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A REVIEW ON SUSTAIN RELEASE BILAYER TABLET

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ABSTRACT

Bilayer Sustained release tablets are widely used for sustained release drug delivery system. Sustained release tablets enhance patient compliance by minimizing dose frequency and increase stability by protecting the active ingredient from hydrolysis and degradation. It releases drugs at fixed and expected rate in a controlled manner either by dissolution or diffusion control mechanism. The active content is uniformly dispersed in the rate controlling agent i.e. polymers, which may be hydrophilic, plastic, lipid, or mineral. The polymer acts as release rate retardants. Hence it controls drug blood level with uniform therapeutic level and avoid fluctuation thus prevent local or systemic adverse reactions. The various approaches for matrix tablet preparation, polymers, factors and evaluating methods are discussed in this review.

Keywords: Matrix tablets, Sustained release, Hydrolysis, Dissolution, Diffusion, Hydrophilic, Polymer

INTRODUCTION

HYPERTENSION:

Cardiovascular (CV) morbidity and mortality are significantly increased by hypertension. Heart failure, coronary artery disease, renal failure, and stroke are among the cardiovascular problems that are less common when blood pressure (BP) is lowered using antihypertensive drugs (1). Two-thirds of the estimated 1.28 billion adults with hypertension globally, who are between the ages of 30 and 79, reside in low- and middle-income nations. Men, women, and the combined group all had pooled prevalence rates of hypertension of 23.66% (95% CI: 23.25 to 24.07%), 23.37% (95% CI: 22.99 to 23.75%), and 16.68% (95% CI: 16.10 to 17.28%), respectively (2) In India, the prevalence of hypertension is rising, particularly among young people and those living in rural areas. The Fifth National Family Health Survey (NFHS-5) and the Indian Council of Medical Research-INDIAB surveys have revealed significant regional differences in the incidence of hypertension, with higher prevalence in the nation's more developed states and districts (3).Currently, there are five primary kinds of antihypertensive medications available:

diuretics (primarily thiazides and thiazide-like diuretics), b-blockers, calcium channel blockers (CCB), and angiotensin II receptor blockers (ARBs) (4).

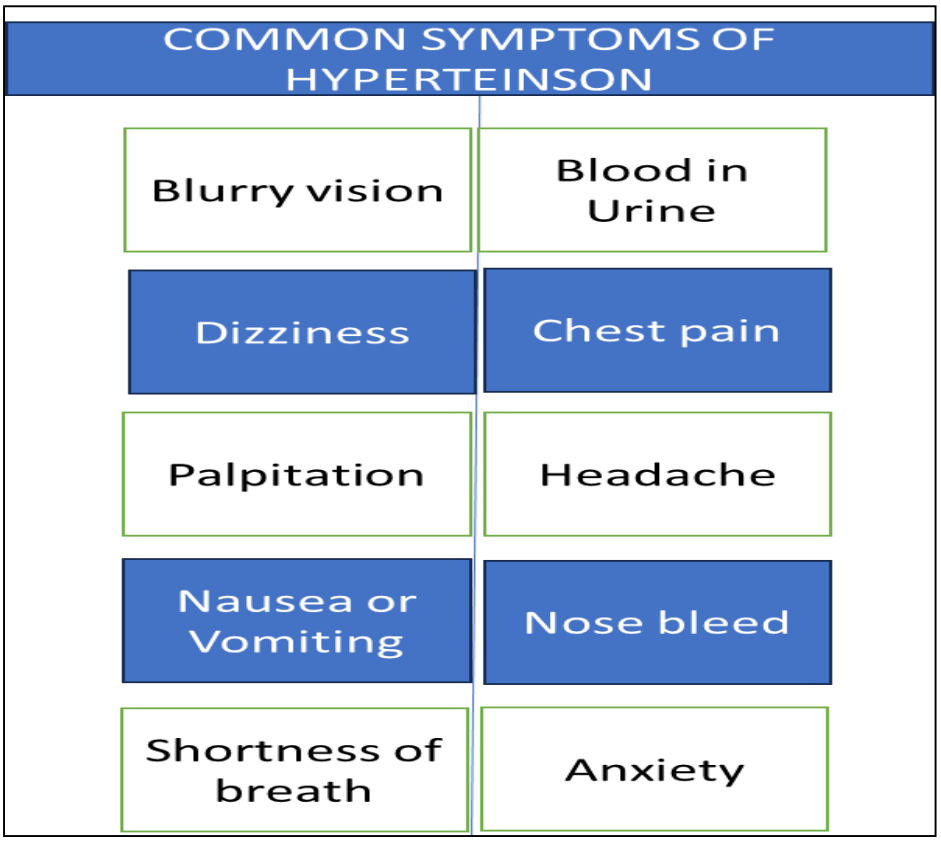

Figure1:Symptoms of Hypertension

PATHOPHYSIOLOGY OF HYPERTENSION

Hypertension is characterized as severe rise of blood pressure therefore causing an increased morbidity and mortality. Here Vascular tone may be increased due to α- adnereceptor stimulation or high release of peptides like Epinephrines and Norepinephrines. The terminal route shows an elevated amount of systolic calcium within the vascular smooth muscle leading to vaso constriction. Various growth factors like angiotensin and endothelins causes a rise of mass in smooth vascular muscles known as vascular remodeling. Elevation of systemic vascular resistance and vascular stiffness argument the load imposed on the left ventricle, which further causes dysfunction hypertrophy and diastolic function in the left ventricular region(5).

