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Brief Overview on Bi-Layer Tablet

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Abstract: *Oral route of drug administration is the most important method of administering drugs for systemic effects. Nevertheless, it is probable Disadvantages of bi-layer tablets that at least 90% of all drugs for systemic effects are administered by the oral route. When a new drug is discovered, one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect for the oral route. If patient selfadministration cannot be achieved, the sale of the drug constitutes only small fraction of what the market would be otherwise of drugs that are administered orally, solid oral dosage forms represent the preferred class of product. Tablets and capsules represent unit dosage form in which one usual dose of the drug has been accurately placed.*

Keywords: *Oral route of drug*

I. INTRODUCTION

Oral route of drug administration is the most important method of administering drugs for systemic effects. Nevertheless, it is probable Disadvantages of bi-layer tablets that at least 90% of all drugs for systemic effects are administered by the oral route. When a new drug is discovered, one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect for the oral route. If patient selfadministration cannot be achieved, the sale of the drug constitutes only small fraction of what the market would be otherwise of drugs that are administered orally, solid oral dosage forms represent the preferred class of product. Tablets and capsules represent unit dosage form in which one usual dose of the drug has been accurately placed (1)

In order to avoid fluctuation or disadvantages of conventional therapy several new techniques have been developed to improve patient compliance which is capable of controlling rate of drug delivery to the site of action. Oral route is one of the best and most widely used routes for administering drug to site of action. Tablets and capsules are the most widely used conventional therapy for the patients because they can be easily administered without any problem. (2)

Now a day's various developed and developing countries are moving towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension, Diabetes and Rheumatoid arthritics. The problem of dose dependent side effects is minimized by combination therapies and is advantageous over mono therapy from last few years, interest in developing a combination of two or more active pharmaceutical ingredients in a single dosage form has increased in pharmaceutical industry. Bi-layer tablets can be a primary option to avoid incompatibilities between APIS by physical separation (3)

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablets in which one layer is immediate release which act as loading dose and second layer is sustained. Release which act as maintenance dose. Bilayer tablet is the most recent form of tablet which comprises of combination of immediate release tablets and sustained release tablets.

It is a type of once-a-day oral dosage form which acts immediately upon administration and provides the action for prolonged period of 12-24hrs (4)

Regardless of the delivery method (immediate, extended, or controlled release) or dosage form design (solid, dispersion, or liquid), all pharmaceutical products intended for systemic delivery through the oral route of administration must be developed within the inherent features of GI physiology. This demonstrates that oral formulation is the most widely used method globally, and the researcher is mostly focused on this area. (5)

Tablets are solid preparations that are typically made by compressing consistent quantities of particles and contain a single dose of one or more active compounds. Tablets are meant to be taken orally. When a tablet is taken orally, it is

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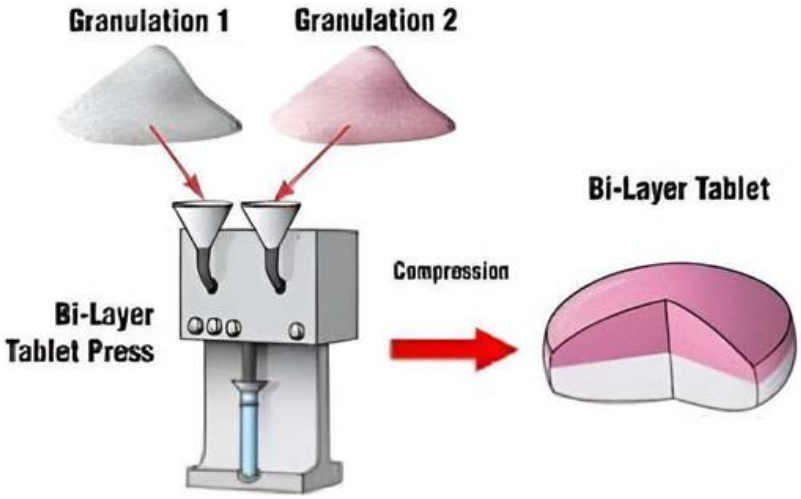
administered in vitro, dissolves, and is absorbed through the gastrointestinal tract (GIT). The medicine is subsequently biodispersed in vivo and enters the systemic circulation. Others are held in the mouth where the active ingredient is released, others are dissolved or distributed in water prior to administration, some are swallowed whole, and some are swallowed after being chewed. With or without excipients such diluents, binders, disintegrating agents, glidants, lubricants, or chemicals that can alter the preparation's behavior, the particles are made up of one or more active ingredients in the digestive tract, flavoring agents, and coloring materials approved by the component authorities.

Conventional dosing forms typically cause unfavorable toxicity and ineffectiveness along with large variations in drug concentration in the blood and tissues. This element repeated dosage and erratic absorption—inspired the idea of a regulated drug delivery system. The main objective of sustained release delivery is to ensure patient compliance and both safety and efficacy of medications. The design of sustained or controlled delivery systems aims to decrease the frequency of dosing or to increase the effectiveness of the drug by localizing at the site of action, lowering the dose required, or providing informed drug delivery.(6)

Diagram of general concept of bilayer tablet



Advantages of bi-layer tablets(7,8)

1. Easy to swallow with least hang up problems.
2. Bi-layer execution with optional single layer conversion kit.
3. Low cost compared to other dosage forms.
4. Greatest chemical and microbial stability compared to other oral dosage forms.
5. Offer greatest precision and the least content uniformity.
6. Objectionable odor and taste can be masked by coating technologies.
7. Flexible concept
8. Fit for large scale production.
9. Bi-layer tablets can be designed in such a manner as to modify release as either of the layers can be kept as extended and the other as immediate release
10. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus maximize the efficacy of combination of two drugs.
11. Separation of incompatible components.
12. Patient compliance is improved leading to improve drug regimen efficiency.
13. Patient compliance is improved because fewer daily dosages are required compared to traditional delivery system.

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14. Maintain physical and chemical stability.
15. Product identification is easy.
16. Easiest and cheapest to package and strip.Low dust formation

Disadvantages of bi-layer tablets

1. Complexity and bi-layer rotary presses are expensive.
2. Insufficient hardness, layer separation, reduced yield.
3. Imprecise individual layer weight control.
4. Cross contamination between the layers.
5. Difficult to swallow in case of children and unconscious patients.
6. Some drugs resist compression into dense compacts, due to amorphous nature, low density nature.

Types of bilayer tablet press: (9)

1. Single sided tablet press.
2. Double sided tablet press,
3. Bilayer tablet press with displacement monitoring.
4. Multilayer Compression Basics

1. Single sided press:

The simplest design is a single sided press with both chambers of the doublet feeder separated from. Each other. Each chamber is gravity or forced fed with different power, producing the two 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:

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

2. Double sided tablet presses :

Most of the double sided tablet press, which automates production control use the compression. Force to monitor and control the weight of the tablet weights. The effective compression force exerted on each individual tablet with the help of the compression system at the main compression of the layer. This system helps into reject out the tolerance tablets and correct the dies fill depth when required..

Advantages:

1. Low compression force exerted on the first layer to avoid chapping and separation of individual layer.
2. Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed.
3. Maximum prevention of cross Contamination between two layers.
4. A clear visual separation between the two layers.
5. Displacement weight monitoring.
6. For accurate and independent weight control of the individual.
7. Laver. Maximized yield.
8. Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet.

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Limitations:

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 a final compression. Bonding is too restricted if the first layer is compressed at a high compression force.

The low compression force required when compressing the first layer, unfortunately reduces the accuracy the weight monitoring/control of the first layer in the case of tablet presses with compression force measurement presses with compression force measurement.

3. Bilayer tablet press with displacement monitoring:

The displacement tablet weight control principle is fundamentally different from the principle hased upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied precompression force.

