1. INTRODUCTION

The latest developments for Chronotherapeutics for chosen diseases are having the multifunction” focused to drug delivery for suitable bioactive agents and also remedy for the diseases. There is a significant and vital demand for chronopharmaceutical research because it challenges the drug delivery. The chronoformulation illustrates therapeutically designed intended for chronotherapy by time of administration and variation of drug category with reasonable cost, would develop the safe, efficient with patient compliance of newer & older drugs. The formulation of new approaches and technologies for chronoformulation having to success the targeting the diseases.¹

Sequentially to enhance the effectiveness of chronotherapeutic system challenges in drug delivery. The activities of the human body appreciably in a day, so this diversity cause changes each in disease condition and also the drug therapy. The human circadian rhythm which is based on sleep activity cycle and body's functions. The rhythmic changes affected in diseases symptoms and sensitivity.²

Chronopharmacology investigates the drug management and response of body accordingly to the chronological structure in the organism receiving it. Thus, both the quantitative (magnitude of the activity) & qualitative (inhibition & reduction) of its result responses alter with time of administration ³

The Therapeutic activity and toxicity of some drugs are depending on the significant correlation between the dosing interval and the rhythms of biochemical, physiological and behavioral processes of human. Several drugs leading to illness and altered homeostatic regulation for alterations to the 24 hrs circadian rhythms. The appropriate timing of chrono drug delivery system to synchronize drug conc. to rhythms in disease activity. ⁴

1.1 Chronopharmaceutics

It is the idea about chronobiology and also pharmacetics. Chronobiology is the science of biological rhythms with its mechanisms. Biological rhythms are the no. of characteristics. Pharmacetics is concerned with scientific and technological aspects of dosage form design to convince their quality, safety, efficiency, and consistency.
INTRODUCTION

It is a branch of biomedical and pharmaceutical sciences. Simply pharmaceutics converts a drug into medicine. The Chronopharmaceutics is a part of pharmaceutics which is biological requirement for disease therapy towards drug delivery systems which give a bioactive agent at a pulse that matches the biologically rhythms. The goal is to distribute the drug in high conc. in the accurate need of time and in less conc. when the requirement is little to reduce side effects. 

1.2 Ideal characteristics of Chronotherapeutic drug delivery system should:

- Should be non-toxic within standard limits
- Should have actual time and triggering biomarker for a particular disease state
- Should have a feedback control system (e.g., self-regulated and adaptive ability)
- To differentiate between sleep and awake status of individual patients
- Should be cost-effective for manufacture point of view
- Should be easy to administer to patients to improve uniformity to dosage regimen.

1.3 Advantages of Chronopharmaceutics:

Suitable delivery of drug can be attained for chronopharmaceutics that are as follow

(1) **First pass metabolism:** Certain drugs like β blockers, and salicylamide, experience widespread first pass metabolism and need quick drug contribution for saturation of metabolizing enzymes for decrease pre-systemic metabolism. It may be refrained by Chronopharmaceutics.

(2) **Biological tolerance:** Constant release drug plasma profiles are usually lead by a fall in the therapeutic effective of the drug, e.g., biological acceptance of nitroglycerin transdermal.
**INTRODUCTION**

(3) **Special chronopharmacological requirements:** It is documented that various symptoms and onset of disease arise for the duration of particular time periods of twenty four hour day, e.g., angina pectoris and asthma attacks are appear generally in hours of early morning.

(4) **Local therapeutic requirements:** To treat the local disorders like inflammatory bowel disease, the compounds delivery to the site of inflammation without loss as the absorption in the small intestine is very enviable to reach the therapeutic effect, also to reduce the side effects.

(5) **Gastric irritation (drug instability in gastric fluid):** For the compounds of gastric irritation or unstable in gastric pH, using sustained release preparation might overcome the above problems.

(6) **Differences drug absorption in different gastrointestinal segments:** Commonly the drug absorption is reasonably slow in stomach, where as fast in small intestine and declining position in large intestine. For altering absorption, compensation of g.i. tract should have vital for few drugs.

1.4 **Chronopharmaceutics applied in diseases**

Chronobiological studies have recognized by circadian rhythm for human body activities for e.g., heart rate, hypotension, temperature, conc. of plasma of a variety of hormones, colonic pH and kidney function.