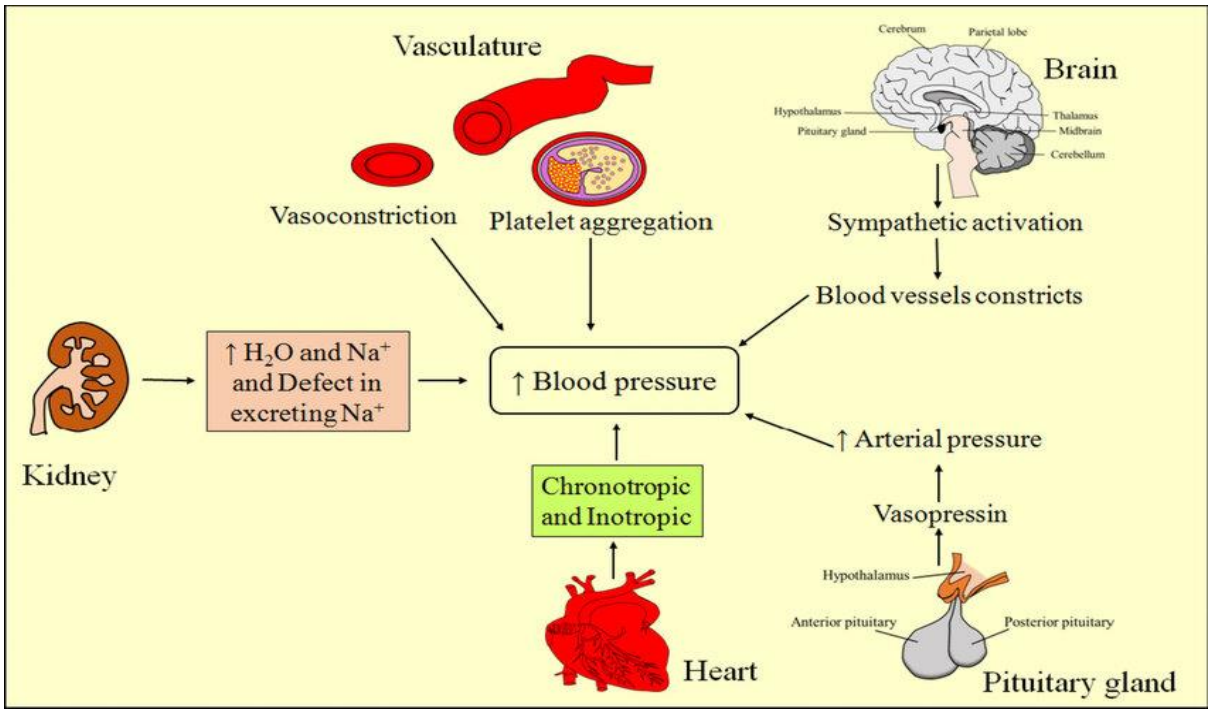

Figure2: Pathophysiology of Hypertension

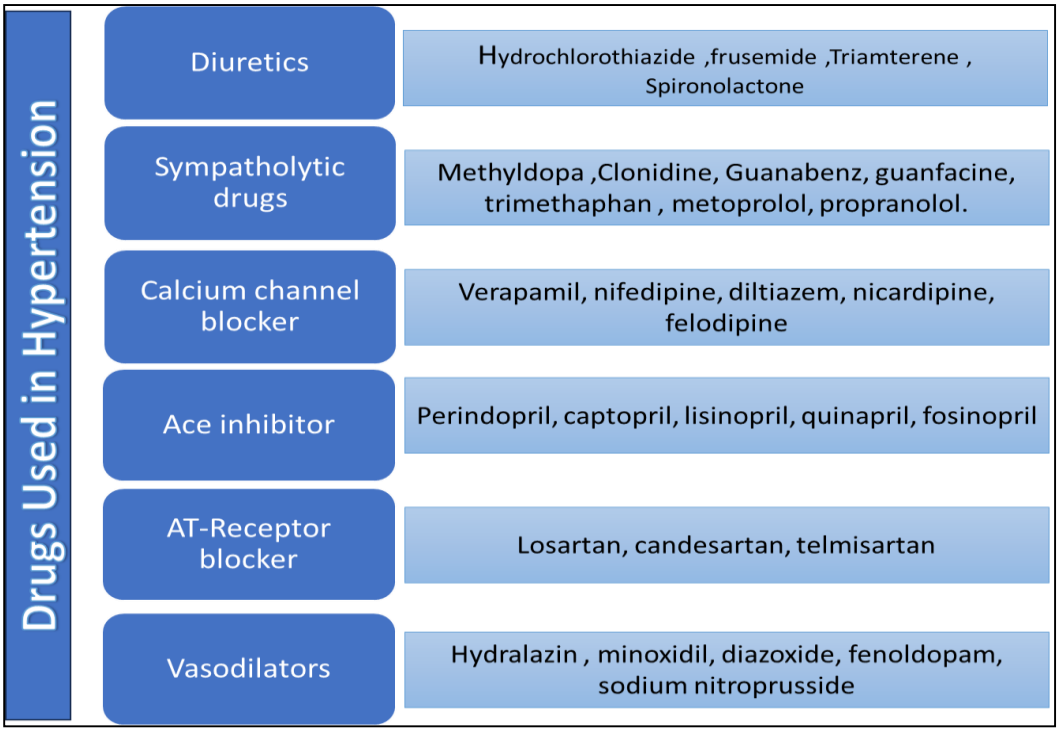

Figure3: Drugs used in hypertension

VALSARTAN

The ARB valsartan is one among them. It binds to type 1 receptors 30,000 times more frequently than type 2 receptors[6]. Valsartan mainly influences pharmacological action by lowering aldosterone production and AII-induced vasoconstriction since it is highly specific for the AT1 receptor. Valsartan and other ARBs block the effects of AII on NADPH oxidase, reducing the quantity of ROS generated [7].

Valsartan is extremely insoluble in water, only slightly soluble in methylene chloride, and readily soluble in anhydrous ethanol and methanol [8]. Valsartan can be used beside other heart failure therapies in place of an ACE inhibitor or another kind of angiotensin II receptor blocker (ARB)**[9].**

Structure of valsartan:

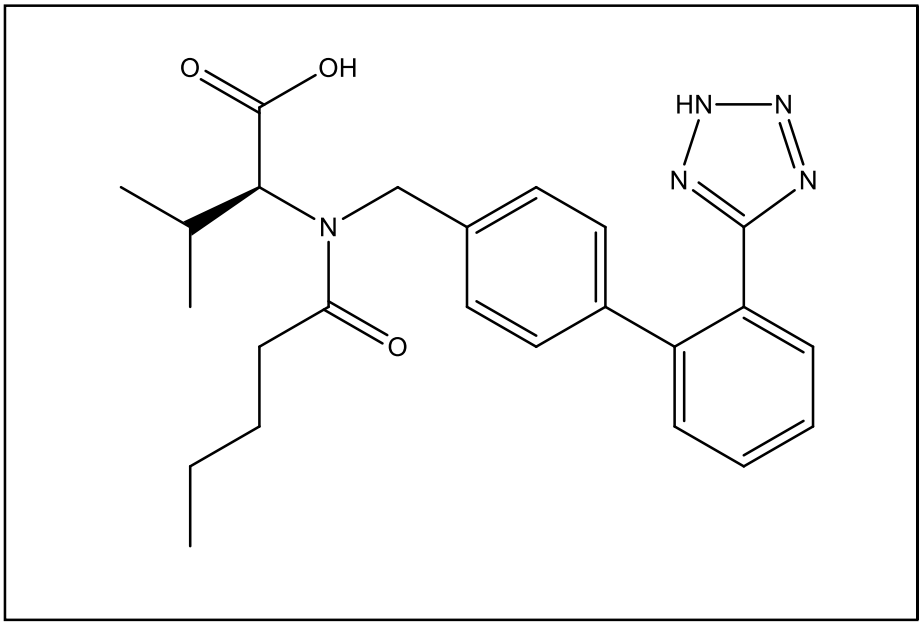

Figure4: Structure of Valsartan

Drug Profile:

- **Chemical name:** N-(-1-oxopentyl)-N-[[2'-(1H-tetrazol-5 yl) [1,1'-biphenyl]-4-yl] methyl]-L-Valine.
- **Category** : Cardiovascular Agent
- **Sub Category:** Angiotensin 2 Receptor Antagonist
- **Molecular weight**: 435.5
- **Proprietary name:** Diovan:Tareg

Mechanism of Valsartan

Valsartan selectively and competitively inhibits the AT1 receptor subtype, which is responsible for most of the actions of angiotensin II that are now known [10].