Advantages:

1. Weight monitoring/ control for accurate and independent weight control of the individual layers.
2. Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
3. Independence from the machine stiffness.
4. Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximurn turret speed.
5. Maximum prevention of cross-contamination between the two layers.
6. Clear visual separation between the two layers and maximized yield.

4. Multilayer Compression Basics:

Presses can be designed specifically for multi layers compression a standard double press can be converted for multipliers. The multilayer tablet concept has been longutilized to develop. Sustained release formulations such tablets have fast releasing layer and may contain players or triple layers to sustain the drug release from the tablet. The pharmacokinetics advantage relies on the fact that drug release from fast releasing granules leads to sudden rise in blood concentration, however the blood level Is maintained at a steady state as the drug is released from the sustained granules

SCHEMATIC PRESENTATION FOR COMPRESSION OF BI-LAYER TABLET(10)

1. Filling of first layer.
2. Compression of first layer.
3. Ejection of upper punch.
4. Filling of second layer.
5. Compression of both layer
6. Ejection of hi-layer table Diagram: schematic presentation for comperssion of bilayer tablet

PREPARATION OF BILAYER TABLETS (11)

Bilayer 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 form8. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers. An additional intermediate layer of inert material may also be included.

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 formulator to achieve these conditions especially in bilayer 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 compaction of a material involves both the compressibility and consolidation.

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Compression: it is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.
Consolidation: it is the property of the material in which there is increased mechanical strength due to interparticulate interaction (bonding).

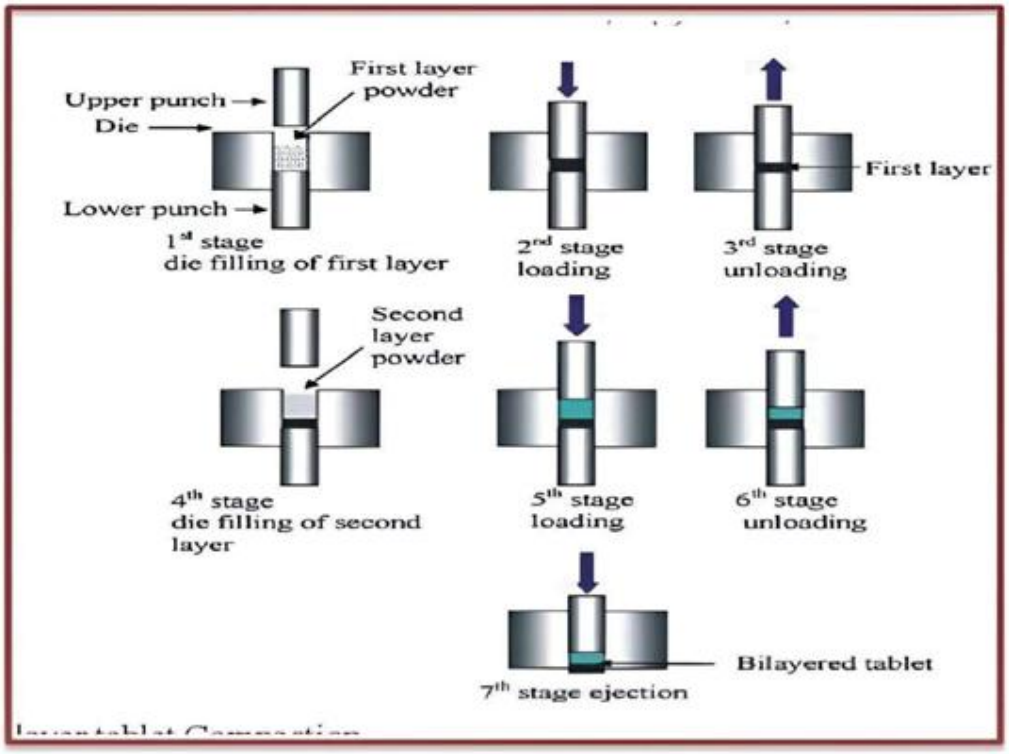

Fig.No.2 schematic presentation for compression of bi-layer tablet

QUALITY AND GMP-REQUIREMENTS (12)

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the Selected press is capable of 5:

1. Preventing capping and separation of the two Individual layers that constitute the bi-layer Tablet
2. Providing sufficient tablet hardness
3. Preventing cross-contamination between the two Layers
4. Producing a clear visual separation between the Two layers
5. High yield Accurate and individual weight Control of the two layers.

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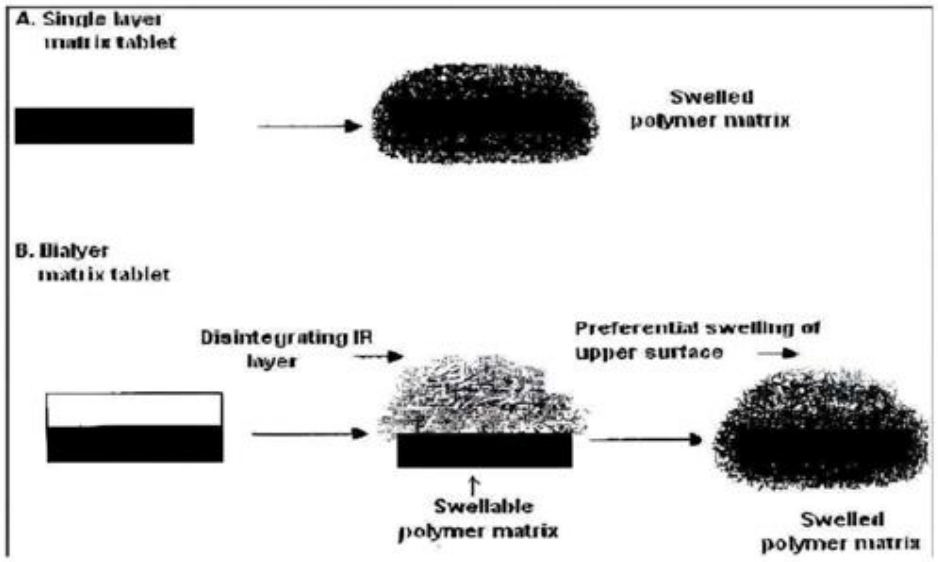

Fig. No.3: Drug release mechanism forms a bilayer tablet comprising an immec release & a sustained release layer

General properties of bi-layer tablet dosage forms (13)

1. It should have graceful product identity free of defects like chips, cracks. Discoloration and contamination.
2. Should have sufficient strength to with stand mechanical shock during its production, packaging, shipping and dispensing.
3. Should have physical and chemical stability.
4. The bi-layer tablet must release drug in a expectable and reproducible manner.
5. Must have a chemical stability shelf life, so as not to follow alteration of the medicinal agents.

Various techniques for bilayer tablet 9.10.11

OROS ® push pull technology : (13)

This system 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 (Fig.5). 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

Fig OROS push full technology

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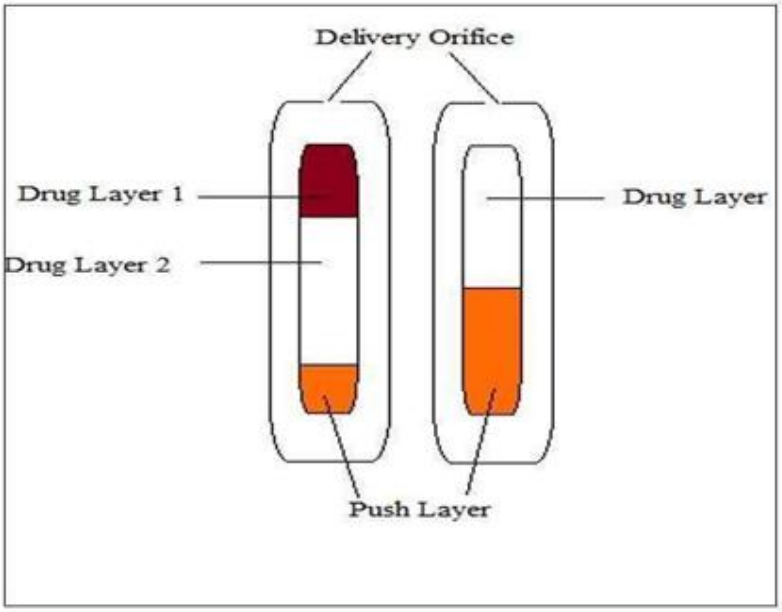

Figure No. 3: OROS ® push-pull technology

L-OROS00 tm technology 1.5.4

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 than a semi permeable membrane, drilled with an exit orifice (Fig.6).

