



**SINGLE PILL COMBINATION THERAPY IN HYPERTENSION BY  
CHRONOTHERAPY APPROACH**

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Article Received on 09/03/2018

Article Revised on 30/03/2018

Article Accepted on 19/04/2018

**ABSTRACT**

Hypertension is one of the serious disease which leads to stroke, congestive heart failure and ultimately leads to death world-wide. The Hypertension is not treated efficiently by single drug thus combination of drug is used for the treatment of Hypertension called single pill combination therapy. Most of the heart patient get die during sleep time between 3 AM to 5 AM due to heart failure which occur due to Hypertension thus to treat the disease at the time when it is at peak, Chronotherapeutic drug delivery system is used which will release the drug in early morning after consuming the dosage form at night time that is after suitable lag time. Various Techniques are used for getting the lag time in Chronotherapeutic drug delivery system like time controlled, stimuli controlled and externally controlled by magnet etc. various dosage form is prepared like core in cup tablet, compression coated tablet. The development of single pill combination in chronotherapy leads to various advantages like decrease in dose of the drug which will leads to decrease side effect, increase patient compliance, disease is treated efficiently.

**KEYWORDS:** Hypertension, Chronotherapy, single pill combination therapy.

**DISEASE: HYPERTENSION**

- Hypertension is defined as sustained systolic blood pressure (SBP) of greater than 140 mm Hg or a diastolic pressure (DBP) of greater than 90 mm Hg.

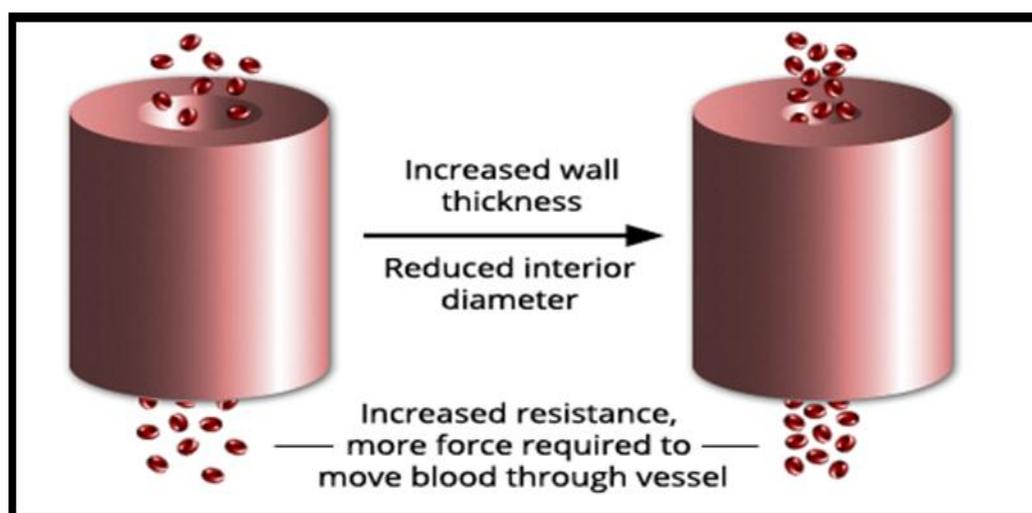


Figure No. 1: Blood vessel of hypertensive patients.