Plenty of research has been done on the role of AT1R (Ang II type 1 receptor) in mediating the classical effects of Ang II, including vasoconstriction, inflammation, oxidative stress, hormone production, and stimulation of renal tubular sodium reabsorption. The AT2R (Ang II [angiotensin II] type-2 receptor) is a component of the renin-angiotensin system (RAS) that is not as widely known. Even though AT2R was discovered and cloned in the early 1990s, its pathophysiological function is still being investigated, and the significance of these roles is ever-changing.AT2R belongs to the GPCR (G protein-coupled receptor) family [11].

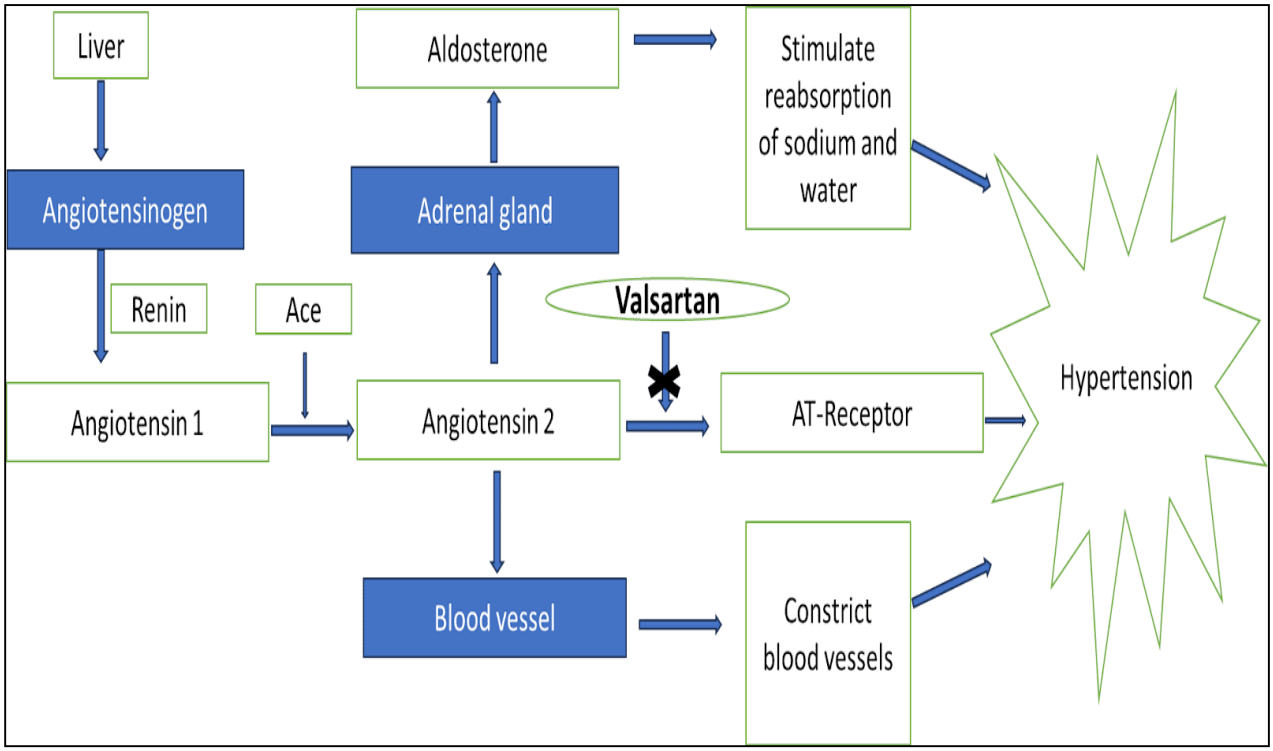

Figure 5: Mechanism ofAction of Valsartan

Polythiazide

Benzthiadiazines as a new class of diuretics. Polythiazide occurs as a white crystalline substance with a molecular weight of 439.9 and a melting point 214-215^{O}C. The compound is insoluble in water but dissolves readily in alkaline solution [12]. Chemically, it is 2- methyl- 3,4 - dihydro- 3 -(2,2,2 -triftuoroethylthiomethyl) -6- chloro -7-sulfamyl-l ,2,4 -benzothiadiazine-l, I-dioxide [13].Polythiazide has a duration of action of 24 to 36 hours, so that the patient would have continuous effect from polythiazide on daily dosage. It is also my experience that 2 mg of polythiazide is equivalent to about 1,000 mg of chlorothiazide [14].

Molecular Weight: 439.882

Chemical Formula: $C_{11}H_{13}ClF_3N_3O_4S_3$

Structure:

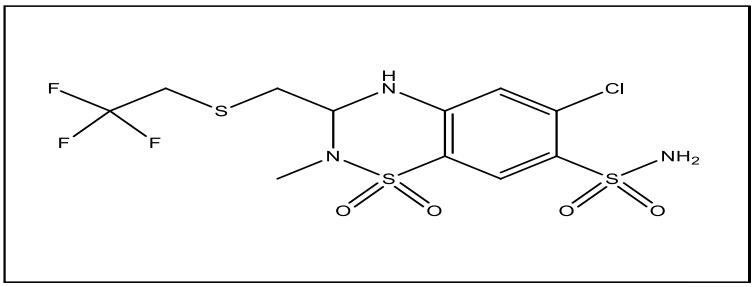

Figure 6: Structure of Polythiazide

Mechanism of Action

As a diuretic, polythiazide inhibits active chloride reabsorption at the early distal tubule via the thiazide-sensitive Na-Cl cotransporter (TSC), resulting in an increase in the excretion of sodium, chloride, and water. Thiazides like polythiazide also inhibit sodium ion transport across the renal tubular epithelium through binding to the thiazide sensitive sodium-chloride transporter. This results in an increase in potassium excretion via the sodium-potassium exchange mechanism. The antihypertensive mechanism of polythiazide may be mediated through its action on carbonic anhydrases in the smooth muscle or through its action on the large-conductance calcium-activated potassium (KCa) channel, also found in the smooth muscle[15, 16].