Fig : L-OROS00 tm technology

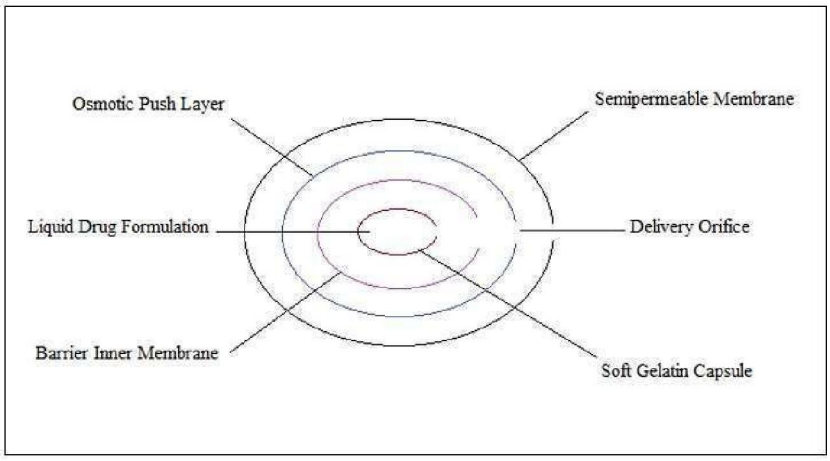

Figure No. 4: L–OROS TM Technology

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1.5.3 DUROS technology:

The system consists from an outer cylindrical titanium alloy reservoir (Fig. 7). 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.

Fig : L-OROS TM technology

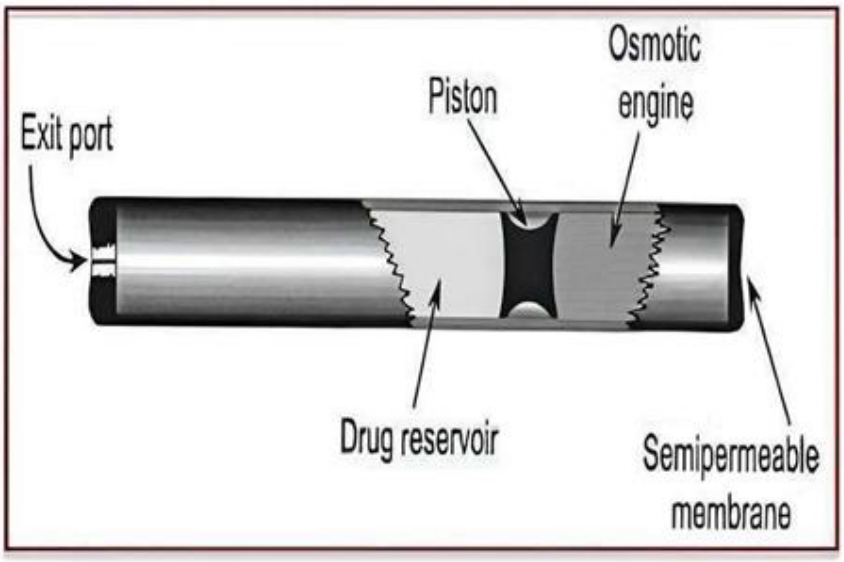

Fig. NO.7: DUROS® technology

1.5.5 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. (Fig. 8)

Fig: No. 8: ENSOTROL® technology

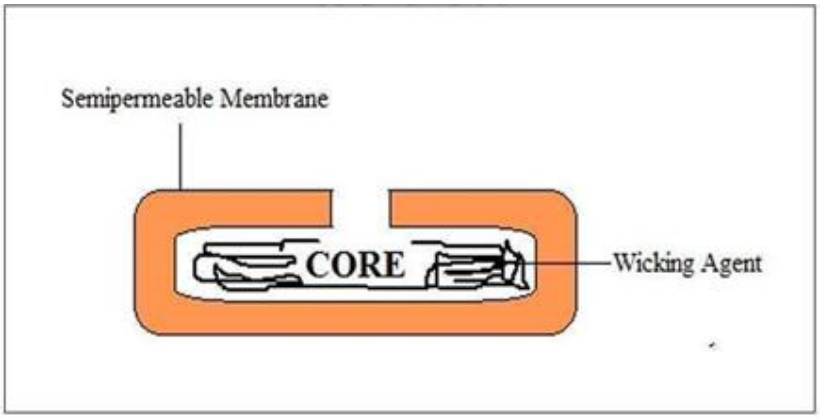

Figure No. 5: EN SO TROL technology

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Need of developing bi-layer tablets(13)

For the administration of fixed dose combinations of different active cycle, buccal/mucoadhesive delivery system, fabricate novel drug delivery system such As chewing device and floating table for gastro-retentive drug delivery. Controlling the delivery rate of either single or two different active pharmaceutical ingredients. To modify the total surface area available for active pharmaceutical ingredient layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release. 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).

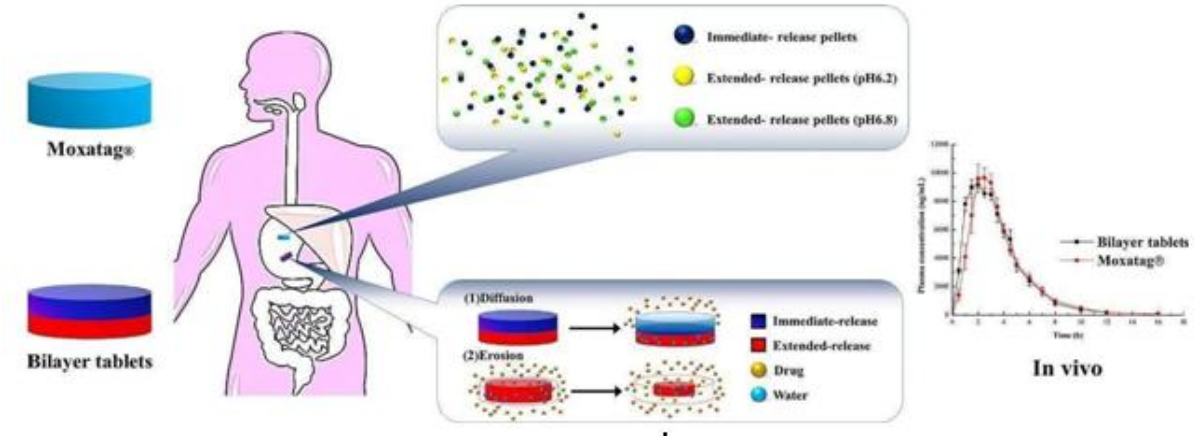


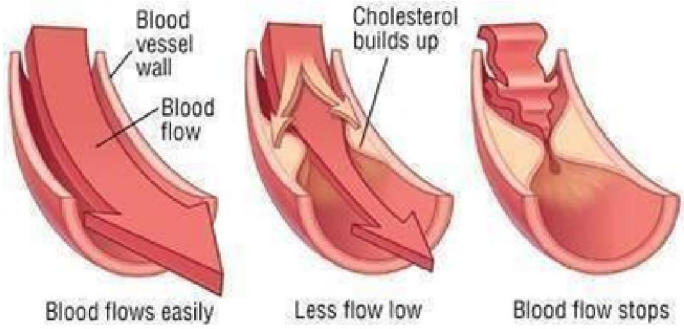
Fig 4: Figure showing immediate drug release from IR layer in stomach