1.5 **Chronotherapeutics**

Chronotherapeutics or medication delivery in conc. that change in accordance with physiological want at varoius times in the dose periods, is almost unique practices in clinical medication The advantages of this therapy, that they can make up-to-date decisions on therapeutic strategies of their patients. It may also involve the reforming or restoration of a disordered or reintegrated circadian timekeeping system or time structure by certain group of medications coined ‘chronobiotics’. The aim of chronotherapeutics is to harmonize the timing of treatment with fundamental timing of sickness. The best therapy is more expected to attain when the accurate quantity of drug is delivered to the proper target site at better suitable time. Drug delivery research is of establish preparation to attain therapeutic requirement revealing to certain pathological criteria. The chronopharmacological field has established the
significance of biological rhythms in drug therapy, and it has brought a novel path in development of drug delivery systems. Many processes like physiological, biochemical and molecular level in exhibit robust and expected changes on a 24-hour schedule on healthy organisms. Problem arises with heart diseases like cardiovascular diseases as hypertension and angina pectoris. With benefit of known biological patterns in disease manifestation, the aim of developing chronopharmaceutic products to optimize the needed effects of drug and reduce its unwanted ones, might attained.

1.6 Chronotherapy
It aims to establish the desire maximum drug effect or reducing undesirable side effects by regulating best biological time for dosing to increase the therapeutic index of the drug. The similar drug release with circadian rhythm of body is used as a vital perception for new drug delivery systems for safety and efficacy of drug by adjusting peak plasma conc. of drug with circadian rhythm of body.

1.7 Advantages of Chronotherapy
- Chronotherapy is drug-free
- Additional effective when patient sleep for several hours.
- To improves their condition and confidence of patients fall asleep in this time
- It is different from other treatments because it got the beginning middle, and an end. So one can forecast easily the point at which it will work.
- It gives a new schedule like getting up and sleeping early which will be quite remarkable for some days but it will give a period to adjust psychologically.

1.8 Disadvantages of Chronotherapy
- It develops a non 24 hours sleep wake syndrome after the treatment as the person sleeps for over 24 hours during the treatment.
- Person may also be sleep deprived, less productive during staying awake till the other schedule will be bit uncomfortable.
- some time off from your busy normal schedule as its time taking therapy.
- Medical supervision is mandatory for this therapy and regular consulting of sleep is recommended.
1.9 Concepts and terminology of chronobiology

Chronobiology is defined as the study of biological rhythms and mechanisms of biological timekeeping. It is undoubtedly significant to the area of medicine, pharmacology, and drug delivery system. Clinically proves that degree of extent of predictable-in-time (rhythmic) differences can be so effective that it can be a big determinant in twenty four hour chronic morbid and mortal events arises and symptoms of many severe medical conditions erupt. Moreover other clinical studies illustrate that when a patient is administered for a diagnostic test or medical treatment can be a big determinant of outcome.\(^\text{14}\)

A biological rhythm is endogenous origin with self-sustaining oscillation that is interpreted by characteristics of period, level, amplitude, and phase. The circumstance is arranged in space, in view of its geography, and in time, in view of its cycles, the most obvios being twenty four hour and yearly photo periodicities. Ecological studies illustrates that the same alcove Judy displays a quiet, accurate temporal organization; its performance is developed by various species applying it at various and usually non-overlapping times. Diurnally active species use it in day and nocturnally active species use it in night for complementary intend.\(^\text{15}\)

1.10.1 Period\(^\text{16}\)

It is the time need for completion only one cycle. The range of biological rhythms is broad. Short-period rhythms are usually common; the oscillations of high frequency in the electrical impulses of the CNS and ANS and the high frequency pulsatile secretions of the neuroendocrine system. The intermediate-period rhythms show oscillations for few hours to maximum six days. However, long-period rhythms showing oscillations may be approximately a week, month or year.

(a) Circadian rhythms: The term “circadian” was derived from Latin words “circa” denotes “about” and “dies” denotes “day”. Completions of Oscillations in our body within 24 hours are coined as circadian rhythms.

(b) Ultradian rhythms: - Completions of Oscillations in a shorter duration of < 24 hrs (> 1 cycle /day).
(c) **Infradian rhythms**: Completions of Oscillations in > 24 hrs (< 1 cycle /day)

1.10.1 **Period**

Period is the duration of time required to complete a only one cycle. The range of biological rhythms is broad. Short-period rhythms are quite common; the high frequency oscillations in the electrical impulses of the central and autonomic nervous systems and the high frequency pulsatile secretions of the neuroendocrine system. The intermediate-period rhythms show oscillations for few hours to as long as 6 days. However, long-period rhythms showing oscillations may be approximately a week, month or year.

(a) **Circadian rhythms**: The term “circadian” was obtained from Latin words “circa” meaning “about” and “dies” meaning “day”. Oscillations in our body that are completed within 24 hours are termed as circadian rhythms.

(b) **Ultradian rhythms**: The oscillation that have completed in a shorter duration of less than 24 hours (more than one cycle per day).

(c) **Infradian rhythms**: The oscillation that have Oscillations that are completed in more than 24 hours (less than one cycle per day).