Table :1 Activity of diuretics

Abacavir	Polythiazide may increase the excretion rate of Abacavir which could result in a lower serum level and potentially a reduction in efficacy.
Abaloparatide	Abaloparatide may increase the hypotensive activities of Polythiazide.
Abciximab	The therapeutic efficacy of Abciximab can be decreased when used in combination with Polythiazide.
Acarbose	The therapeutic efficacy of Acarbose can be decreased when used in combination with Polythiazide
Acebutolol	The therapeutic efficacy of Acebutolol can be increased when used in combination with Polythiazide.

SUSTAINEDRELEASE:

The important role of a novel drug delivery system that improves the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and or targeting the drug to the desired site. Any drug delivery system aims to provide a therapeutic amount of drug to the specific site in the body to achieve promptly and then maintain the desired drug concentration. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance, such as the type of delivery system, the disease being treated, the patient, the length of therapy, and the properties of the drug. Sustain release system includes any drug delivery systems that achieve slow release of a drug over a prolonged period [17].

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and

retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), Hydroxyethyl cellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene oxide) and crosslinked homopolymers and copolymers of Acrylic acid. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface [18].

Matrix tablets are solid oral medications where the active drug is uniformly dispersed or dissolved within either hydrophilic or hydrophobic polymeric matrices. These tablets are designed to provide sustained or controlled release of the drug, ensuring consistent therapeutic levels in the bloodstream for an extended duration. Hydrophilic polymer matrices are commonly employed in these formulations due to their ability to achieve desired drug release profiles, cost-effectiveness, and widespread regulatory acceptance. The release of the drug from hydrophilic matrices involves a complex interplay of dissolution, diffusion, and erosion mechanisms. Matrix tablets are preferred for sustained-release formulations as they involve minimal processing variables, utilize standard manufacturing facilities, and can accommodate large drug doses. There is ongoing interest in developing innovative formulations that achieve sustained drug release using readily available and affordable excipients through matrix-based formulations [19].

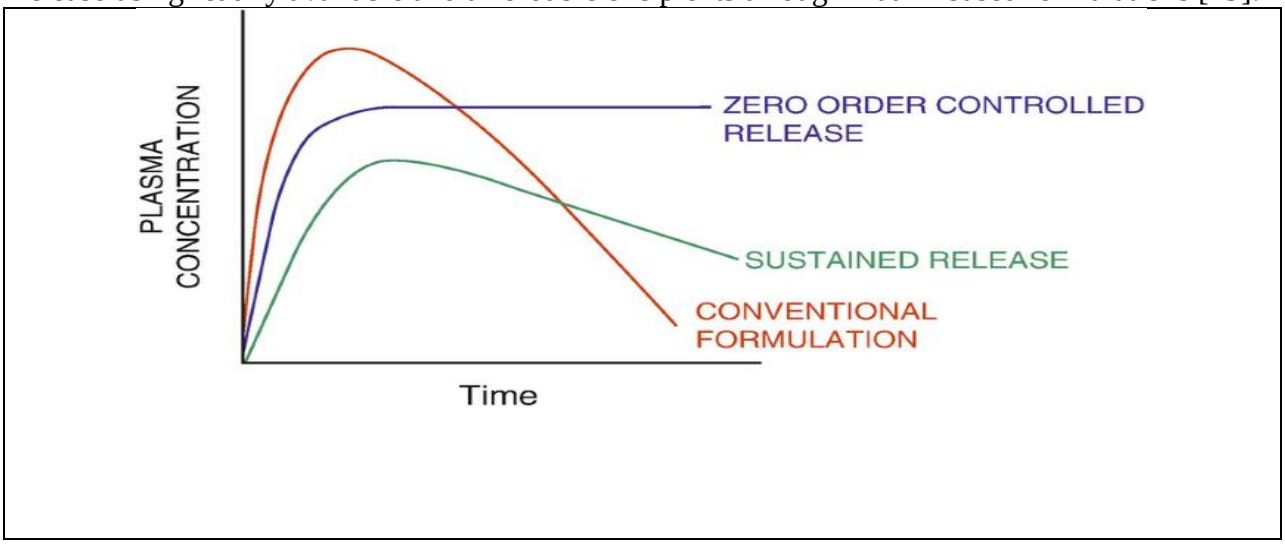

Figure 7: Plasma drug concentration vs time profile for sustained release formulation

Conventional tablet or capsule formulation and zero order-controlled release formulation.

To ensure that the therapeutic concentration of the drug in the body remains constant, two conditions must be fulfilled, namely:

- **a.** The zero order rate of drug release must determine the absorption rate of the drug, and
- **b.** The rate at which the drug is released from maintenance dose (and subsequently the absorption rate) should be equal to the rate of drug elimination at the required steady-state concentration a list of important terms that describe different modified release dosage forms are defined below [20].

1. Modified release dosage forms

Those dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic and/or convenience objectives not offered by conventional dosage forms.

2. Controlled release

The drug is released at a constant (zero order) rate and the drug concentration obtained after administration is invariant with time.

3. Delayed release

The drug is released at a time other than immediately after administration.

4. Extended release

Slow release of the drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time usually between 8 and 12 hours.

5. Prolonged release

The drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

6. Repeat action

Indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

7. Sustained release

The drug is released slowly at a rate governed by the delivery system [21].

Figure 8: Comparison between conventional and sustained-release drugs

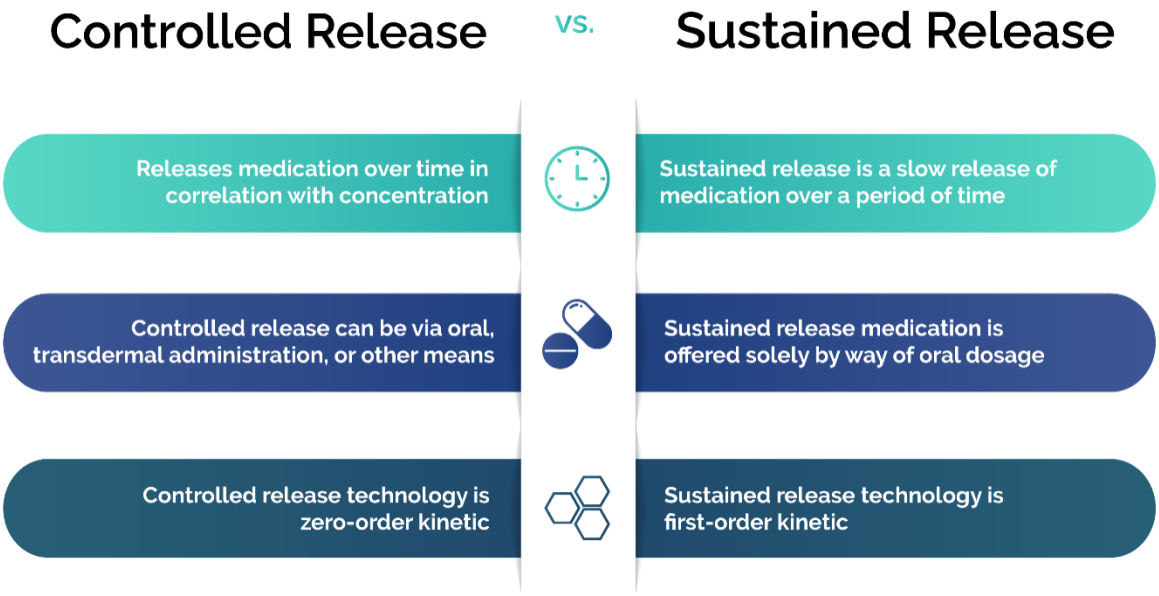

Figure 9: Controlled and sustained release comparison

Criteria to be met to incorporate the drug in sustained release dosage form: [22]