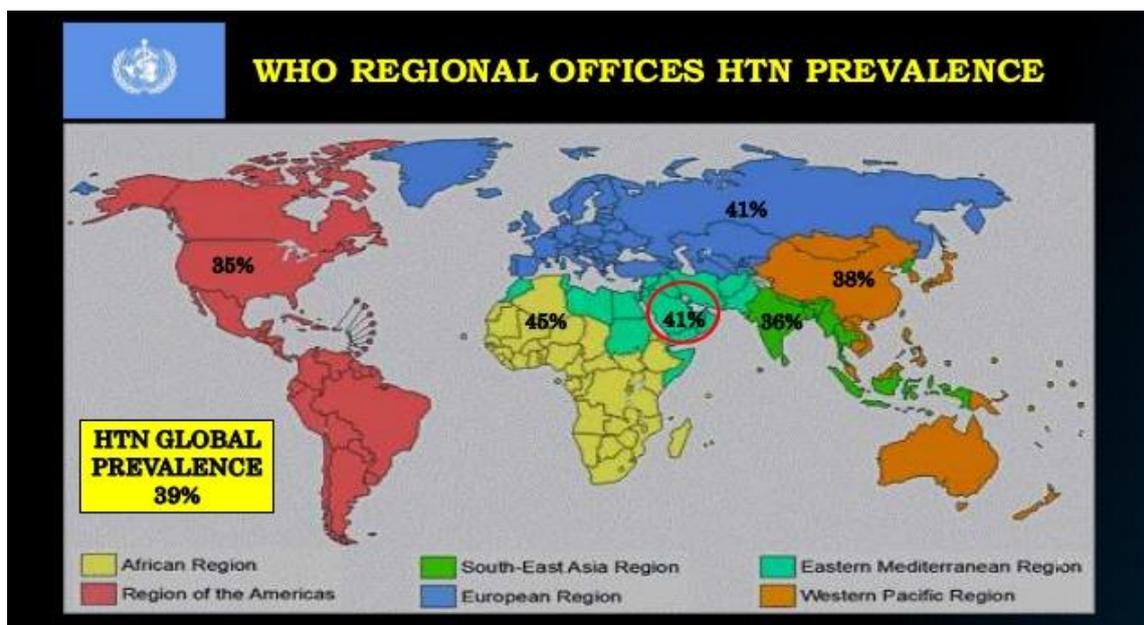


Figure No 2: Hypertension global prevalence.

- Hypertension is the most common cardiovascular disease, its prevalence increases with increase in age. Hypertension is the principle cause of stroke, coronary artery disease and is a major contributor to cardiac failure, renal insufficiency, and dissecting aortic aneurysm.<sup>[1]</sup>
- Hypertension results from increased peripheral vascular smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of venous system to transfer the blood.

Chronic hypertension leads to cerebrovascular accidents like stroke, congestive heart failure, myocardial infarction and renal damage.<sup>[2]</sup>

#### CLASSIFICATION OF HYPERTENSION

A clinical classification of hypertension has been describe by joint national committee of WHO/ International society of hypertension.<sup>[3]</sup>

Table No 1: Clinical classification of Hypertension.<sup>[3]</sup>

CATEGORY	SYSTOLIC (mm Hg)	DIASTOLIC (mm Hg)
Normal	<130	<85
High normal	130-139	85-89
Hypertension		
Mild (stage 1)	140-159	90-99
Moderate (stage 2)	160-179	100-109
Severe (stage 3)	180-209	110-119
Very severe (stage 4)	>210	>120
Malignant Hypertension	>200	>140

#### CLASSIFICATION OF HYPERTENSION<sup>[4]</sup>

- Primary Hypertension: This hypertension is also called essential hypertension or idiopathic hypertension. A number of factors which increase BP are (1) obesity (2) insulin resistance, (3) high alcohol intake (4) high salt intake (in salt-sensitive patients) (5) aging and perhaps (6) sedentary lifestyle (7) stress (8) low potassium intake and (9) low calcium intake.<sup>[5]</sup>

- Secondary Hypertension: This is caused due to other disease like Renal artery stenosis, Renal parenchymal disease, Primary aldosteronism, Pheochromocytoma, Cushing's syndrome, Obstructive sleep apnoea, Medication like oral contraceptives, NSAIDs and steroids will increase the chances of Hypertension.<sup>[6]</sup>