<table>
<thead>
<tr>
<th>Period (τ)</th>
<th>Major rhythmic components</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short</strong> [τ&lt;0.5 h]</td>
<td>Pulsatiles (0.1s &lt; τ &lt; 1s)</td>
</tr>
<tr>
<td><strong>Intermediate</strong> [0.5 h&lt;τ&lt;6 days]</td>
<td>Circadian (20 h&lt; τ&lt;28 h)</td>
</tr>
<tr>
<td></td>
<td>Ultradian (0.5 h&lt;τ &lt;20 h)</td>
</tr>
<tr>
<td></td>
<td>Infradian (28 h &lt;τ&lt;6 days)</td>
</tr>
<tr>
<td><strong>Long Period</strong> [τ&gt;6 days]</td>
<td>Circamensual (τ~30 days)</td>
</tr>
<tr>
<td></td>
<td>Circaseptan (τ~7 days)</td>
</tr>
<tr>
<td></td>
<td>Circannual (τ~1 year)</td>
</tr>
</tbody>
</table>

Table No:1.1  Spectrum of biological rhythm
1.10.2 Level
It is the baseline where rhythmic variation arises. The stage of circadian rhythms oscillation occurs in a certain intime approach during month in young women and over the year in both men & women and bring about respective to menstrual and annual biological rhythms.

1.10.4 Amplitude
Amplitude is a measurement of the degree of the definite in time variability due particularly to a biological rhythm, that are of very elevated amplitude, computing for twenty five to fifty percentage of the total variability detected in a specified procedure or objective in 24 hr. With aging rhythms amplitude may be alter e.g. in diurnally of active young adults, circadian rhythm in anti-diuretic hormone that controls formation of urine and also volume, having very high amplitude. The peak ADH conc. arises in night to make sure decreased formation of urine and also volume at time of sleep; therefore formation of urine and also volume in young adults are much higher in diurnal activity than night sleep. With aging amplitude of ADH rhythm reduces; as a result, peak of the circadian rhythm in formation of urine and its volume shifts to the mid- night as a result continual interruption in sleep due to need of urination. The amplitude of assured circadian rhythms may also differ with variation of health condition. For example, amplitude of circadian rhythm in airway caliber of normal lungs is quite small, equal to about five percentage of the 24hrs level; however, in mild asthma it is typically raised to twenty five percentage and in acute asthma it can be raised to fifty to sixty percentage of 24-h mean level.

1.10.5 Phase
This refers to the beating of definite features like peak and trough values, of a rhythm relative to equivalent time scale. For example, phase of high-amplitude circadian rhythm of serum cortisol conc. is specified by its outstanding morning peak (20 µg/dl) about 8 a.m. and its trough (as low as 0 µg/dl) in night sleep.

1.11 Mechanisms of biological timekeeping
Hereditary master clock network regulates Circadian rhythms, composed of coupled suprachiasmatic nuclei which are located in hypothalamus and pineal gland. The rhythmic activities of precise, so-called, clock genes, and their gene products, in addition the cyclic (nocturnal) secretion of melatonin from pineal gland include central timekeeping mechanism. This network are both period and phase of whole
host of submissive peripheral circadian clocks that are found in cells, tissues, and organ systems. The end effect is a quite delicate temporal association of biological processes and functions. It is a progress form to a circumstance that is arranged in time, exhibiting separate and essential cyclic experience. Thus temporal organization of biological processes and functions in the 24 hrs period assures peak functioning of the diurnal human species in daytime activity and renovation and having restored at night rest. It assures a priori biological adjustment to definitive-in-time alteration and challenges along with various seasons of annum.\textsuperscript{19}

1.12 Synchronizers of biological rhythms
It is an environmental time indication which influence rhythm period and rhythm phase. The master and deferential peripheral circadian clocks are coordinated to accurate 24hrs environment and social cycles by definite particular exterior time cue. Characteristics of normal light–dark cycle differ expectably over 24 hr, month and year. The central circadian clock network depends on environment that may natural or be artificial 24-h light–dark cycle to titrate its duration to accurately 24 hour to calculate its phase. The phase of circadian rhythms of persons whose time organization is adapted to a regular of nocturnal activity and work alternating with diurnal sleep will be totally opposite to that of persons whose time organization and activity alternating is reverse (diurnal work & nocturnal sleep). So clock time, per se, is not representative of biological time. The timing of the peaks and troughs of circadian rhythms is quite certain from one day to next in most people who stick on to a practically regular action sleep schedule. However, for persons those are working in rotating shift or those in variable rest–activity routine, prediction of phase of 24-h rhythms is less. It is of research and clinical importance one. The activity–sleep schedule observes after peak and trough of different circadian rhythms arise with indication to the 24-hrs timescale.\textsuperscript{20,21}