Table 2: Physicochemical parameter for drug selection

S.No.	Parameters	Criteria
1.	Molecular size	< 1000 Daltons
2.	Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
3.	Apparent partition coefficient	High
4.	Absorption mechanism	Diffusion
5.	General absorbability from all GI segments	Release should not be influenced by pH and enzyme

Table 3: Pharmacokinetic parameter for drug selection

S No.	Parameters	Comments
1.	Elimination half-life	Between 2 to 8 hrs
2.	Absolute bioavailability	Should be 75% or more

3.	Absorption rate constant(Ka)	Must be higher than release rate
4.	Apparent volume of distribution (Vd)	Larger Vdand MEC, larger will be the required dose
5.	Total clearance	Not dependent on dose
6.	Elimination rate constant	Required for design
7.	Therapeutic Concentration (Css)	The lower CSS and smaller Vd, the less amount of drug required
8.	Toxic concentration	Apart the value of MTC and MEC safer the dosage form

Bilayer Tablet Technology as a Sustain Release Drug Delivery System:

Conventional monolayer tablets however have the limitations of frequent dosing and unpredictable absorption window that may result in wide range of fluctuation in drug concentration in the blood stream and tissues, with subsequent undesirable toxicity and poor therapeutic efficiency. These limitations have led to the concept of controlled drug delivery system; even though controlled drug delivery systems sometimes fail to achieve adequate release of the initial bolus and site specific drug delivery or may result in dose dumping. On the basis of these considerations, the bi-layer tablet was proposed [23].

Bilayer tablets are a type of oral solid dosage form consisting of two layers of compressed powders or granules of different drug substances that are arranged in a sandwich-like structure. The bilayer tablet is designed in a way that each layer can be made of different drug formulations, allowing for a combination of drugs with different release profiles or therapeutic effects [24].

Bilayer tablet releases two drugs in combination sequentially, it is suitable to separate two incompatible drugs and also for sustained release tablet in which one layer is immediate release (IR) as initial dose and second layer is sustained release layer as maintenance dose. Bilayer tablets have been developed to attain controlled delivery of various drugs with pre-determined release profiles **[25]**

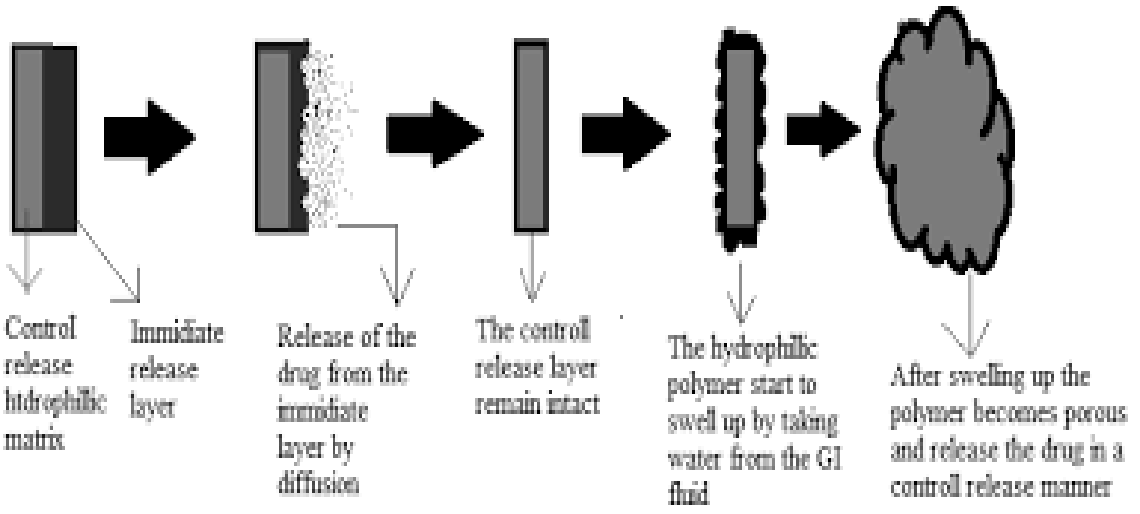

Figure 10: Bilayer Tablet Technology as a Sustain Release Drug Delivery System:

Need of developing bi-layer tablets

For the supervision of fixed dose combinations of drugs, prolong the drug product life cycle, manufacture novel drug delivery systems such as floating or mucoadhesive bilayer tablets for gastro - retentive drug delivery systems.

1. Controlling the delivery rate of either single or two different active pharmaceutical ingredients (API'S).
2. To adapt 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 controlled release.
3. To divide the API's which are incompatible with each other, & to control the release of one layer by using the functional property of the other layer (such as osmotic property) [25].

Advantages of Bilayer sustained release tablet:

- Flexible concept.
- Coating technology can mask odors and bitterness.
- Cost is inexpensive compared to all other oral dosages form.
- Dosage accuracy and minimal content variation.
- Easier to swallow and less prone to hang-ups.
- Highest chemical and microbial stability.
- Two different drugs with different release pattern can be compressed in single dose.

Disadvantage of bilayer sustained release tablet:

- Due to their amorphous nature and low-densitynature, some drugs are difficult to compress into dense masses.
- cross-contamination may occur between layer.
- Inadequate hardness, delamination, low yield.
- Optimal absorption in Gastro Intestinal Track (GIT) is high.
- Difficult to use bilayer tablet formulations drugs with poor wettability and slow dissolution [26].