1.6 Introduction to Hyperlipidemia 16,17 (14)

An overabundance of fatty compounds, known as lipids, primarily cholesterol and triglycerides, in the blood is known as hyperlipidemia. Because these fats are linked to proteins and move through the blood, it is also known as hyperlipoproteinemia. These fatty compounds can only stay dissolved in the bloodstream in this manner. The national cholesterol education program (NCEP) released the third report of the adult treatment panel (APT III), the most latest cholesterol management guidelines, in May 2001. Rethink the recommended blood cholesterol treatment levels. The previous NCEP guidelines (ATP II) differ in a number of ways from these new evidence-based recommendations. According to the American Heart Association, hyperlipidemia is characterized by a high blood fat content. These fats are known as Triglycerides and cholesterol are examples of lipids. Depending on whether blood lipid levels are elevated, hyperlipidemia can take many various forms.

Hyperlipidemia in general can be divided into two subcategories;

1. Hypercholesterolemia, in which there is a high level of cholesterol
2. Hypertriglyceridemia, in which there is a high level of triglycerides, the most common form of fat



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7.2 Hyperlipidemia Description Overview Lipoproteins are the fat-protein complexes found in blood. Low-density lipoprotein (LDL) and high-density lipoprotein (HDI) are the two most well-known lipoproteins. A heart attack is ultimately caused by artery obstruction, which is exacerbated by excess LDL cholesterol. Population studies have unequivocally demonstrated that the risk of heart disease increases with LDL cholesterol levels. This holds true for all adult age groups, men and women, and many racial and ethnic groups. LDL cholesterol has been dubbed the nasty cholesterol as a result.by a rise in triglyceride levels in the blood. High triglyceride levels have been linked in studies to a higher risk of coronary heart disease. Hyperlipidemia can greatly raise the risk of coronary heart disease, also known as coronary artery disease or coronary disease, even though it does not make you feel sick. The arteries in the heart muscle thicken or harden in those who have coronary disease. A heart attack, chest pain, or both may result from this. People with hyperlipidemia are frequently advised to receive therapy due to these dangers.An arteryhardening process known as atherosclerosis can be accelerated by high cholesterol levels. The inside of arteries is generally smooth and free of blockages, but as you age, plaque—a sticky material—forms in the artery walls. Lipids and other substances that circulate in your blood make up plaque. Your arteries may narrow and become more rigid as more plaque accumulates. Your arteries may eventually become less able to carry blood due to the accumulation of plaque. The main cause of heart disease and stroke, atherosclerosis, has been linked to hyperlipidemia.

Thankfully, it could be possible to lower elevated cholesterol levels, so preventing or delaying the development of atherosclerosis. Changes in lifestyle, such as may be able to lower elevated cholesterol levels, thereby preventing or delaying the development of atherosclerosis. A healthy diet and regular exercise can also help lower your cholesterol levels, and these lifestyle modifications are frequently the initial step in treatment.

Classification of Antihyperlipidemic drugs:

1. HMG-CoA reductase inhibitors (Statins): Lovastatin, Simvastatin, Pravastatin, Atorvastatin, Simvastatin
2. Bile acid sequestrants (Resins): Cholestyramine, Colestipol
3. Activate lipoprotein lipase (Fibric acid derivatives): Clofibrate, Gemfibrozil, Bezafibrate, Fenofibrate.
4. Inhibit lipolysis and triglyceride synthesis: Nicotinic acid
5. Others: Ezetimibe, Gugulipid.

Simvasatatin as antihyperlipidemic : It looks like you may be referring to Simvastatin, which is a well-known antihyperlipidemic (lipid-lowering) drug. Simvastatin belongs to the statin class of medications and is used primarily to lower elevated levels of low-density lipoprotein (LDL) cholesterol and triglycerides, while slightly increasing high-density lipoprotein (HDL) cholesterol

Pharmacological Action of Simvastatin:

Simvastatin is a lipid-lowering agent that primarily works by:

1. Inhibiting HMG-CoA Reductase Simvastatin is a prodrug that gets converted in the liver to its active form. It inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a key enzyme in the cholesterol biosynthesis nathway. ↓ It inhibits 3-hydroxy-3-methylglutaryl- coenzyme A (HMG-CoA) reductase, a key enzyme in the cholesterol biosynthesis pathway. This reduces the production of mevalonate, a precursor for cholesterol synthesis.
2. Lowering LDL Cholesterol By inhibiting HMG-CoA reductase, the liver compensates by increasing the number of LDL receptors on hepatocytes This enhances the clearance of low- density lipoprotein (LDL) from the bloodstream. It also decreases very-low-density lipoprotein (VLDL) and triglyceride levels.
3. Increasing HDL Cholesterol Simvastatin modestly raises high-density lipoprotein (HDL) cholesterol levels, which is beneficial for cardiovascular health
4. Anti-Inflammatory and Endothelial Effects It has pleiotropic effects, including reducing vascular inflammation and improving endothelial function. It lowers C-reactive protein (CRP), which is linked to cardiovascular risk.

Mechanism of Action of Simvastatin: Simvastatin is a HMG-CoA reductase inhibitor (statin) that works by: Inhibiting HMG-CoA Reductase: Simvastatin is a prodrug that is converted into its active form in the liver. It competitively

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inhibits HMG-CoA reductase, the enzyme responsible for converting HMGCoA to mevalonate, a key step in cholesterol synthesis. This results in reduced cholesterol production in the liver.

Upregulation of LDL Receptors: Due to reduced intracellular cholesterol, hepatocytes increase the expression of LDL receptors. This enhances the clearance of LDL (low-density lipoprotein, "bad cholesterol") from the bloodstream.

Reduction in VLDL and Triglycerides: By decreasing hepatic cholesterol levels, Simvastatin also reduces VLDL (very low-density lipoprotein) secretion, leading to a decrease in triglycerides.

Increased HDL ("Good Cholesterol"): Simvastatin can slightly increase HDL (high-density lipoprotein) levels, contributing to cardiovascular protection

Adverse Effects: Simvastatin, a statin medication used to lower cholesterol, can cause several side effects. These range from mild to severe,

including Common Side Effects:

1. Headache
2. Nausea
3. Constipation
4. or diarrhea
5. Abdominal pain
6. Muscle pain
7. or weakness
8. (mild) Fatigue

Introduction to hypertension20:

One of the most prevalent conditions, especially after middle age, is hypertension. Although it is a significant risk factor for cardiovascular mortality and morbidity, it is not a disease in and of itself. It is arbitrary to choose the cutoff manometric reading between normotensives and hypertensives.

Practically speaking, "hypertension" could be defined as the blood pressure level at or above which cardiovascular mortality can be decreased by long-term antihypertensive medication. Although risk seems to grow even above 120/80 mm Hg, the JNC 7* (2003) and WHO-ISH@ guidelines (2003) define it as 140 mm Hg systolic and 90 mm Hg diastolic.

According to epidemiological research, the risk of cardiovascular disease increases with systolic, diastolic, or both blood pressure levels. The cause of essential (primary) hypertension is unknown in the majority of instances. The sympathetic and reninangiotensin systems influence blood vessel tone and c.o. in hypertensives, just as they do in normotensives, regardless of whether they are hyperactive. Numerous antihypertensive medications disrupt these regulatory mechanisms in one way or another. Antihypertensive medications may reset the barostat to operate at a lower blood pressure level by consistently reducing blood pressure.