1.12.1 Phase–response of biological clocks and rhythms
The influence of dosing medications at various times of day or night on the phase of circadian clocks and rhythms, as a pharmaco therapeutics adverse effect, is not healthy esteemed because it is not evaluated as a probable adverse effect in clinical trials. An aim of all pharmacotherapy need to prevent of phase change of circadian system, exception being usage of specific chemical, physical, or other therapy to renovate anomalous circadian clock function to usual.\textsuperscript{22,23}
1.12.2 Biological rhythms — shift, and night work

The reliability of the circadian time structure is important to efficient biological and psychological functioning and maintenance of health, itself. Workers of night and rotating shift bear equivalent interruption of circadian time structure with difference in each shift which needs change of sleep–wake routine and relate to time accompanied exposure to natural light as rhythm synchronizers wake pattern and/or usual exposure to light in night changes, or more inhibits.\textsuperscript{24}

1.13 Circadian time structure

Circadian rhythms are endogenous in nature driven by “Oscillators” or Clocks and persist under free running conditions. The rhythm in human body temperature that is timed by biological clocks has an about 24 hours period under free running circumstances. Thus circadian variations in gastric acid secretion and PH, drug protein binding, gastric emptying time, glomerular filtration, hepatic bloodflow, gastrointestinal bloodflow, liver enzyme activity, renal bloodflow, motility, urinary pH, and tubular reabsorption may play a role in such kinetic variations.\textsuperscript{25}. The human circadian time structure is to describe peak time of 24hrs rhythms on a clock like diagram like that exposed. Figure-1 shows the peak time of human circadian rhythms in relation to the typical synchronizer routine of the majority human beings sleep in darkness and activity during the light of the day.

![Human Circadian Time Structure](image)

*Figure 1* Approx. peak time of circadian rhythms for 24 hrs for selecting biological variables in persons heeding to usual routine of day activity & alternating with night sleep.
1.14 CIRCADIAN RHYTHMS IN OCCURRENCE AND SEVERITY OF DISEASE

The strength of symptom of medical situation and incidents of life-threatening medical emergencies showing evidence of rather accurate timings. Diseases like peptic ulcer attacks are most regular at night and pulmonary edema, congestive heart failure and asthma get worse nocturnally. The symptoms of allergic rhinitis and rheumatoid arthritis are effective over night or in morning upon wakening. Migraine headache usually is triggered in night time sleep or sharp early morning hours. The heart diseases like unexpected cardiac death angina pectoris, arrhythmia, hypertensive crises, stroke, pulmonary embolism, and myocardial infarction are commonly in morning. Depression is generally in morning. Symptoms of osteoarthritis generally in late afternoon or sharply at evening. The bleeding ulcer is generally in afternoon.

Figure 2 Human circadian rhythm in human diseases

1.15 Chronopharmacology: biological rhythms and medications

The theory of homeostasis indicates both kinetics and dynamics of medications are comparable nevertheless time of day, month and year of their administration. However, their behavior can be affected by circadian rhythms of ingestion, infusion application of medications. Chronopharmacology is learning of behavior and range to which endogenous biological rhythms precisely affects kinetics and dynamics of medications and also the way dosing time of medications affect biological timekeeping and the features of biological rhythms. These chronostudy showing that
time of drug administration, particularly in allusion with circadian rhythms, can influence kinetics and dynamics of different class of medications.\textsuperscript{27,28} Chronopharmacology of living organisms are combination of rhythms with different frequency ranging from seconds to seasons. As the chronobiological frequency is circadian rhythm that approx. 24 hr rotation in earth. Chronopharmacology study deliberates the side effects of the drug on the temporal changes in biological functions. The rate of absorption, hepatic conjugation and urinary excretion contributes towards variation in receptivity of the remedy in human circadian rhythm. The timing for drug administration for certain diseases like asthma, arthritis, hypertension, angina and epilepsy. The drug therapy can be optimized for the dosing schedule based on chronobiological model.\textsuperscript{29}

1.16 Chronopharmacokinetics

It is the certain rhythmical variations depends on dosing. Pharmacokinetics means ADME which are affected by physiological functions that change with dosing. The administration of a drug or toxic agent may affect response of organism. Chronopharmacokinetics studies are needed for enhanced appreciative of non-linear performance of a drug. The gastric acid secretion, gastric motility, blood flow and urinary pH plays a vital function as time dependent variation of drug plasma conc. in Circadian rhythm. Thus quantitative response of an organism, as well as qualitative response changes with time of administration. Chronopharmacokinetics includes the temporal aspects of ADME of the drug are affected by various physiological functions that changes with time. So pharmacokinetic parameters along with peak drug plasma conc. ($C_{\text{max}}$), time to reach ($t_{\text{max}}$), area under concentration-time curve (AUC), volume of distribution (Vd), protein binding, elimination half-life ($t_{1/2}$) and also clearance (CL) which are typically treated to be constant in time are circadian time dependent. Chronokinetics of definite drugs may involve variation from a single to a multi compartmental model as a function of drug dosing time.\textsuperscript{30}