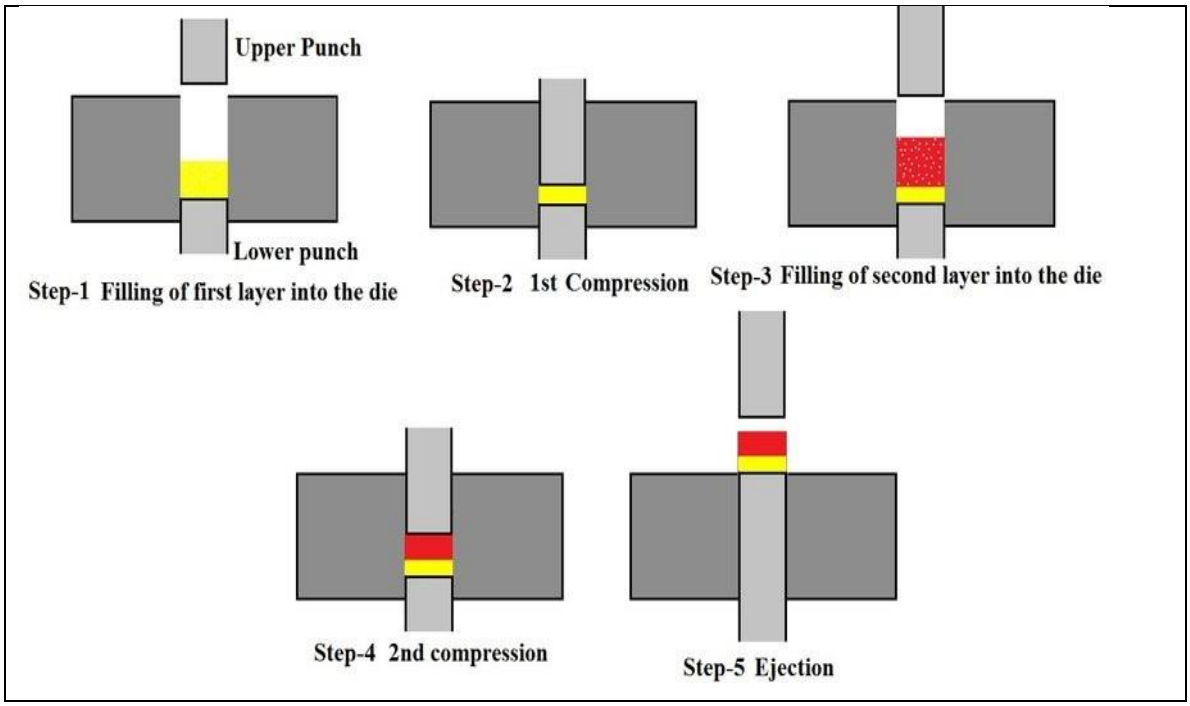

Figure 11: Compression Punching Bilayer Tablet process

TYPES OF BILAYER TABLET PRESS [27,28]

- Single sided tablet press.
- Double sided tablet press.
- Bilayer tablet press with displacemen monitoring.
- Multiple compression

Single sided tablet 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 powers, thus producing the two individual layers of the tablets. 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.

Dwell time: Dwell time is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are a major factor in producing a quality tablet, especially when compressing a difficult formulation.

Compression force: Many bilayer formulations requires a first layer compression force of less than 100 daN in order to retain the ability to bond with the second layer. Above 100daN, this ability may be lost and bonding between both layers may not be sufficient, resulting in low hardness of the bilayer tablet and separation of the two layers.

Limitations of single sided press:

- No weight monitoring / control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping, and hardness problems.

Double sided tablet press:

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 the main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablets and correct the die fill depth when required.

Bilayer tablet press with displacement:

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.

Multiple compression:

The basic press specifically designed for multi-layer compression, or a standard double press can be rebuilt for a multiplier. Multi layer tablets have long been developed delayed formulations such tablets can contain up to triple layers that maintains drug release from tablets. The pharmacokinetic advantage is that the drug release from immediate release granules provides a sudden surge blood concentration, but the blood concentration does not change steady state when drug is released from steady state granules. [27,28].

VARIOUS TECHNIQUES FOR BILAYER TABLET [29,30,31,32,33,34]

Various bilayer tablet techniques are employed to generate the desired quality of bilayer tablets. The techniques involved in this process include:

1. osmotic-release oral system (OROS) push-pull technology,
2. En so troll technique,
3. L-OROS Tm technology,
4. DUROS Technology,
5. Duredas technology/Elan drug technology,
6. Geomatrix technologies,
7. Geminix technology,
8. programmable oral drug absorption system (Prodas), and
9. erodible multilayer drug system.

1. **OROS® (Osmotic Controlled Released Oral Delivery System) push pull technology**

   Mainly this system comprises of either two or three different layers. Here one or two layer will be loaded with drug and rest layer is push layer. Drug layers will be loaded with drugs and other APIs where drug will be in very poorly soluble form. Osmotic agents and suspending agents are further added with it. A semi permeable membrane finally surrounds the tablet core.

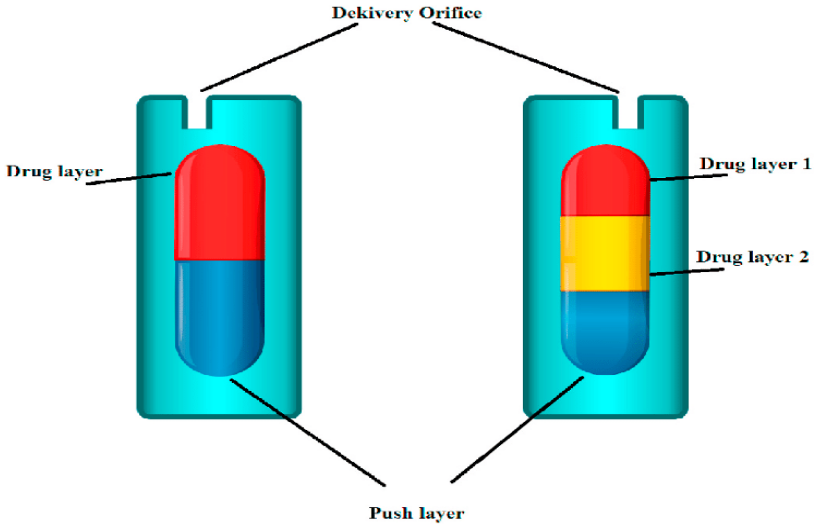

Figure 12: OROS® (Osmotic Controlled Released Oral Delivery System) push pull technology

2. **EN SO TROL technology**

Shire laboratory has developed an integrated approach into drug delivery mainly focusing on solubility enhancement in order of magnitude to create optimized formulation. System is mainly based on identification as well as addition of particular identified enhancer into the controlled released technologies.

RoTab bilayer

Software. It is software related to a modular design that can have extra functions added to it. Fast graphical evaluations can be attained along with accurate results with the help of the advanced PC system having a 15-inch touch-screen.