## PATHOPHYSIOLOGY OF HYPERTENSION

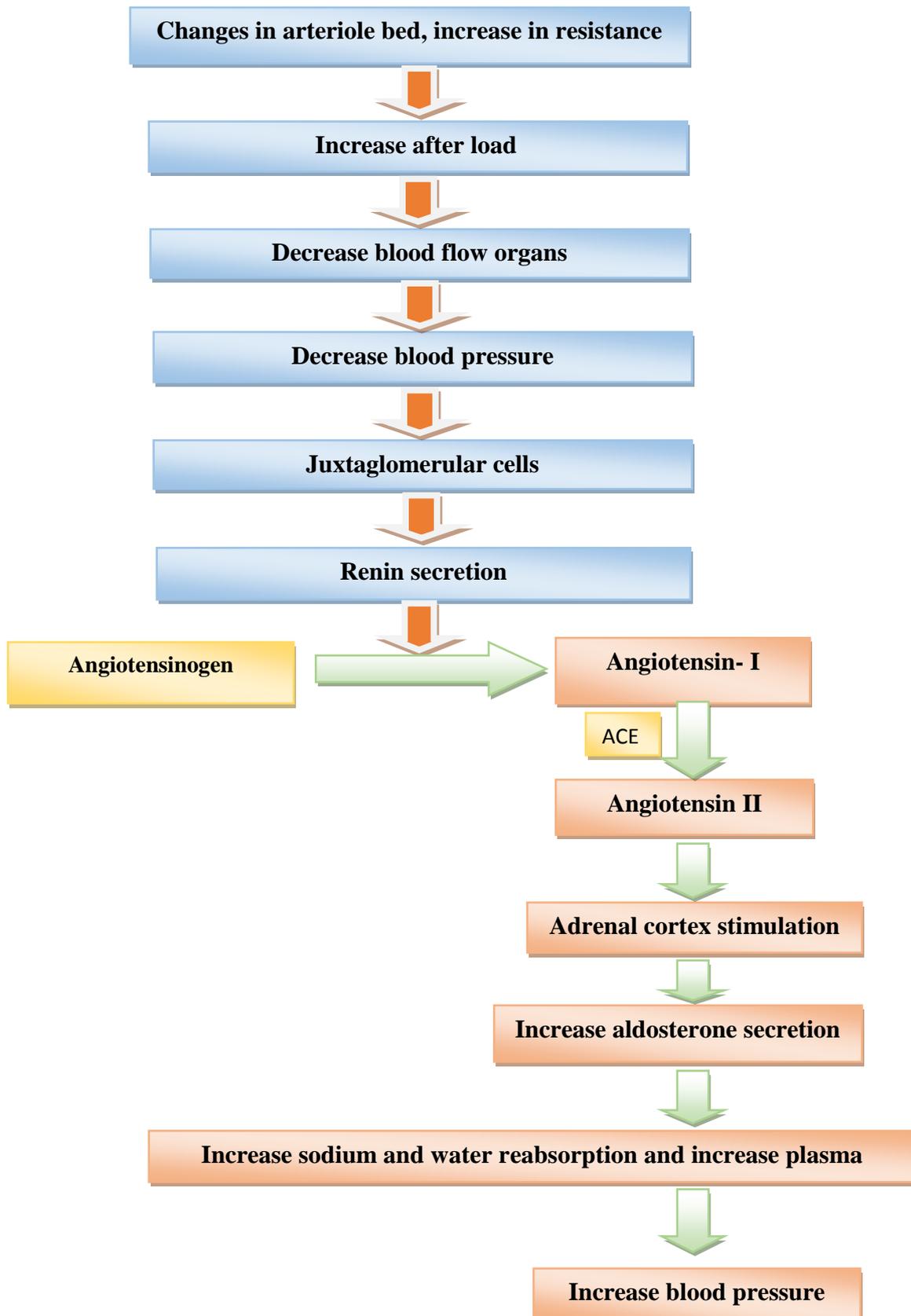


Figure No. 3: Pathophysiology of Hypertension.

**NEED TO TREAT HYPERTENSION**

As hypertension leads to damage to various organs like.<sup>[7]</sup>

- 1. Central nervous system** – Stroke is a common complication of hypertension. Hypertensive encephalopathy is a rare condition characterized by high blood pressure and neurological symptoms including disturbances of speech or vision, fits and loss of consciousness.
- 2. Retina** – It causes hypertensive retinopathy and leads to retinal ischaemia and papilloedema.
- 3. Heart** – Hypertension leads to coronary artery disease. High blood pressure places a pressure load on the heart and may lead to left ventricular hypertrophy. It also leads to atrial fibrillation due to diastolic dysfunction. Severe hypertension causes left ventricular failure.
- 4. Kidneys** – Long standing Hypertension may cause proteinuria and progressive renal failure.