The time of administration for variation in the pharmacokinetics of a drug. The pharmacokinetic changes depend on either sex, age of patient. Dosing time-dependent changes of sustained-release indomethacin was illustrated in younger not in elder subjects. Comparison of slow and fast acetylor types of young healthy subjects has showing statistically marked variation in chronokinetic design of such drugs.\textsuperscript{31}
Chronopharmacokinetics of drugs also of humans, with acute and chronic administration have been validated for sustained release formulations of $t\frac{1}{2}$ 84 hrs for variety of species. Several physiological factors like g.i., cvs, hepatic and renal changes varies with time of day. Therefore, both synchronization and dosing time of a drug should for correct elucidation of pharmacological data. For oral absorption depends on gastric pH, gastric motility, gastric emptying time, gastrointestinal blood flow, time for gastric emptying; distribution occurs via blood flow through an organ and binding capacity of plasma proteins. Metabolism occurs via hepatic flow, xenobiotic metabolizing enzymes and excretion occurs via renal blood flow, glomerular filtration, tubular reabsorption, transporters, electrolytes and urinary pH of drugs may change according to the circadian clock with regard to physical properties of drugs.

1.17 CIRCADIAN DEPENDENCE OF DRUG PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral: Gastric pH, gastric motility, gastric emptying time, gastrointestinal blood flow, transporter.</td>
</tr>
<tr>
<td>Parenteral: Transdermal permeability, ocular permeability, pulmonary permeability.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow, albumin, ol-acid glycoprotein, red blood cells, transporter.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver enzyme activity, hepatic blood flow, gastrointestinal enzyme.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal, biliary, intestinal, Glomerular filtration, renal blood flow, Urinary pH, electrolytes, Tubular resorption, Transporter.</td>
</tr>
</tbody>
</table>

**Table-1.2:** Possible physiological factors influencing circadian stage-dependent pharmacokinetics of drugs
INTRODUCTION

Time-dependent changes in kinetics may result from circadian variations at each step that is ADME. At each of these steps, biological rhythms may affect drug kinetics as shown in Table 2.

Each process is affected by status like active-rest cycle, posture and schedule of feeding, and lipophilicity or hydrophilicity of drug.\(^{34}\)

1.1.1.2 Circadian rhythms in absorption

In humans, for orally administered drugs, absorption was shown to be precious by circadian rhythm as secretion of gastric acid and gastric pH, motility, gastric emptying time, and also blood flow of gastrointestinal differ accordingly to the day time.\(^{35,36}\)

These changes may have an impact on the time anf pH dependent of drug absorption. For design circadian changes may be affecting drug ionization to its physico-chemical properties. Alternatively, gastric emptying time is a major factor in absorption of drugs. Gastric emptying rates have been comparing between morning 8 am to evening 8 pm. The gastric emptying t½ for evening meal was considerably longer for solids but not for liquids compareing with of the morning meal.\(^{37}\)

The increase in evening meal, gastric emptying time may cause a delay in attaining peak plasma conc. for some drugs. The variations occurred due to physico-chemical properties of a drug, since some of lipophilic drugs indicating to be absorbed quicker during morning in compare to evening.\(^{38}\)

The mechanisms essential the chronokinetics of lipophilic drugs engage a quicker gastric emptying time and a high g.i. perfusion in morning. However, these variation have not been shown for hydrophilic drugs.\(^{39}\)

1.1.1.2 Circadian rhythms in distribution

In biological fluids and tissues, circadian changes connected to distribution of drug are shown to varies in accord to duration of day. Blood flow rely on regulating aspects allowing for the sympathetic & parasympathetic systems whose behavior are identified to be circadian time-dependent with a major diurnal effect. Thus, daytime increases and night time decreases the blood flow and local tissue blood flows may clarify a potential difference in drug distribution according to dosing time. The liver activity vary due to circadian rhythm. As a result the levels of plasma proteins (albumin, globulins) changes from day time to night time. The plasma protein concentrations including albumin, and α-glycoprotein
INTRODUCTION
descend to their lowest during at night time, increase by day time and reaches to highest about noon. Circadian rhythms in plasma protein binding have been established for several mood stabilizers, valproic acid, 5-fluorouracil, ketoprofen, carbamazepine, diazepam, lidocaine, prednisone, and cisplatin. From toxicological point of surveillance, drugs with a small volume of distribution and/or high protein-binding capacity and drugs which have a narrow therapeutic index may be affected by the changes in circadian rhythm and wrong dosing of such drugs in night time may cause mild to moderate toxicity.  