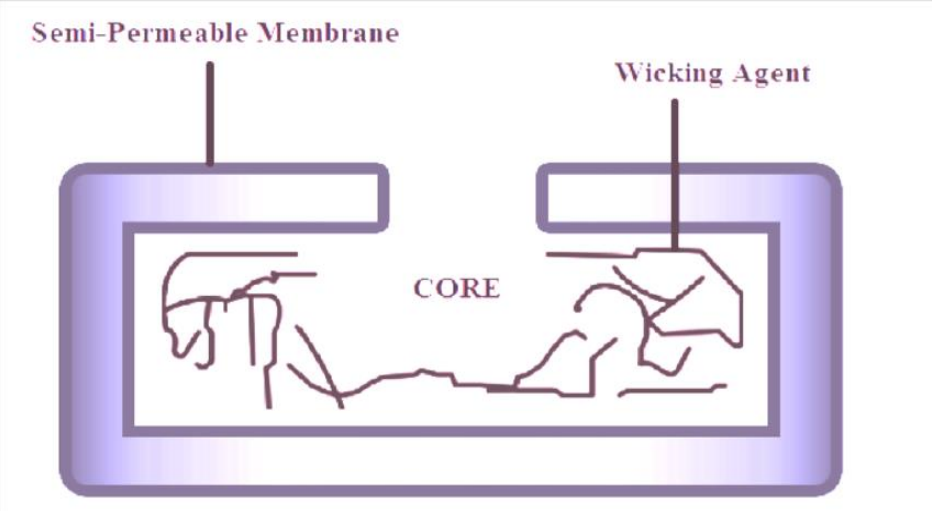

Figure 13: RoTab bilayer

Working. RoTab bilayer is a system that regulates automatically when it is used for the production mode that is switched towards it. It helps in the automatic regulation of the dose and compression force through the adjustment of the filling speed and die table. It also helps in regulating the hardness upon requirement.

R and D modified technique. R and D modified RoTab Bilayer helps in graphical visualization and evaluation with the help of the measuring points on which they are present. These play significant functions, like adjusting the punch tightness. These contain R and D plus along with the likeliness of a sudden up-gradation.

R and D plus. R and D Plus are a significant element in tableting technology and provide improved standards. They help to control the significant functions like controlling punch tightness, forcedisplacement display, and tablet's scraper force [32, 33, 34]

3 L-OROS tm technology

In case of solubility issue, generally this system is used. A soft gel product of lipid is loaded with the drug is manufactured and then coating is done by a barrier membrane followed by osmotic push layer and then a semi permeable membrane and finally drilling with an exit orifice is done.

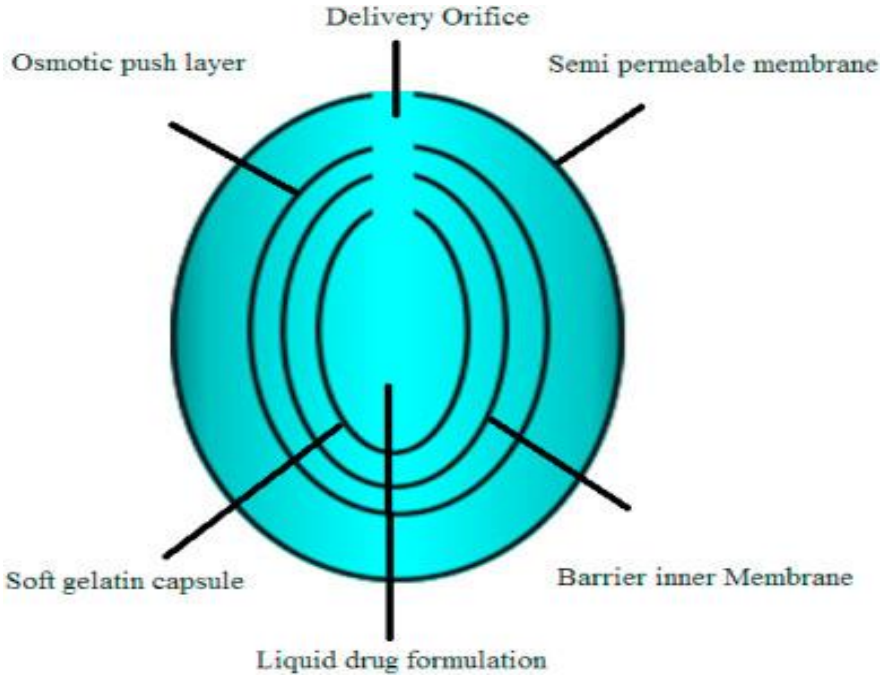

Figure 14: L-OROS tm technology

4. DUROS Technology

An outer cylindrical reservoir of titanium alloy is there in the system. Drug molecules are protected from enzymes by this reservoir and this reservoir has very high impact strength. It is a miniature dispensing system of medicines, which opposes the miniature syringe, amount of concentrated form in consistent and continues from over duration of months or Year.

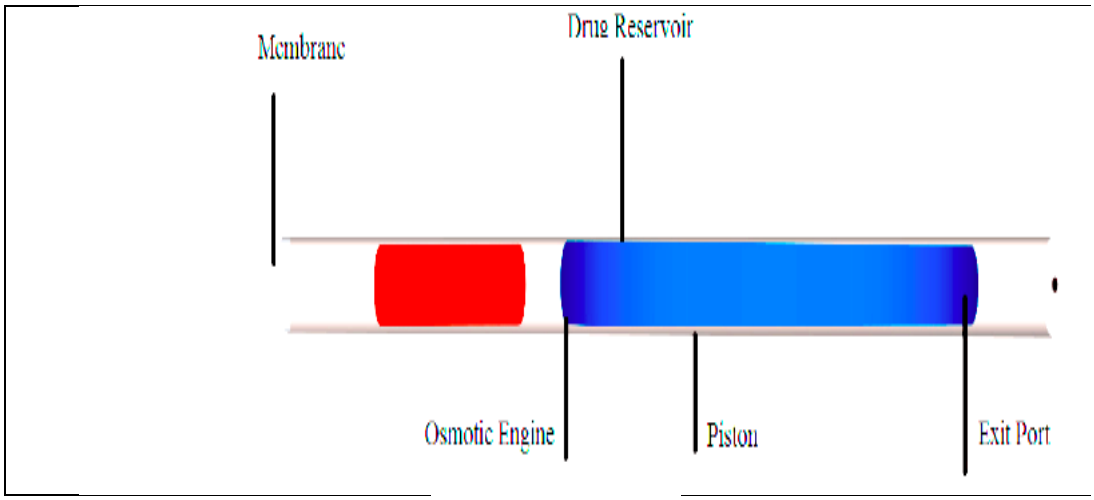

Figure 15: Duros Technology

1. Duredas technology/Elan drug technology (DUREDAS™)

DUREDAS™ Technology is a technology of bilayer tablet formulation that can bring both immediate and sustained release of two or more drugs in combination or with different release pattern in one dosage form. The manufacturing process of the tablet can provide an immediate release granules as well as a hydrophilic matrix complex with modified-released

pattern as separate layers in single tablet. Due to the result of combination of different hydrophilic polymers, the modified released properties can be achieved.