When the exact reason of the blood pressure increase is unknown, the condition is referred to as primary or essential hypertension. Secondary hypertension is caused by vascular (renal artery disease), endocrine (Cushing's syndrome), and renal (chronic diffuse glomerulonephritis) factors.

Elevated diastolic blood pressure, normal cardiac output (in most cases), elevated peripheral vascular resistance, and distinctive pathologic alterations in the arterials are the hallmarks of the essential hypertension syndrome. Untreated hypertension shortens life expectancy and causes a number of incapacitating cardiac, cerebrovascular, and renal complications.

1.8.1 The Etiology of primary hypertension

Although the exact cause of primary hypertension is unknown, some factors are thought to play a role in its development. It Is well known that blood pressure increases with aging in adult populations. However, the overall population's blood pressure rises unevenly with age. As a result, these people's blood pressure management differs quantitatively from that of the rest of the population. Essential hypertension exhibits a substantial familial clustering, and its inheritance appears to be polygenic. Peripheral resistance and cardiac output both affect arterial pressure. Both

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are easily impacted by a number of variables. Typically, there are two primary types of systems that regulate blood pressure.

Blood pressure is controlled by two main types of system as:

a) The adrenergic nervous system which operates through the baroreceptors and is mainly responsible for the contracting acute changes in the blood pressure Baroreceptor reflexes protect the circulation against stresses which would tend to alter arterial pressure acutely.

b) The normal rennin – angiotensin system which has a slow response and is probably important in long term regulation of arterial pressure. It operates through the kidneys and involves various in humoral agents.

Rennin a protiolytic enzymes is produced and stored in the kidneys. It is released in response to reduction in renal perfusion pressure.

> Reduction in sodium delivery to the macula densa.

➤Increase in the sympathetic activity.

A few humeral considerations Rennin and a serum globulin (angiotensinogen, a reanin substrate) react to produce an inactive form of angiotensin I, which is then converted to an active form by an additional enzyme called angiotensin converting enzymes (ACE) during phase II. The most potent direct vasoconstrictor is angiotensin II. Although it has a stronger effect on the adrenal cortex, angiotensin II also mimics the production and release of aldosterone from the adrenal circulation. So, the kidney actively regulates vasoconstriction and volume, the two main factors that affect blood pressure and tissue flow, and so plays a significant role in setting blood pressure levels.

1.8.2 Classification of Antihypertensive Drugs

The drugs used in the treatment of hypertension can be classified according to site of action as follows.

1. Drugs Acting on centrally

Alpha 2 adrenergic receptor stimulants eg. Clonidone and Methyldopa.

> Selective imidazole receptor (I-receptor) stimulants, e.g., Moxonidone

2. Drugs Actin on Autonomic Ganglia

Ganglion blocking agents e.g. Trimethaphan

3. Drugs Acting on the postaganglionic Sympathetic Nerve Endings Adnergic neuron blockers:

Guanethidine, Debrisoquine, Catecholamine deplitors: Reserpine.

4. Drugs Actin on Adrenergic Receptors

> Alpha-adrenergic blocking agents: phenolamine phenoxybenzamine

> Beta-adrenergic blocking agents: Propranol Atenolol Metoprolol Both alpha and beta adrenergic blocking drugs: Labetalol.

5. Drugs Acting Directly on the vascular smooth muscle (vasodilator) Arteriolar vasodilators: channel blockers: Hydralazine Arteriolar-venular vasodilators: Sodium Nitroprussid

6. Potassium channel Activators e.g. Diazoxide, Minoxidil, Pinacidil, Nicorandil. 6. Drugs which blocks Rennin-Angiotensin- Aldesternon Axis

Those which blocks rennin release: Beta-adrenergic blockers.

> Those which block the conversion of angiotensin I to angiotensin II by inhibiting the angiotensin converting enzyme (ACE): e.g., captopril

> Those which competitively block angiotensin II at the vascular receptor sites: e.g. Losartan.

8. Those which counteract the action of aldosterone: Spironolactone.

9. Oral Diuretics:e.g. Thizides

10. Miscellaneous. e.g. Metyrosine.

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Lisinopril As Antihypertensive: Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor used primarily to treat hypertension (high blood pressure), heart failure, and to improve survival after a heart attack.

Pharmacological Actions of Lisinopril:
ACE Inhibition:
Lisinopril blocks the angiotensin-converting enzyme (ACE), preventing the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor.
This leads to vasodilation (widening of blood vessels), reducing blood pressure
Reduction in Aldosterone Secretion:
By reducing angiotensin II levels, lisinopril decreases aldosterone secretion from the adrenal glands.
This leads to less sodium and water retention, lowering blood volume and further reducing blood pressure.

Increased Bradykinin Levels:
ACE normally degrades bradykinin, a vasodilator.
Inhibiting ACE allows bradykinin to accumulate, promoting vasodilation and reducing blood pressure.
This mechanism is also responsible for the dry cough seen in some patients.
Cardioprotective Effects:
Reduces afterload and preload on the heart, improving heart function in heart failure. Protects against cardiac remodeling (thickening of the heart muscle) after a heart attack.
Renal Protection:
Used in diabetic nephropathy and chronic kidney disease to reduce proteinuria (excess protein in urine).
Lowers glomerular pressure, slowing kidney damage progression.

Lisinopril as mechanisms action:
Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor used primarily to treat hypertension and heart failure.
Its mechanisms of action include:
Inhibition of ACE: Lisinopril blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. This leads to:
Vasodilation: Reduced blood vessel constriction lowers blood pressure.

Decreased aldosterone secretion:
This reduces sodium and water retention, lowering blood volume and pressure.
Reduction of Bradykinin Breakdown:
ACE normally degrades bradykinin, a vasodilator. By inhibiting ACE, lisinopril increases bradykinin levels, enhancing vasodilation.
This contributes to lower blood pressure but can also cause a persistent cough in some patients.
Cardioprotective Effects:
Reduces afterload and preload on the heart, improving cardiac output. Prevents left ventricular remodeling in heart failure patients.
Protects kidneys by reducing glomerular hypertension, beneficial in diabetic nephropathy While it is generally well-tolerated, some common and serious side effects can occur:
Adverse Effects of Lisinopril: While it is generally well-tolerated, some common and serious side effects can occur:
Common Side Effects Cough (dry, persistent) Dizziness or lightheadedness, Headache, Fatigue, Nausea.

II. LITERATURE REVIEW

• The study by Gattani SG, Khabiya SS, Amrutkar JR, and Kushare SS (2012) et. al. focuses on the formulation and evaluation of bilayer tablets containing metoclopramide and diclofenac sodium. The Courtoy-S292F Tablet Press, Designed for Quality Bi-layer Tablets" by Jan Vogeleer et al., published by Niro Pharma Systems, explores the

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importance of specialized technology in the production of high-quality bi-layer tablets. The paper emphasizes the need for advanced tablet pressing technology, such as the Courtoy-S292F tablet press, which is specifically designed to handle the complexities involved in manufacturing bi-layer tablets. These tablets require precise control over the layering process to ensure the correct release profile, tablet integrity, and overall quality. The authors discuss the unique capabilities of the Courtoy-S292F press in achieving consistent and reproducible results, addressing issues such as material segregation, improper layer adhesion, and the impact of press speed on tablet quality. The research highlights that for bi-layer tablets to meet strict pharmaceutical standards, specialized equipment and technology are essential for optimizing the production process and achieving high-quality products.