1.17.3 Circadian rhythms in Metabolism
Hepatic drug metabolism is usually implicit to rely on liver enzyme action and/or hepatic blood flow: both have been appeared to be circadian-time-dependent Enzyme activities showing the circadian-time-dependent different organ like brain, kidney, and liver. Conjugation, hydrolysis and oxidation have been shown to be circadian time-dependent. Certain drugs with a high extraction ratio, metabolism for liver depends on hepatic blood flow. Circadian fluctuations in blood flow of liver induce to alter in liver perfusion and, so chronological changes in the clearance of these drugs. Clearance indicating the highest values in the early morning of in healthy volunteers.
Conjugation provides lipophilic compounds to be hydrophilic adequate to prime regulate and ease their excretion into bile, faces and/or urine.

1.17.4 Circadian rhythms in excretion.
The renal physiological functions like glomarular filtration and tubular reabsorption showing the circadian time-dependent variation with high values at day time. The circadian rhythmic variations affects to alter in drug urine excretion. The urine pH changes ionization of drug so the acidic drugs like sodium salicylate and sulfasalazine are excreted quicker after evening administration. Those changes are more prominent for hydrophilic drugs. The circadian timing system exhibit a major role in alteration of drugs toxicity in affecting their metabolisms in liver and chronic the biliary drainage.

Chronopharmacodynamics
It deals with rhythmic changes in the drug including effects indicating temporal but not randomly distributed drug susceptibility or sensitivity of organisms or target tissues down to the cellular or sub cellular level. It means to ‘dosing-time’ i.e., variation
in the medications effects. The differences in time are because of rhythms in free-to-bound drug fraction, quantity and conformation of the drug-specific receptors and the ion channel after drug administration and rate limiting steps in the metabolic pathways. Both the favorable and adverse effects of medications can differ markedly in accord to their time of administration.

**Schematic representation of Chronological condition of diseases**

**Chronotoxicology**
It is a characteristic of chronodynamics and completely to dosing time, i.e., variation in the rhythm dependent and asperity of undesirable effects and as a result, in tolerance of patient to medication. Classes of medication which are of higher risk of adverse effects and low limited therapeutic range. It is showing marked dosing-time difference in safety.

**Chronesthesia**
Medications also other chemical substance are usually show dose and/or conc.-response relation. Moreover, study of chronopharmacology occasionally expose high difference in effect with different applications of biological times, even though both pharmacokinetic and conc. are the same. This is coined as chronesthesia. It is theme in pharmacology that refer to rhythm-dependent difference in compassion of target system to medication which cannot be illustrated by equivalent administrations-time difference in pharmacokinetics phenomenon.

Chronesthesies are confirmable by direct use of medication to their action site and by difference in blood/tissue conc. biological responses to medication if administered at
various times in the twenty four hours. The mechanism of chronesthesies have not yet fully explained. It is considered that they reveal rhythm in receptor no. and conformation, 2nd messenger dynamics, membrane permeability, or rate-limiting step of metabolic pathway in drug-targeted tissue.\textsuperscript{49}

**Chronoprevention:**

Chronoprevention is defined as time of medication or other intervention in accord to biological rhythms conditions as mode of preventing disease or decrease in health level. These strategy takes into reflection same elements as in chronotherapeutics one. So, the aim of chronoprevention is prevention of diseases, pathology, and other lethal phenomena which include heath, that the aim of chronotherapeutic is managing or setback of accessible acuteorchronic medical conditions.\textsuperscript{50}

**Circadian rhythm of clinical diseases**

Predictable circadian variation can be useful in diagnosis of below, are the disease with set oscillatory rhythms in their pathogenesis