Generally, immediate released granules are first compressed and then controlled released elements are added and compressed onto the previous. The characteristic bilayer effect may be achieved in this way. On the other hand, both the layer may also contain controlled released elements too to maximize the therapeutic effect. As far so many marketed formulations, using this technology has been evaluated. Initially The DUREDAS™ technology was employed for the development of a various OTC controlled release analgesics. Because fast onset of action is needed in case of analgesic. Therefore, immediate release components will be there in one layer and drug release from another layer will be controlled by the application of some hydrophilic polymers. Controlled release of the drugs will be due to the combination of erosion and diffusion via the polymer matrix which is hydrophilic in nature.

5. **Geomatrix technologies**

Geomatrix technology generates a multilayer tablet, wherein an active ingredient is present inside a matrix core surrounded by one or more modulating layers (acting as a barrier) bonded to the central matrix in the course of the tablet generating process. The basic tasks of these obstacles are to avoid contact between core and dissolution medium. The drugs such as diltiazem hydrochloride, nifedipine, and diclofenac sodium are sold through this technology. The eight Geomatrix techniques which are designed to acquire an extensive range of therapeutic objectives are:

- Zero-order release Geomatrix technology is employed for a constant medicine discharge rate over a long duration of time.
- Binary-release geomatrix technology is utilized for the measured discharge of two distinct drugs present in a particular dosage.
- Quick-slow release geomatrix technology involves a fast discharge of dosage tailed by a continual discharge for a specific period.
- Slow-quick release geomatrix technique, this is anti-parallel to the quick-slow release technique. It involves a slow constant release of drug followed by an immediate discharge at a fixed time.
- Positioned released geomatrix technique involves the transport of the medicine to a specific location in the gastrointestinal tract earlier to the discharge of the main dosage.
- Accelerated release geomatrix technology includes the constant accelerating release of the core drug.
- The delayed-release geomatrix technique is utilized when a prearranged time delay of the actual dosage is required.
- Multiple pulse geomatrix technology is employed whereby a prior quick burst is required followed by a prearranged time of no release.

6. **Geminix technology**

This technology helps massively in increasing the therapeutic effectiveness of the drugs while also minimizes their side effects. It delivers one or more drugs having different release rates through a single dose. It is extremely beneficial for patients as well as the industry and is largely used by pen west in for cardiovascular diseases, CNS disorders, diabetes, cancer, and central nervous system (CNS) disorders

7. **Programmable oral drug absorption system (PRODAS)**

PRODAS, also known as multi particulate drug technology (Elan Corporation), encapsulates mini-tablets of controlled drug release, with size ranging from 1.5 to 4 mm. The technology is a combination of multiparticle and hydrophilic matrix tablet technologies and is used for providing the combined benefits of these drugs in one dose. PRODAS technology is beneficial in the targeted delivery of the drugs for targeting to GIT. Different release rates of the mini-tablets, such as immediate, delayed, or controlled release, are combined in the form of a single dosage for providing the wanted release rate. The Minitab are sometimes combined with various APIs for forming products with anticipated release patterns.

8. **Erodible molded multilayer tablet**

The Egalet delivery technology consists of erodible, molded, multilayered tablets. This technology is made according to the standard plastic injection molding and contains a coat and a matrix. The release pattern for the Egalet erodible molded tablets is the erosion of the matrix portion. This technique helps to deliver zero-order or delayed-release pattern of the drug while not affecting the GI conditions [75]. The release pattern of this technology is controlled by the design and engineering of the coat's and matrix's geometry. The drug is spread in the matrix for the zero-order release. Moreover, the coat is biodegradable and has minimal water permeability. The erosion of the matrix happens if it is in contact with the existing water or GI fluids and is promoted by the gut movements in the GI tract. The technique is highly beneficial for the drugs that having issues regarding stability if contacted by water, including chemical and physical stability issues. It also promises reproducibility, accuracy, and low production costs.

EVALUATION PARAMETER OF BILAYER TABLET

1. **Pre-compression Evaluation [35]**

- **Angle of Repose:**

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation.

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

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

- **Bulk Density:**

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing.

- **Compressibility Index:**

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

$$\text{Carr's index } (\%) = [(TBD - LBD)/TBD] \times 100$$

- **Hausner's ratio:**

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula.

Hausner's ratio = Tapped density/Bulk density [35].

2. **Post compression Evaluation**

- **Thickness:**

Thickness of each tablet was measured by using digital Vernier Callipers (Mitutoyo digital Thickness Gauge, Mitutoyo, Japan). Ten tablets of bilayer tablets from each formulation were randomly selected and used for thickness determination. The results were expressed as mean values of ten readings, with standard deviations. According to specification tablet thickness should be controlled within a±5% variation of standard value.

- **Tablet hardness:**
  Bilayer tablets were subjected to hardness measurement by using Monsanto hardness tester (Cad Mach). From each formulation the crushing strength of ten tablets with known weights was recorded in kg/cm2 and average, were calculated and presented with standard deviation. According to specifications of USP hardness values of 5-7 kg/cm2 for bilayer matrix tablet is considered as acceptable limit.
- **Friability:**
  weighed ten bilayer tablets from each batch were taken in Roche friabilator (Secor India). After100 revolutions of friabilator, tablets were recovered. The tablets were then made free from dust and the total remaining weight was recorded. Friability was calculated from the following formula.

$$\%F = (Wi - Wf)/ Wi \times 100$$

  Where Wi and Wf Weight variation test were the initial and final weight of the tablets before and after friability test. For compress tablet, lose between 0.1 to 0.5 % and maximum up to 1% of the tablet weigh are consider acceptable [36].
- **Weight variation:**
  According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130 mg or less is 10% whereas for average weight between 130-324 mg is 7.5% and for average weight more than 324 mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5% and no tablet deviates by more than 15% [37].
- **Swelling index:**
  The swelling index of selected bilayer matrix tablets were determined by placing the tablets in the basket of dissolution apparatus maintaining dissolution medium at 37±0.5 °C. After every one hour interval and up to 12 h, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax 120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.

$$\text{Swelling Index (SI)} = Wf - Wi /Wi \times 100$$

  Where Wf and Wi In-vitro drug release study is called as wet and dry weight of the tablet respectively [36].

CONCLUSION

Oral Sustained release tablet is one of the safe, effective and convenient route dosage forms. Different types of Sustained release system can be design by using different polymers. The successful preparation of matrix tablet system is dependent on various biological and physicochemical parameters of drug and excipients.

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