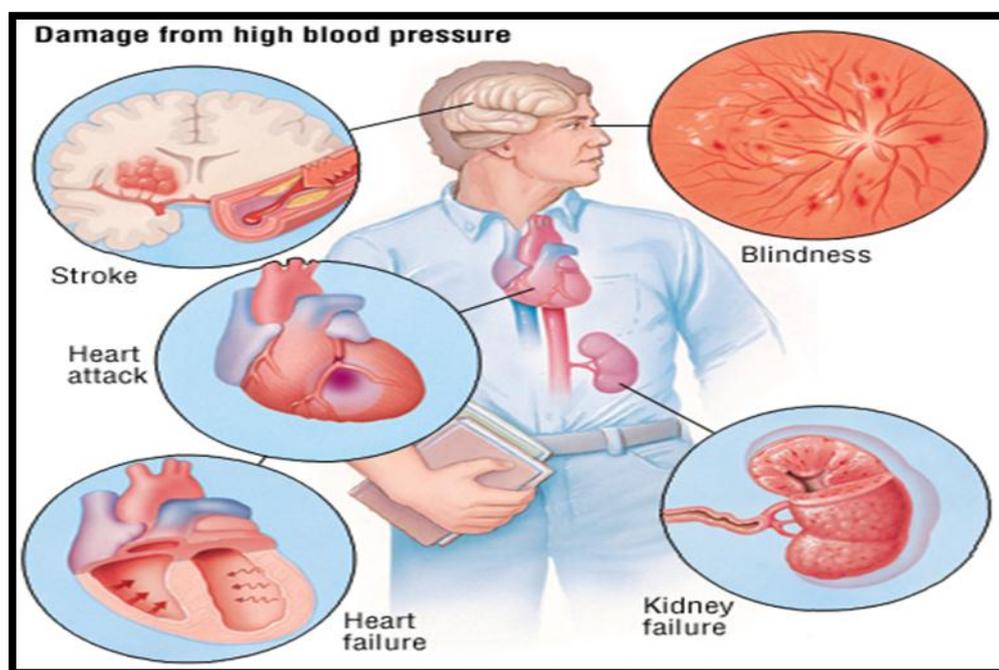


Figure No. 4: Damage due to Hypertension.

**CAUSES, SYMPTOMS AND DIAGNOSIS OF HYPERTENSION****CAUSES OF HYPERTENSION**

- Obesity
- High salt intake
- lack of physical activity

**SYMPTOMS:**

- Headache
- Chest pain
- Vision problem etc

**DIAGNOSIS**

- Sphygmomanometer
- Urinalysis for blood, protein and glucose

**MANAGEMENT FOR HYPERTENSION<sup>[2]</sup>**

Table No. 2: Management of Hypertension.<sup>[2]</sup>

DRUGS	EXAMPLE
Diuretics	Hydrochlorothiazide, <u>Chlorthalidone</u> , Furosemide
Beta-blockers	Metoprolol, Propranolol, Atenolol, Carvedilol, Metoprolol, Timolol
ACE inhibitor	Captopril, Lisinopril, Ramipril
Angiotensin receptor blocker	Olmесartan, <u>Azilsartan</u> , Telmisartan, Candesartan
Renin inhibitor	Aliskerin
Calcium channel blocker	Amlodipine, Nifedipine

### COMBINATION THERAPY

Many times the blood pressure of the patient is not decreased by using the single drug and then the dose of that single drug is increased which leads severe side effects and also there is chances that if the drug is not able to decrease the blood pressure then it might also not be able to treat, at high dose.

If, then also the blood pressure is not reduced then drug is changed, if then also if it is not able to control the blood pressure then single pill combination therapy proves to be beneficial for treating the Hypertension.

### POTENTIAL ADVANTAGES OF COMBINATION THERAPY

- There may be enhancement of each drug's antihypertensive effect, which may be synergistic, rather than simply additive e.g. ACE inhibitors/ARBs and calcium channel blockers.
- Since the single-pill combination exerts its action through different modes of action, there is potential for a smoother onset and longer duration of action.
- By keeping both drugs at low dose the incidence of side effects from each is minimised.
- In some cases the combination of the two drugs can offset each other's side effect profile to some degree e.g. the hypokalaemia caused by thiazide diuretics can be prevented by concurrent use of an ACE inhibitor.
- Different mechanisms may exert different beneficial effects beyond just the benefits of blood pressure reduction e.g. trials have shown certain combination therapies reduce renal damage and cardiac hypertrophy more than monotherapy.
- Combination therapies, particularly low dose therapies.<sup>[8]</sup>

### TREATMENT GUIDELINES<sup>[7]</sup>

Step 1- A or B (younger than 55 years). C or D (for older than 55 years old).