<table>
<thead>
<tr>
<th>SL.NO</th>
<th>Diseases / Syndrome</th>
<th>Circadian rhythmicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Allergic rhinitis</td>
<td>Symptoms worse in early morning</td>
</tr>
<tr>
<td>2.</td>
<td>Bronchial asthma</td>
<td>Exacerbations more common during the sleep period</td>
</tr>
<tr>
<td>3.</td>
<td>Arthritis rheumatoid</td>
<td>Symptoms most intense rheumatoid upon awakening</td>
</tr>
<tr>
<td>4.</td>
<td>Osteoarthritis</td>
<td>Symptoms worse in the middle/latter portion of the day</td>
</tr>
<tr>
<td>5.</td>
<td>Anti cancer agents</td>
<td>Doxorubicin, Cisplatin, methotrexate</td>
</tr>
<tr>
<td>6.</td>
<td>NSAIDs</td>
<td>Ibuprofen, Indomethacin, Tenoxicam, Acetylsalicylic acid</td>
</tr>
<tr>
<td>7.</td>
<td>Angina pectoris</td>
<td>Chest pain and ECG changes more common during the early morning</td>
</tr>
<tr>
<td>8.</td>
<td>Myocardial infarction</td>
<td>Incidence greatest in the infarction early morning</td>
</tr>
<tr>
<td>9.</td>
<td>Peptic ulcers</td>
<td>Symptoms worse after gastric emptying and in the early morning (sleep period)</td>
</tr>
<tr>
<td>10.</td>
<td>Stroke</td>
<td>Incidence greatest in early morning</td>
</tr>
<tr>
<td>11.</td>
<td>Epilepsy</td>
<td>Incidence greatest in early morning</td>
</tr>
</tbody>
</table>

*Table :3* Circadian Rhythm and Extremity or Indication of Clinical Diseases
Table 1.4 Design and development of new chronotropic DDSs in accordance with circadian rhythm of human body
**INTRODUCTION**

**TECHNOLOGY USED IN CHRONOTHERAPEUTIC DRUG DELIVERY.**

The delayed and pulsed release included site specific and time controlled release formulations. The time-controlled or pulsed release formulations are appropriate for steady state plasma drug levels for chronotherapy, treatment of early morning symptoms. The peak of plasma concentration and the no. of doses daily can be reduced is obtained at an optimal time by intended to drug administration and the first-pass metabolism and its tolerance can also be avoided. Different types of technologies are developed for time controlled oral drug delivery systems for chronotherapeutics. These following systems are discussed below:

**Enteric-coated systems**

The enteric coatings are used to confirm drug release in the stomach. Normally the enteric coatings are time and p^H_ sensitive i.e. the drug is released when the intestinal fluid pH above 5. The time-controlled drug release system, where the lag time is desired. The unpredictability of gastric secretion occurs in case of time-controlled drug release. Theophylline drug which is treated for nocturnal asthma. The dosage form containing a drug with barrier coating which is dissolved in intestinal fluid of pH above 6 has been considered in case of. This system which is two film coated polymers to the core tablet(Fig.3), first with HPMC and next with a gastro-resistant polymer (Eudragit L-100 and S-100). The lag phase can be controlled by the thickness of the HPMC layer.
Layered systems
These systems consist of impermeable or semi permeable polymeric coatings useful on both portion of the core. The biphasic drug release allowed three-layer tablet system was also developed, in which both the two layers are containing the drug dose. These two layers were separated by an intermediate layer, made up of swellable polymers. Furthermore, the outer drug layer contains the immediately release dose of drug, and the inner layer which consists of film of an impermeable polymer layer containing the other dose of drug. Sometimes the first layer may also incorporate a drug-free hydrophilic polymer barrier to provide delayed (5 h) drug absorption. The night-time and early-morning symptoms of Parkinsonism can be avoided by using a dual-release formulation, which allows daily doses of drug to be reduced and leads to extent of bioavailability 40% greater than when a conventional controlled release formulation is employed.  

Time-controlled explosion systems (TCES)
It has a four layered spherical pellet structure, consisting of an inert core surrounded by a layer of drug, a swelling agent and a water insoluble polymer membrane made up of ethyl cellulose. It is characterized by rapid drug release with a programmed lag time. When the water penetrates through the polymer membrane, the swelling agents expands, leading to destruction of membrane with subsequent release of drug. The lag time is controlled by the physiochemical properties and permeation and polymer coating.
**INTRODUCTION**

**Sigmoidal release systems (SRS)**
This system applied for reservoir pulsatile systems with diffusive polymer coating. It is multiparticulate DDS comprising of drug/succinic acid mixture loaded on nonpareil seeds and outermost Eudragit RS film applied by spray coating. The lag time is controlled by water inflex through the polymeric membrane. The reservoir wall dissolved succinic acid and the core and the acidic medium sequentially increases the permeability of the hydrated polymer film by interaction with quaternary ammonium groups combined in acrylic polymer thereby permitting the dissolved drug to diffuse out. Beyond the lag time the drug releasing rate from the surface, to initiate the independent of coating thickness.