• Panchal Hiten Ashok and Tiwari Ajay Kumar, published in IRJP, 2012 et. al, Vol. 3(5), pp 44-49, presents an overview of the bi-layer tablet technology, which offers an innovative approach in pharmaceutical dosage forms. This technology is designed to provide a controlled release of drugs, ensuring more efficient treatment regimens. The paper reviews the formulation and development aspects of bi-layer tablets, which are beneficial in delivering two different drugs or two release profiles in a single dosage form. The authors discuss the advantages of bi- layer tablet formulations, including the potential for improved therapeutic efficacy, reduced side effects, and enhanced patient compliance. Challenges involved in the design and manufacturing processes are also highlighted, with a focus on ensuring stability, proper layering, and optimal drug release. The review concludes by emphasizing the future potential and growing significance of bi-layer tablets in modern drug delivery systems.

• The study by Pateriya A, Bhowmick M, Pandey GK, Joshi A, and Dubey BR (2013) et.al focuses on the formulation and evaluation of bilayer tablets containing candesartan (an angiotensin II receptor antagonist) and hydrochlorothiazide (a diuretic), both of which are commonly used in the treatment of hypertension. The aim of the study was to develop a bilayer tablet that combines both drugs in a single dosage form to provide both immediate and sustained therapeutic effects. The immediate-release layer was designed for the rapid release of hydrochlorothiazide to initiate the diuretic action, while the sustained- release layer was formulated to slowly release candesartan, ensuring prolonged antihypertensive effects. Various excipients were employed to optimize the drug release profiles, and the tablets were evaluated for their physical properties such as hardness, friability, and weight variation. In vitro drug release studies demonstrated the successful design of a bilayer tablet with controlled release of both active pharmaceutical ingredients, offering a potential solution for improving patient compliance and effectively managing hypertension.

• Sandeep N and Gupta MM. Immediate Drug Release Dosage Form: A Review. JDDT. 2013; 3(2):155-161. et. al. The review by Sandeep N and Gupta MM (2013) provides a comprehensive overview of immediate drug release (IDR) dosage forms. IDR formulations are designed to deliver the drug quickly into the systemic circulation, achieving rapid onset of action. The review discusses the various technologies employed in the development of IDR formulations, including granulation methods, direct compression, and fast-dissolving technologies. It also highlights the advantages and challenges associated with IDR formulations, such as enhanced patient compliance and the need for precise formulation to avoid dose dumping. Furthermore, the review covers the factors affecting drug release, including excipient selection, compression force, and tablet characteristics. The authors emphasize the importance of optimizing these factors to achieve the desired therapeutic effect for conditions that require fast relief. The article serves as a valuable resource for researchers and pharmaceutical formulators working on the development of immediate release dosage forms.

• Soham Shukla, Vikram Pandya, Praful Blardia, Nitin Jonwal, and Deepak Ithatt (2013) et.al discusses the concept of the bilayer tablet system as an innovative drug delivery trend. Bilayer tablets combine two different drugs or drug-release mechanisms in one tablet, offering distinct advantages over single- layer formulations, such as improved therapeutic efficacy, controlled release, and enhanced patient compliance. This review highlights the design, development, and challenges associated with bilayer tablet systems, including the selection of excipients, formulation strategies, and the optimization of drug release profiles. The authors also examine the various applications of bilayer tablets in the treatment of chronic conditions requiring multi-drug therapy, such as hypertension, diabetes, and pain management. The article further discusses the future potential of bilayer tablet technology in improving drug delivery systems and overcoming limitations associated with conventional dosage forms. Overall, the study presents bilayer tablet technology as a promising approach to the controlled release of multiple drugs in a single dosage form.

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• The study by Reddy RK and Srinivas N (2014) et. al investigates the formulation and evaluation of bilayered tablets of losartan potassium, an angiotensin II receptor antagonist used in the treatment of hypertension. The primary objective was to design a bilayer tablet that offers both immediate and sustained release of losartan potassium. The immediate release layer was developed to provide rapid drug absorption, while the sustained release layer aimed to maintain therapeutic plasma levels over an extended period, thus improving patient compliance. Various formulation techniques and excipients were employed to achieve desired drug release profiles. The tablets were evaluated for their physical properties, including hardness, friability, weight variation, and in vitro drug release behavior. The results indicated that the bilayer tablet formulation successfully controlled the release of losartan potassium, providing both quick and prolonged therapeutic effects. The study suggests that the bilayer tablet system may offer significant advantages over traditional single-layer formulations in the management of hypertension.

• Mandadi Pavani et al 2015(41), To formulate and evaluate immediate release tablets of Rosuvastatin containing super disintegrants. The objective of the study was to achieve commercial viability of Rosuvastatin which has great market potential. The present study provides Rosuvastatin stable formulations in immediate release tablets. Various trails were conducted by using various super disintegrants in various concentrations and compare it with innovator product. Super disintegrants like Sodium starch glycol ate, cross povidone, cross Carmellose sodium were used in various concentrations to improve the immediate release of the tablets by direct compression technique. Pre compression and post compression parameters like flow properties, thickness, hardness, weight variation, disintegration and dissolution were evaluated. Among all the formulations, formulation with croscarmellose sodium (F9) showed better release which is considered an optimized formulation, which is pharmaceutically equivalent to the innovator product. Accelerated stability studies were performed for optimized formulation for three months under the conditions of 400c ± 20c/75% RH ± 5%

• Swetanshu, Vijay Sharma, Journal of Drug Delivery & Therapeutics. 2019; 9(4):704-708 et. al. Hypertension or high blood pressure occurs when the high cardiac output exerts pressure on the arterial wall as the blood flow increases. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an extended release manner. Bi-layered tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose.

• Courtoy-S292F Tablet Press, Designed for Quality Bi-layer Tablets" by Jan Vogeleer et al., published by Niro Pharma Systems, explores the importance of specialized technology in the production of high-quality bi-layer tablets. The paper emphasizes the need for advanced tablet pressing technology, such as the Courtoy-S292F tablet press, which is specifically designed to handle the complexities involved in manufacturing bi-layer tablets. These tablets require precise control over the layering process to ensure the correct release profile, tablet integrity, and overall quality. The authors discuss the unique capabilities of the Courtoy-S292F press in achieving consistent and reproducible results, addressing issues such as material segregation, improper layer adhesion, and the impact of press speed on tablet quality. The research highlights that for bi-layer tablets to meet strict pharmaceutical standards, specialized equipment and technology are essential for optimizing the production process and achieving high-quality produc

III. AIM AND OBJECTIVES

Aim- To formulate bi-layer tablet of a model drug to meet the defined objectives.

Objectives- The objective of the study is:

1. Combined use of medications for the purpose of enhancing the convenience of utilizing medications, reducing side effects of medications and offer more efficacy than each drug given alone.
2. Formulation and process optimization of bilayer tablets
3. To carry out pre formulation studies and drug-excipients compatibility study.
4. To study the effect of different polymer in the formulation.
5. To control weight variation during tableting.

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6. Formulation of such a bilayered tablet that is resistant to capping with good crushing strength, superior integrity and delivering the two active ingredients in the desired manner.
7. To carry out the stability studies for optimized formulation.