Step 2- A (or B) + C or D

Step 3- A (or B) + C + D

Step 4 – Add either alpha blocker or spironolactone or other diuretic.

**Table No. 3: Abbreviation**

A= ACE inhibitor or ARB blocker
B= Beta blocker
C= Calcium channel blocker
D= Diuretic (thiazide and thiazide like)

### INTRODUCTION TO CHRONOTHERAPEUTIC DELIVERY SYSTEM

#### CHRONOTHERAPY CONCEPT<sup>[9]</sup>

- Some conditions demands release of drug after a lag time, that is a period of no drug release. thus chronotherapeutic drug delivery system is used to deliver the drug, completely after a lag time which will increased patient compliance.

- Chronotherapy refers to the use of circadian, ultradian, infradian & seasonal or other rhythmic cycles in the application of therapy. Circadian rhythm regulates many body functions in humans, like - metabolism, physiology, behaviour, sleep patterns, hormone production etc.
- Lag time is defined as the time between when a dosage form is placed into an any media and the time at which the active ingredient begins to release from the dosage form. These systems are also called time-controlled as the drug released is independent of the environment.
- It is beneficial to give drug at the time when disease condition is at peak at any time of the day like Blood pressure is at peak in early morning so the dosage form is given to deliver the drug at that time also platelets agreeability is higher in morning and also non- dipping pattern is observed in hypertensive patient which will further worsen the hypertension in the patient. So to deliver the drug at that time would be beneficial in the treatment.

#### There are three types of mechanical rhythms in our body<sup>[10]</sup>

1. **Circadian** : The term “Circadian”, coined by Franz Hal berg, comes from the Latin word circa “around”, and diem or dies, “day”, meaning literally “approximately one day”. Our bodies appear to be genetically programmed to function on roughly a 24-hour cycle. These rhythms allow organisms to anticipate and prepare for precise and regular environmental changes.
2. **Ultradian** : These rhythms have period shorter than 24 hours. e.g. 90 minutes sleep cycle.
3. **Infradian** : These rhythms have a frequency ranging from 28 hrs to 6 days. e.g. Monthly menstruation.

**DISEASES REQUIRING CHRONOTHERAPEUTIC DRUG DELIVERY<sup>[11-12]</sup>****Table No. 4: Disease Requiring Chronotherapeutic Drug Delivery System**

DISEASE	CHRONOLOGICAL BEHAVIOUR	DRUGS USED
Peptic Ulcer	In the afternoon and at night Acid secretion is high	H <sub>2</sub> blockers
Asthma	During night or at early morning hour	B <sub>2</sub> -agonist, Antihistaminics
Cardiovascular Disease	Chest pain & ECG changes more common in the midnight, early morning & after awakening	Nitroglycerin, calcium channel blocker, ACE inhibitors etc
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Diabetes Mellitus	Increase in blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Hypercholestrolemia	During night Cholesterol synthesis is generally higher	Atorvastatin (HMG CoA reductase inhibitor)

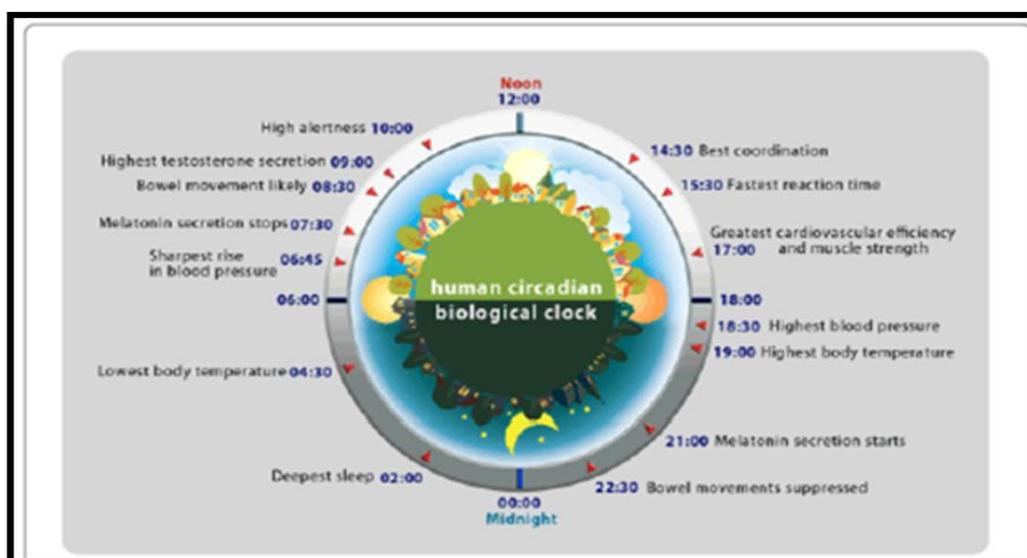
**CHRONOTHERAPY IN CARDIOVASCULAR DISEASE**

