (e.g., during storage, packaging, shipping). In addition, if the compacted layers are too soft or too hard, they will not bond securely with each other which can lead to compromised mechanical integrity. Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se (inefficient or uncontrolled process) and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process. Since the adjacent compacted layers of a bilayer tablet are bonded together by mechanical means, understanding what influences the stress state, the mechanical properties of each layer and the resultant bilayer tablet, and compression parameters along with specialized techniques to predict failure as a function of layer properties and compression conditions are primordial to successfully developing bilayer tablets.

1.1 Bi-Layer Tablets:

Bi-layer tablets are tablets made by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for two or three layers. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes.
Steps for compression cycle for bi-layer tablet:

- Filling of first layer.
- Compression of first layer.
- Ejection of upper punch.
- Filling of second layer.
- Compression of both layer together.
- Ejection of bi-layer tablet.

Marketed Formulation of Bi-layer tablet:

- Glycinorm M containing Gliclazide (30 mg) and Metformin (500 mg).
- Glyree M1 containing Glimepiride (1 mg) and Metformin (500 mg).
- Piomed M containing Pioglitazone (15 mg) and Metformin (500 mg).
- Tenolol D containing Atenolol (25 mg) and Indapamide (1.5 mg).

1.1.3 Layer Thickness

Layer thickness can be varied within reasonable proportions within the limitations of the tablet press. Thinness is dependent on the fineness of the granulation.
1.1.4 Sizes and Shapes

Size is limited by the capacity of the machine with the total thickness being the same as for a single-layer tablet. Many shapes other than round are possible and are limited only by the ingenuity of the die maker. However, deep concavities can cause distortion of the layers. Therefore, standard concave and flat-face beveled edge tooling make for the best appearance, especially when layers are of different colors.

1.1.5 Granulations

For good-quality tablets with sharp definition between the layers, special care must be taken as follows:

1. Dusty fines must be limited. Fines smaller than 100 mesh should be kept at a minimum.
2. Maximum granule size should be less than 16 mesh for a smooth, uniform scrape-off at the die.
3. Materials that smear, chalk, or coat on the die table must be avoided to obtain clean scrape-off and uncontaminated layers.
4. Low moisture is essential if incompatibles are used.
5. Weak granules that break down easily must be avoided. Excessive amounts of lubrication, especially metallic stearates, should be avoided for better adhesion of the layers.
6. Formulation of multilayer tablets is more demanding than that of single-layer tablets. For this reason, selection of additives is critical.

1.1.6 Tablet Layer Press

A tablet multiplayer press is simply a tablet press that has been modified so that it has two die-filling and compression cycles for each revolution of the press. In short, each punch compresses twice, once for the first layer of a two-layer tablet and a second time for the second layer. Three-layer presses are equipped with three such compression cycles. There are two types of layer presses presently in use—one in which each layer can be ejected from the press separately for the purpose of weight checking, and the second in which the first layer is compressed so hard that the second layer will not bond to it, or will bond so poorly that upon ejection the layers are easily separated for weighing. Once the proper weight adjustments have been made by adjusting the die fill, the pressure is adjust to the proper tablet hardness and bonding of the layers. One hazard of layer tablet production is the lack of proper bonding of layers. This can result in a lot of 100,000 tablets ending up as 200,000 layers after several days if the layers are not sufficiently bonded. In
a two-layer tablet press, two hoppers above the rotary die table feed granulated material to two separate feed frames without intermixing. Continuous, gentle circulation of the material through the hoppers and feed frames assures uniform filling without segregation of particle sizes that would otherwise carry over to the second layer and affect layer weight, tablet hardness, and, in the case of differently colored granulations, the press with three hoppers for the tree granulations instead of two.

1.1.7 Limitations of the single-sided press

Various types of bi-layer presses have been designed over the years. The simplest design is a single-sided press with both chambers of the double feeder separated from each other. Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet. 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 steps (two = pre- and main compression).