IV. PLAN OF WORK

Present proposed research work has been planned as follow-

- Literature survey
- Selection of drug and polymer& other excipients.
- Procurement of drug and polymer& other excipients.
- Preliminary study of drug and polymer.
- Formulation of bilayer tablet
- Evaluation of bilayer tablet –

a. Thickness
b. Hardness
c. Friability
d. Disintegration test

5. Material and Equipment

Table 1. List of Reagents

Sr. No.	Materials
1.	Simvastatin
2.	Lisinopril
3.	Ethyl Cellulose
4.	HPMC K100M
5.	Lactose
6.	Microcrystalline Cellulose
7.	Cross Povidine
8.	Sodium Starch Glycolate
9.	Croscarmellose Sodium
10.	PVPK-30
11.	Isopropyl Alcohol
12.	Aerosil
13.	Talc
14.	Magnesium Stearate
15.	Methylene Blue

Table 2. List of Instruments

Sr. No.	Equipments
1.	Dissolution Test Apparatus
2.	Electronic Balance
3.	UV-Visible Spectrophotometer
4.	pH Meter
5.	Hot Air Oven
6.	Distillation Apparatus
7.	Vernier Caliper
8.	Single Punch Tablet Machine

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9.	Roche Friability Tester
10.	Monsanto Hardness Tester
11.	Laboratory Sieves
12.	Disintigration Test Apparatus
13.	FTIR

VI. EXPERIMENTAL WORK

Drug and Excipient Preformulation Studies:

Preformulation is the study of the physical and chemical characteristics of the medicinal ingredient both by itself and in combination with excipients. The initial stage in the logical development of a pharmacological substance's dosage form is preformulation research

Preformulation research aims to create a portfolio of data regarding the drug's constituents so that formulation can be developed with the help of this data. Preformulation studies are intended to find the excipients and physicochemical characteristics that could affect the final product's pharmacokinetic-biopharmaceutical characteristics, manufacturing process, and formulation design. Thus, the program's objectives are

To ascertain its kinetic release rate profile. Therefore, physical test determination and compatibility studies are part of a preformulation study on the medication sample that was collected.

1) to determine a new medicinal substance's essentia physicochemical properties To ascertain its compatibility with various excipients

6.1.1 Description

The drug was analyzed for color, odor and taste.

6.1.2 Melting point

Melting point determination of Simvastatin & Lisinopril was done by open capillary method

6.1.3 Solubility Characteristics

A semi quantitative determination of solubility can be made by adding a solute in small incremental amount to fixed volume of solvents, distilled water, phosphate buffer pH 6.8, buffer pH 1.2, methanol, alcohol, isopropyl alcohol. After each addition, the system is vigorously shaken and examined usually for any undissolved particle Formulation and optimization of bilayer tablet containing release layer of Simvastatin and Lisinopril

I. Development of sustained release layer by direct compression

All the powders were passed through 60 # sieve Required quantities of drug-polymer and diluent were mixed thoroughly tale and magnesium stearate were finally added as glidant and lubricant mixed well with powder blend for 5 minutes.

II. Development of immediate release layer by wet granulation method

Weighed and sifted Simvastatin lactose Microcrystalline cellulose through 40 # sieve and mix well. Sifted sunset yellow through 100 # sieve and mix with the above material. PVP was dissolved in isopropyl alcohol. Granulated the mixture obtained in above mentioned step with the solution. the wet mass passed through 14 #sieve the granules prepared were dried in tray at 45±5 0c for 60 minutes till loss on drying (LOD) not more than 3% achieved. The dried granules were passed through 16# sieve Calculated extragranular materials based on the yield of granules obtained sifted super disintegrating agent like (CCS,CP, SSG.) and Acrosil through 40 # sieve; sifted tale through 60 # sieve and mixed well all the ingredients. Lubricated the

PPgranules using magnesium stearate previously passed through 60 # sieve.

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III. Compression of Bilayer Tablet

In the present study bilayer tablet was prepared manually using single station punching machine. accurately weighed amount of SR powder mixture was fedmanually into die cavity. SR layer was compressed at mild compression force (3-4 kg/cm2). After that accurately weighed IR powder mixture was manually fed into the die on SR layer and compressed using 12-mm circular punches. Both the layers were identified on the basis of color since the immediate release layer had sunset yellow color and the sustained release layer has white colourP

Table No.3: Formulation of Sustained release layer (Lisinopril)

Ingredients	L1	L2	L3	L4	L5	L6
Lisinopril	120	120	120	120	120	120
HPMC- K100M	100	50	33.33	66.66	25	-
Ethyl cellulose	-	50	66.66	33.33	75	100
MCC	60	60	60	60	60	60
PVP K-30	10	10	10	10	10	10
Mg. stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total	300	300	300	300	300	300

Table No.4. Formulation of Immediate release layer Simvastatin

Ingredients	S1	S2	S3	S4	S5	S6
Simvastatin	10	10	10	10	10	10
Lactose	46.25	46.25	46.25	46.25	46.25	46.25
Microcrystalline Cellulose	49	46	49	46	49	46
PVP K-30	6	6	6	6	6	6
Isopropyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s
SSG	3	6	-	-	-	-
CCS	-	-	3	6	-	-
CP	-	-	-	-	3	6
Aerosil	1.2	1.2	1.2	1.2	1.2	1.2
Talc	1.2	1.2	1.2	1.2	1.2	1.2
Mag. Stearate	0.6	0.6	0.6	0.6	0.6	0.6
Methylene Blue	0.25	0.25	0.25	0.25	0.25	0.25
Total	120	120	120	120	120	120

6.2. Pre-formulation study:

Bulk Density (Db);

The mass of the powder was divided by the bulk volume in cm' to determine the loose bulk density. A 25 ml graduated cylinder was carefully filled with the 10 g sample. After recording the powder's volume, the bulk density was computed. It was computed using the following equation.

Df = M/Vp

Where,

D = Loose bulk density

M = Weight of samples in grams

Vp = Final volumes of granules in cm^3.

Tapped Density (D):

The mass of a powder was divided by the tapped volume in centimeters to determine the tapped bulk density. A 25 ml graduated cylinder was carefully filled with the 10 g sample. The cylinder was dropped 100 times from a height of 1

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inch onto a hard wood surface at 2-second intervals. The final tapped volume in cm' of the sample contained in the cylinder was then divided by the sample weight in grams to determine the tapped bulk density of each formulation. It was computed using the following equation.

Do = M/Vp

Where,

D. Tapped bulk density.

M= Weight of samples in grams.

Vp = Final tapped volumes of granules in cm3

Compressibility Index and Hausner ratio:

In recent years, the compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and the Hausner ratio are determined by measuring both the bulk density and the tapped density of a powder.

% Compressibility = $\rho t - \rho 0$ x 100
ρt

Where,

ρo= Bulk density, ρt =Tapped Density, Hausner Ratio:

Where

ρt = Tapped density ρ0 = Bulk density Hausner ratio = ρt
$\rho 0$

Table No.5: Relationship between percent compressibility and flowability

Compressibility Index %	Flow Property	Hausner Ratio
≤ 10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 - 31	Poor	1.35 – 1.45
32 - 37	Very Poor	1.46 – 1.59
>38	Very Very Poor	>1.60

Angle of repose :

The flow characteristics of solids have been described using the angle of repose. One property associated with interparticulate friction, or resistance to particle movement, is angle of repose. This is the greatest angle that can exist between the granule or powder pile's surface and the horizontal plane.

tan Θ = h / r Θ = tan-1h / r

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Where,

Θ = Angle of repose. h = Height. r = Radius

A funnel was attached over the platform at a height of about 2 cm. The loose powder was gradually moved along the funnel's wall until a powder cone formed. Measure the height of the powder cone and the radius of the powder heap to find the angle of repose.

Table No. 6: Relationship between angle of (Θ) and flowability

Flow Property	Angle of Repose (degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable may hang up	41-45
Poor-must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

6.3. Post compression parameter of bilayer tablet:

Hardness test:

Although hardness test is not an official, tablet should have sufficient handling during packing and transportation. Hardness of tablet was measured by using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying the force. The hardness of 3 tablets, from each batch was determined and mean hardness was taken into account, which was expressed in kg/cm².

Friability test:

Friability tests are used to evaluate the impact of shocks and friction, which frequently result in tablet chipping, breaking, or capping. For this, Roche Friabilator was utilized. This apparatus uses a plastic chamber that rotates at 25 rpm to subject several tablets to the combined effects of shock and abrasion, dropping the tablets six inches apart with each revolution. The friabilator was filled with a pre-weighed sample of tablets and rotated for 100 revolutions. The tablets were reweighed after being dedusted.No more than 1% of the weight of compressed pills should be lost

The percentage friability was measured using following formula

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F-Friability in percentage, Wo- Initial weight of tablet,

W-Weight of tablets after revolution.