Early morning blood pressure is not controlled by giving the antihypertensive drugs once in early morning, when the antihypertensive drugs were given once daily in the early morning.<sup>[13]</sup>

The impact of antihypertensive treatment and the time of therapy according to the circadian pattern of blood pressure in 585 hypertensive patients with diabetes mellitus had studied by the author. Blood pressure was measured at 20 min intervals from 07:00 to 23:00 hour and at 30 min intervals at night for 48 consecutive hour. Blood pressure was reduced during active hour, but not during nocturnal sleep, as compared to untreated patients (P<0.001). Results from this study indicates that there is a need to establish a proper chronotherapeutic pattern that could reduce BP and modify the altered circadian profile into a dipper BP pattern, associated to a lower cardiovascular risk.<sup>[14-15]</sup>

The author had also conducted a chronotherapeutic test for  $\beta$  – blockers to prevent the morning surge of hypertension by evening administration of Carvedilol. In this study, they treated 5 female and 12 male patients with hypertension for 4 weeks at controlled blood pressure. The patients exceeding blood pressure 140/90 mmHg were treated with 10 mg/day carvedilol as single dose in the evening. The studied results revolved that, the morning surge was suppressed with carvedilol and the 24 h mean systolic pressure was also reduced.<sup>[16]</sup>

- Several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms.
- For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day.
- Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood.
- This several factors lead to Hypertension

**Figure No. 5: Chronotherapeutic Rhythm.**

1. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events.
2. Cardiac events also occur with a circadian pattern. Numerous studies have shown an increase in the incidence of early-morning myocardial infarction, sudden cardiac death, stroke etc. The circadian pattern of BP has been well documented. BP is at its lowest during the sleep cycle and rises sharply during the early morning.
3. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive

persons, although hypertensive patients have an upward shift in the profile.

#### DEVELOPMENT OF CHRONOTHERAPEUTIC DELIVERY SYSTEMS

A basic chronotherapeutic system consists of a drug containing core and a barrier layer of polymer to control drug release from the core. Several techniques have been developed and applied to design chronopharmaceutic delivery systems for desired drug release. These techniques are broadly classified into following three major categories.<sup>[17]</sup>

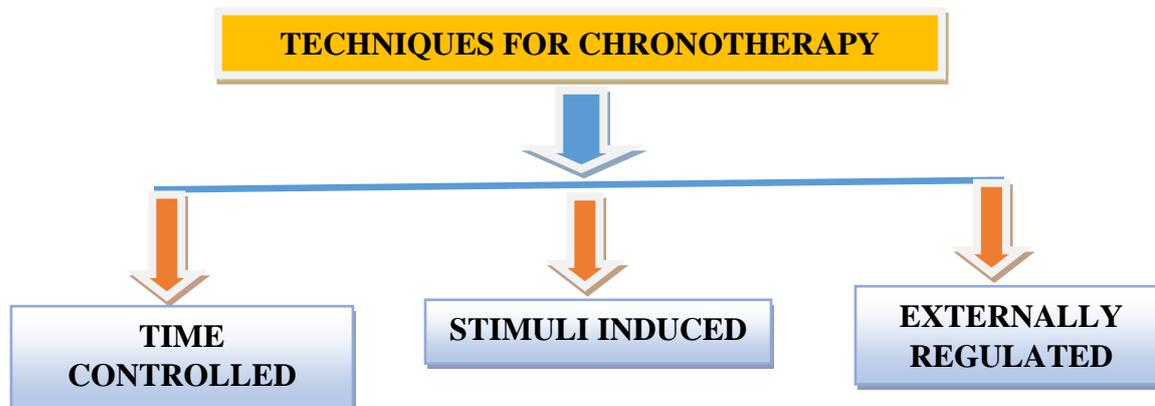


Figure No. 6: Techniques for Chronotherapy.