The two layers in the die mix slightly at their interface and in most cases bond sufficiently so that no layer-separation occurs when the tablet is produced. This is the simplest way of producing a bi-layer tablet. The limitations of such single-sided press are:

- No weight monitoring/control of the individual layers
- No distinct visual separation between the two layers

The fact that it is not possible to monitor and control the weight of the individual layers raises the question whether we can consider this production GMP? Individual layer-weight control on a single-sided press requires some form of measurement of the first layer and of the total tablet. The first control loop indirectly monitors weight and controls the fill depth of the first layer. The second loop indirectly monitors the total tablet weight, but adjust only second-layer fill depth. In general, compression force is used to monitor tablet- or layer-weight. But to do so it is necessary to apply a compression force to the first layer before adding the second layer-powder. To apply a compression force to the first layer prior to adding the second layer, it is necessary to use two separate powder feeders with a compression station in-between. This can be achieved on a single-sided press by installing an additional feeder between the pre- and main-compression station. Very often the precompression roller must be reduced to a much smaller size in order to create the pace required for the second feeder. Additional limitations of such single-sided press are:
• Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, 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.
• Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

To eliminate these limitations, a double-sided tablet press is preferred over a single-sided press. A double-sided press offers an individual fill station, precompression and main compression for each layer. In fact, the bi-layer tablet will go through 4 compression stages before being ejected from the press.

1.1.8 Bi-layer tablets: limitations of “compression force” - controlled tablet presses
Separation of the two individual layers is the consequence of insufficient bonding between the two layers during final compression of the bi-layer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet. Bonding is severely restricted if the first layer is compressed at a too-high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with “compression force measurement”. 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 that layer.

1.3 Multi-layer tablet dosage forms are designed for variety of reasons:
1. To control the delivery rate of either single or two different active pharmaceutical ingredient(s) .
2. To separate incompatible Active pharmaceutical ingredient (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).
3. To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.
4. To administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery\textsuperscript{13}.

1.4 **Advantages of the bi-layer tablet dosage form are:**
1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
2. Cost is lower compared to all other oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strip.
5. Easy to swallowing with least tendency for hang-up.
6. Objectionable odour and bitter taste can be masked by coating technique.
7. Suitable for large scale production.
8. Greatest chemical and microbial stability over all oral dosage form.
9. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

1.5 **Disadvantages of Bi-Layer Tablet Dosage Form are:**
1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
4. Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

1.6 **General properties of Bi-Layer Tablet Dosage Forms:**
1. A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
2. Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
3. Should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.

4. Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents\textsuperscript{14}.

1.2 FIXED DOSAGE COMBINATION\textsuperscript{15}

A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses. Most essential drugs should be formulated as single compounds. Fixed ratio combination products are acceptable only when the dosage of each ingredient meets the requirements of a defined population group and when the combination has a proven advantage over single compounds administered separately in its therapeutic effects, safety or compliance. Combination therapy with two or more agents having complementary mechanisms of action represents a type of incremental innovation that has extended the range of therapeutic options in the treatment of almost every human disease. Combination product also known, as fixed dose combination of two or more active drugs produced in a single dosage form. They provide the advantages of combination therapy while reducing the number of prescriptions and the attendant administrative costs. More than one-third of all the new drug products introduced worldwide during the last decade were fixed dose combination (FDC) preparations. However, there is lack of statistical data for the developing countries, although, the trend seems to be the production and prescription of FDC’s. The World Health Organisation (WHO) lists nearly 325 essential drugs, including only 19 of such drug combinations. Whereas the national list of essential medicines have 354 essential drugs, including 14 deficiencies to cardiovascular diseases. There are many popular FDC’s in the Indian Pharmaceutical market. However, the safety profile of the established drugs will alter when they are combined together. Maximum FDC preparations comprise vitamins; cough suppressants; anti-diarrhoeal iron preparations, antacid, analgesics, tonics, antidiabetic, & Cardiovascular preparations.

1.2.1 Importance of FDC

- A clinical need is of course an absolute requirement for an FDC.
- The ingredients should all be necessary and should contribute towards the therapeutic goal. Since the components are combined in one formulation, the ingredients must be
pharmaceutically compatible and their release and bioavailability should be unimpaired even after combination.

- The dose range of the constituents needs to be narrow as the implicit individualization of dosage or flexibility is not required.
- If the combination effect is more than that corresponding to the sum of the individual activities, then it is known as potentiation. Although, in the case of mixed preparations, this effect is given prominence by the manufacturers, one should not forget that it is not quite simple to show the experimental proof of a potentiation, as it takes place very rarely.