Weight variation test:

Weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average USP weight variation test. The table No.9 given below shows the weight variation tolerance for uncoated tablets.

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Table No.7: Weight variation tolerance for uncoated tablets

Average weight of Tablet (mg)	Maximum percent deviation allowed
80mg or less	10%
80mg to 250mg	7.5%
More than 250mg	5%

Thickness:
The thickness of the tablet was measured using Vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated

Disintegration test :
Disintegration test is a method to evaluate the rate of disintegration of tablets. It is also defined as break down of solid dosage form into smaller particles when it is disintegrated. Place 1 tablet in each of the 6 tubes and added a disc to each tube. Maintain the temperature of the disintegration media at 37±2°C as specified+ in the monographs. At the end of time limit specified, left the basket from fluid.

VII. RESULT AND DISCUSSION

7.1 Characterization of Simvastatin and Lisinopril

7.1.1 Organoleptic characterization and Melting point determination

The organoleptic character and melting point was found to be as per standard drug so drug used in the formulation was found to be pure according to I.P. specification.

Table No.10: The physicochemical characteristics of Simvastatin

Sr. No.	Test	Observations
1.	Colour	White Crystalline Powder
2.	Odour	Slight
3.	Taste	Bitter
4.	Melting Point	156^0– 160^0c
5.	pH	4.5 – 6.0

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7.1.2 Solubility analysis:

The solubility of pure drug in 10mg/10ml of solvent was carried out and it reveals that it is soluble in methanol and dichloromethane, sparingly soluble in water. soluble in phosphate buffer pH 6.8.

Table No.11: Solubility profile of Simvastatin

Sr. No.	Solvent	Solubility
1.	Water	Sparingly soluble
2.	Buffer solution 6.8	Soluble
3.	Methanol	Soluble
4.	Dichloromethane	Soluble

7.1.3 Organoleptic characterization and Melting point determination

The organoleptic character and melting point was found to be as per standard drug so drug used in the formulation was found to be pure according to I.P. specification.

Table No.12: The physicochemical characteristics of Lisinopril

Sr. No.	Test	Observations
1.	Colour	White Crystalline Powder
2.	Odour	Odourless
3.	Taste	Bitter
4.	Melting Point	$210^0 - 215^0$c
5.	pH	4.5 – 6.0

Solubility analysis:

The solubility of pure drug in 10mg/10ml of solvent was carried out and it reveals that it is soluble in water, sparingly insoluble in methanol and dichloromethane, soluble in phosphate buffer pH 6.8.

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Table No.13: Solubility profile of Lisinopril

Sr. No.	Solvent	Solubility
1.	Water	Sparingly soluble
2.	Buffer solution 6.8	Soluble
3.	Methanol	Insoluble
4.	Dichloromethane	Insoluble

7.2 Formulation & Development of Bilayer tablet

7.2.1 Preparation of Bilayer (Immediate release Simvastatin sustained release Lisinopril) Tablets

7.2..1.1 Immediate release layer

Various immediate release Simvastatin tablets were formulated with MCC as diluents, cross povidone, sodium starch glycolate and croscarmellose sodium used as a super disintegrants in 6% and 12% concentration in the formulations S1, S2, S3, S4, S5, and S6 respectively. Magnesium Stearate. Talc,and Aerosil were used as a lubricant and glidant Methylene blue was used as a colorant.

7.2..1.2 Sustained release layer

The second layer (sustain release layer) of Lisinopril tablets were prepared by using HPMC K100 M and Ethyl cellulose in different ratios, magnesium stearate and tale were incorporated as lubricant and glidant.

7.2.1.3 Bilayer tablets

Bilayer tablets were prepared using various formulations of Simvastatin and Lisinopril. Initially weighed quantity of sustained release formulation of Lisinopril was added to die cavity then slightly compressed to get uniform layer and form loose bond between them. The tablet was compressed finally by adding layer of Simvastatin. Also color to immediate release layer useful for identification and observation of dissolution of final bilayer tablets.

Granules for immediate release Simvastatin tablets showed angle of repose (<33) indicate good flow properties of the granules, Carr's index < 20 indicates good flow properties.

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Table No.16: Precompression evaluation parameters for immediate release layer of Simvastatin

Formulation	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner Ratio
S1	0.6217±0.02	0.6993±0.01	30.9±0.02	11.0%	1.12
S2	0.5570±0.02	0.6189±0.02	29.5±0.01	10.0%	1.11
S3	0.5577±0.04	0.6458±0.04	28.1±0.01	13.6%	1.15
S4	0.5729±0.04	0.6493±0.03	30.8±0.03	11.7%	1.13
S5	0.6026±0.03	0.7156±0.05	33.5±0.03	15.7%	1.18
S6	0.5698±0.01	0.6368±0.02	30.7±0.02	10.5%	1.11

Each sample was analyzed in triplicate (n=3)

The results of angle of repose (< 30) indicate good flow properties of the Sustained release powder blend This was further supported by lower Carr's index index values. Carr's index values up to 20% result in good to excellent flow properties. All the drug and excipients were found good to excellent flow properties.

VIII. SUMMARY & CONCLUSION

8.1 Summary

The aim was to design bilayer tablets of Simvastatin and Lisinopril to give immediate release of Simvastatin and sustained release of Lisinopril . The immediate release of Simvastatin granules was prepared with different super disintegrants like Cross povidone. sodium starch glycolate and croscarmellose sodium and Lisinopril the sustained release layer prepared by direct compression techniques using different polymer HPMC K100M and ethyl cellulose (with different ratio of HPMC K100M and ethyl cellulose) as the release retarding polymers. Preformulation studies were performed prior to compression. The bilayer tablets were evaluated for various parameters. Thickness of bilayer tablets ranges from 3.92-4.01 mm The hardness of these bilayer tablet ranges between 6.8- 7.5 kg/cm Percentage buoyancy was in the range of 88- 99.27%. Results of the in vitro drug release indicated that the Simvastatin released in 30 mins & Lisinopril released in 12 Hrs. Results of in-vitro release profile indicated that Immediate release layer formulation S2, S5 and S6, and Sustained release layer formulation L3, L5 and L6 were the most promising formulations as the extent of drug release from this formulation was high as compare to other Immediate release layer formulations up to 30 mins. and sustained release layer formulations up to 12 hrs. The in vitro release of Bilayer tablet of Simvastatin & Lisinopril were found in the release of drug from the bilayer tablet depends on the different super disintegrants and different concentration of polymer were used As per all satisfactory evaluation parameters, the batch S6 and L6 is found to be optimized batch The IR spectrum studies revealed that there was no disturbance in the principal peaks of pure drugs. This further confirms the integrity of pure drugs and no incompatibility of them with excipients.The stability studies were carried out for the optimized batch for one month and it showed that there was no change in the formulation after 30 day

8.2 Conclusion

It can be concluded that the preparation of bilayer tablets using combination of two drugs Simvastatin and Lisinopri lwith immediate release of the former and sustained release of the later has been achieved for the treatment of antihypertensive and hypercholesteremia. By using this polymer HPMC K100M and ethyl cellulose concluded that increase the drug release of Lisinopril up to 12 hrs. and croscarmellose sodium as a super disintegrant for immediate release of Simvastatin up to 30 min. The various pre-formulation studies like bulk density, tapped density, carr's index,

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angle of repose of granules and powder drug and polymer are compatible with each other that studied. By formulating Simvastatin and Lisinopril we can improve stability of formulation, fixed dosing, increase patient compliance & also bioavailability of drug.

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