#### ❖ TIME CONTROLLED CHRONOTROPIC SYSTEMS

The drug is released as a burst within a short period of time immediately after a predetermined off release period.

1. Time controlled chronotropic systems based on capsules
2. Time controlled reservoir systems with rupturable polymer coating
  - Capsule system composed of insoluble body, swellable and degradable plugs of hydrophilic polymer. The lag time is controlled by swellable plug which is pushed after swelling (by absorption of the media) or by erosion and then drug is released from the capsule which is insoluble.<sup>[17]</sup>
  - In reservoir system with rupturable polymer coating, The core is coated with a protective polymeric rupturable layer and an outer layer is of water insoluble semi permeable rate controlling membrane. Various agents like gas producing effervescent agents or osmogens, swelling agents are required to rupture the coating.<sup>[18-21]</sup>

#### STIMULI INDUCED PULSATILE DRUG DELIVERY SYSTEM

In this system drug is released when stimuli will activate the system. This system is mainly used for targeting the drug to specific site in the body. Biological stimuli like release of, hormones, pH of the target site, enzymes, temperature of the site, antibodies, concentration of biomolecules (glucose, inflammatory mediators,

neurotransmitters) etc acts as stimuli to trigger the release of drug from these types of drug delivery systems.

Based on the stimuli it is classified to following classes.

1. pH sensitive pulsatile release chronotropic systems
2. Enzyme catalyzed pulsatile chronotropic systems
3. Chemical stimuli induced pulsatile drug delivery systems
4. Temperature induced pulsatile drug delivery systems

#### ❖ EXTERNALLY REGULATED PULSATILE DRUG DELIVERY SYSTEMS

External stimuli like ultrasound, electrical effect, magnetic field, and irradiation are needed to control the drug release from these systems. By applying this external factors on the delivery system, conductors which are present in the delivery system get sensitized to trigger the release of drug from the delivery system.

#### DOSAGE FORMS USED FOR CHRONOTHERAPY

1. Core in cup tablets

These systems are made up of a core tablet containing active ingredient, an impermeable outer shell and a top cover layer-barrier of a soluble polymer. The cover layer erosion is responsible for drug release.<sup>43</sup>

2. Compression coated/press coated tablets

In this core tablet containing the drug is coated with the powder by compression.

Table No. 5: Some Chronotherapeutic Antihypertensive Products.

Product	Generic name	Manufacturer
InnoPran XL	Propranolol	GlaxoSmithKline, USA
Cardizem LA	Diltiazem	Biovail Corporation Mississauga, Canada
Verelan PM	Verapamil	Schwars Pharma Monheim, Germany
Covera HS	Verapamil	G. D. Searle (a division of Pfizer), NY, USA

**ADVANTAGE AND DISADVANTAGE****ADVANTAGE**

- Improved patient acceptability and compliance
- Minimization of side effects
- Biological tolerance
- Protection of stomach mucosa from gastric irritation drugs
- Drugs with high first pass effects can be delivered efficiently without loss of drug
- Drug targeting to specific sites such as colon is possible

**DISADVANTAGE**

- Lower drug loading.
- Incomplete release.

**DESIGN OF CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM**

Principle – Time dependant drug delivery after the pre-determined lag time.