1.2.2 Rationale for combination therapy:
All drugs have unwanted side effects in addition to the desired therapeutic effect. The idea of combining two or more drugs with complementary modes of action is to produce additivity of the desired therapeutic effect but not of the side effects. Fixed dose combinations are valuable only when they have been developed based on sound pharmacokinetic and pharmacodynamic criteria. As an example, at least five classes of drugs are commonly used to treat hypertension: diuretics, beta-blockers, ACE-inhibitors, angiotensin receptor blockers, and calcium channel blockers. The antihypertensive effects of an ACE-inhibitor and a calcium channel blocker, for instance, are additive, but these drug classes have different spectra of side effects, none of which are additive. Because the combination produces the same antihypertensive effect as higher doses of either constituent, the exposure to side effects is reduced and the therapeutic ratio is increased. The therapeutic ratio can be increased in certain instances by the phenomena of potentiation and cancellation. Potentiation is a synergistic effect on Drug A by adding a dose of Drug B without a therapeutic effect. An example is the combination bisprolol or enalapril with a low dose of hydrochlorothiazide itself without antihypertensive effect. Cancellation is a phenomenon in which the adverse effects of one drug are nullified by the addition of second. Although combination therapy is typically a matter of two different classes of drugs with a common therapeutic effect, there are many types of combinations.

1.2.3 Advantages of Combination products:
- Combination products have the advantages of combination therapy as well as advantages related to reducing the number of pills to be taken.
• Reduced administration costs stem from simplified packaging, fewer prescriptions, and fewer dispensing fees and co-pays.

• It has been known for many years that there is an inverse relationship between patient adherence and the complexity of the drug regimen. Reducing the number of pills diminishes the complexity of the regimen, so that improved patient adherence is expected with combination products.

• Combination products make particular sense in the treatment of infectious diseases, where partial adherence can lead to the development of drug-resistant strains and a threat to public health.

• The likelihood of a strain acquiring resistance to a constituent of combination therapy is zero or 100% and reaches a maximum at intermediate levels of adherence.

• With combination products, patients take either all of the drugs or none of them, and the possibility of the serial development of strains resistant to each constituent drug taken individually is eliminated.

1.2.4 The disadvantages of Fixed Dose Combination:

• The fixed dose combinations can lead to polypharmacy
• Dose of one ingredient can not been altered.
• Different pharmacokinetic properties can pose difficulty in frequency of administration and in case of development of an ADR.
• It is difficult to withdraw the suspected drug alone.
• The greater are the number of ingredients, the less likely the prescriber or the physician is to know what FDCs are and what their adverse reactions are. A combination makes it more difficult to pinpoint the offending agent responsible for the adverse reaction.
• Another drawback with FDCs is that they may lead to an ineffective dosage. In certain cases like heart failure, it becomes necessary to determine the strength of the dose against the appropriate end point. It is better to handle individual drugs rather than combinations in such life threatening conditions
• Some FDCs when combined lead to increased toxicity. For instance, the anti-TB drugs, streptomycin, kanamycin and capreomycin cannot be combined, as they have the same side effects.
If the biological half-life of different compounds of a FDCs are different, it may considerably affect the pattern of drug availability in the plasma, and hence, the overall efficacy of the preparation.

Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few.

National Harris interactive survey for hypertension, in the United States revealed that out of 90% patients taking medication only 50% to 60% were involved in some form of lifestyle change to control BP. Thus majority of patients with hypertension rely on medication for the control of their BP. Meticulous control of blood pressure is required in patients with hypertension to produce the maximum reduction in clinical cardiovascular end points, especially in patients with comorbidities like diabetes mellitus where more aggressive blood pressure lowering might be beneficial. Recent clinical trials suggest that the approach of using monotherapy for the control of hypertension is not likely to be successful in most patients. Combination therapy may be theoretically favored by the fact that multiple factors contribute to hypertension, and achieving control of blood pressure with single agent acting through one particular mechanism may not be possible. Regimens can either be fixed dose combinations or drugs added sequentially one after other. Combining the drugs makes them available in a convenient dosing format, lower the dose of individual component, thus, reducing the side effects and improving compliance. Classes of antihypertensive agents which have been commonly used are angiotensin receptor blockers, thiazide diuretics, beta and alpha blockers, calcium antagonists and angiotensin-converting enzyme inhibitors. Thiazide diuretics and calcium channel blockers are effective, as well as combinations that include renin-angiotensinaldosterone system blockers, in reducing BP. The majority of currently available fixed-dose combinations are diureticbased. Combinations may be individualized according to the presence of comorbidities like diabetes mellitus, chronic renal failure, heart failure, thyroid disorders and for special population groups like elderly and pregnant females.