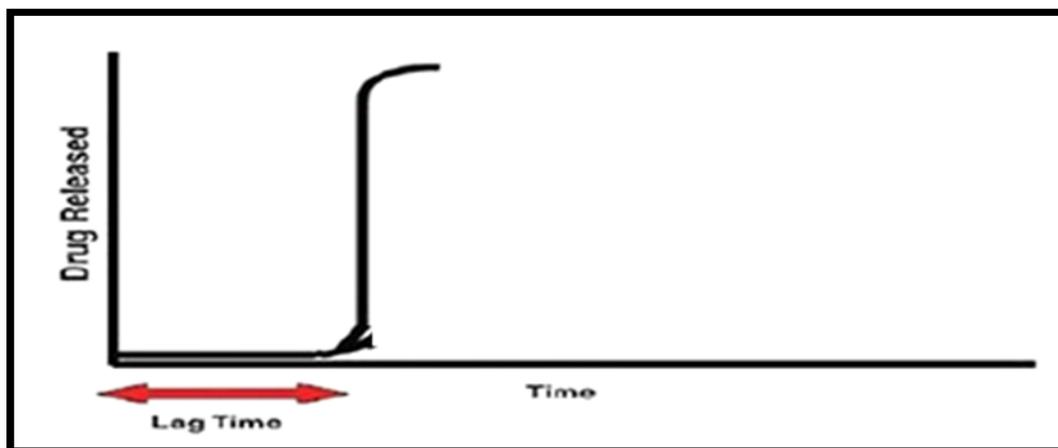


Figure No.7: Principle for chronoherapeutic drug delivery.

**COMPONENT INVOLVE FOR DOSAGE FORM:**

- 1) Drug core : It includes
  - Drug
  - Disintegrant
  - Binder
  - Glidant
  - Lubricant
- 2) Coating of Core tablet.
  - Polymers

**COMPRESSION COATING<sup>[22]</sup>**

- The system in which the entire surface of an inner core having the drug is totally surrounded by the coat these coats prevent drug release from the core until the polymeric or drug coat is fully eroded, dissolved or removed.

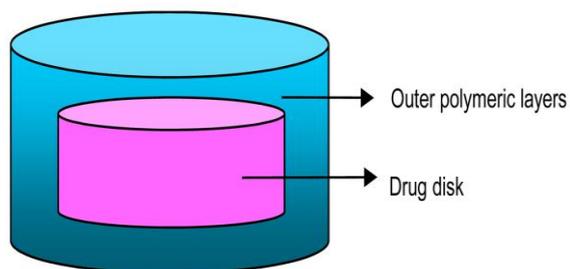


Figure No. 8: Design of Dosage Form.

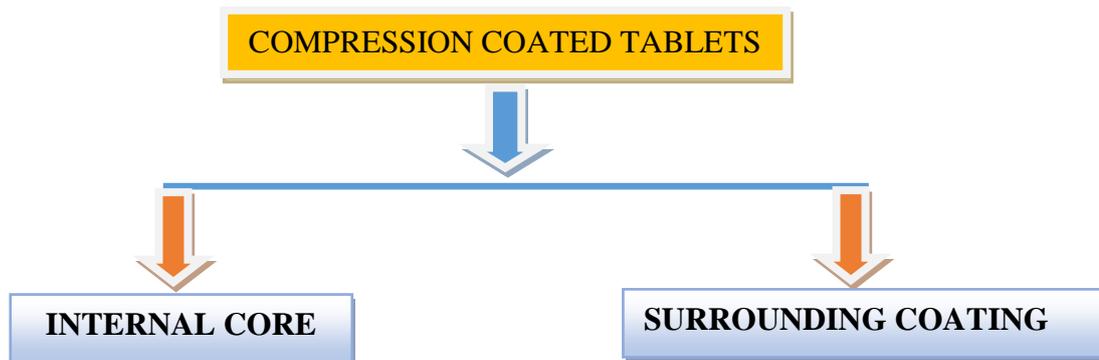


Figure No. 9: Parts of compression coated Tablets

- It is simple and unique technology used to provide tablets with a programmable lag phase, followed by a rapid, or rate controlled drug release. Release of drug depends upon the thickness and the polymer used for coating layer. It has a solvent-free coating and facilitates manufacturing process. It can be used to deliver one or more drugs.

#### ADVANTAGES

- This technique is simple and inexpensive.
- The organic solvents useful in this technique are required in very less quantity and hence the hazard to the environment is very less using this method
- The pharmacokinetic drug-drug interaction can also be avoided by this method
- This technique is a short manufacturing process requires less time as compared to liquid coating.

#### DISADVANTAGES

- The erosion of the core tablet may occur during the second compression of coat
- Specially designed tablet compression machine are required to prepare compression coated tablets
- Polymer mixing during the compression may alter the release pattern of the drug.
- Unequal width of coat diameter may occur in this method.

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