**Press-coated systems**
Generally, delayed and intermittent-release formulations can be achieved compression coating, which the inner portion is core tablet and the outer portion is coating layer. The core tablet containing a large amount of disintegrate with active ingredient which is pres coated with outer shell of as hydrophilic cellulosic polymers are used. Comparatively huge amounts of coating solution are necessary in this techniques and difficult to arrangement the cores for the coating process. A press coated device is developed in which the inner portion contains the drug, and the outer portion is coated with different types and conc. of polymers. The external barrier, which controls the drug release, may be either swellable or erodible. Here the lag times can be varied by altering the barrier formulation or the coating thickness. Furthermore, a press-coated tablet can be designed for timed release by modulating the coat instead of drug core by making swellable, soluble, erodible or disintegratable which detaches itself from drug core after log time and it is followed by a rapid dissolution of drug from the core. Figure No. 5. Illustrated as below a 

![Schematic representation of press coated system]
INTRODUCTION

PULSINCAP SYSTEMS

This technique is designed as capsular pulsatile systems with polymeric plug. Pulsincap which is composed of a water soluble cap, an insoluble body filled with drug and sealed with PEG hydrogel plug. On administration the water-soluble capsule cap dissolves thereby allowing the hydrogel plug swells and expands. After a controlled and predetermined lag time which is governed by the size of hydrogel plug, it is swollen to an extent that to eject from the capsule body thereby releasing the drug. Pulsincap may be enteric coated to avoid of gastric emptying. Another variation of pulsincap is use of hydrogel plug have been replaced by an erodible plug, which has a fit in capsule to avoid the entering of fluid. During the drug release it erodes away from the mouth of the capsule. It will effect the amount, types and ratios as well as conc. of hydrophilic polymers used in erodible tablet. The erodible tablet weight was signifying to maintain predetermined lag time and rate of drug release profiles.

Design of Pulsincap system
ADVANCE TECHNOLOGY FOR CHRONOTHERAPEUTICS

1) CONTIN Technology

This technology includes the molecular coordination complexes are formed in between cellulose polymer and aliphatic alcohol, which is substituted with an aliphatic group by solvating the polymer and the aliphatic alcohol reacted by the cellulose polymer. Sustained release tablet forms of aminophylline, theophylline, morphine fromed by this technology. On administration of theophylline tablets in the evening as a rational dosing schedule for asthma patient for better bronchoconstriction in the morning. Thus, evening time administred of theophylline may block in lung function. This technology provides for the quantity drug release to the blood stream and decreasing the number of doses that benefits to patients in and provided successful managing disease as well as falling unnecessary side effects.

2) Physico-chemical modification of the API

In this approach, technique is used to change the physicochemical properties of the active drug to accomplish the chrono-pharmaceutical purpose. The physiochemical properties such as solubility, partition coefficient, permeability, particle size, salt form, crystal forms, complexation. It will affect the time to achieve the maximum plasma concentration for these compounds. For example, lovastatin and simvastatin are lactone prodrugs, are modified in liver to active hydroxyl acid forms. Since, they are less water soluble than other statins. Other physico-chemical strategies to chronopharmaceutical drug delivery may include selection of salt forms, chirality and control of particle size.

3) OROS technology

It is techniques where the bolus drug dose delivered a in specific time to the gastrointestinal tract. It is based on an osmosis system. This system is composed of two compartments, the drugvessel and the osmotic engine cap. Whilst the system is exposed to an aqueous medium the water permeates into the osmotic engine cap via rate controlling membrane. The osmotic engine hydration leads to its expansion, which exerts a driving force beside the ridge of the drugvessel.
These two compartments separate from each other by sliding apart. After disengaging, the open mouth of the drug vessel is exposed to the fluid environment. The Chronoset can deliver the whole essentially dose and minimize the drug residue in the drug vessel after the operation. The vessel is made of water impermeable ethylene co-vinyl acetate copolymer while the cap is made of water-permeable blends of polycaprolactone and flux enhancers. The drug released from these systems is independent of pH and other physiological parameters to a huge level and also possible to adjust the release characteristic by optimizing the properties of drug and system. (Fig-7)

Ex: Push- Pull OROS Delayed System, also known as controlled onset extended release. This is enabled delayed, overnight release of verapamil to avoid the potentially dangerous surge in BP which can take place in the early morning.

7) Chronomodulating infusion pumps

The systems contain core tablet coated with cellulose acetate polymer. The core tablet contained drug which is low bulk density and disintegrating agent. When the system comes in contact with water, water penetrates into the core and the lipid material displaces. After depletion of lipid material, the inner pressure increases until one critical stress is reached, causing the rupture of coating and release of drug for chronotherapeutic applications. However, these infusion pumps recently used for cancer and diabetes.  

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Schematic representation of OROS Technology
The marked products are melodie, panomat V5infusion, and rhythmic pumps which is suitable for chronotherapy.

8) TIMERx technology

This system can be controlled the release of the active drug substance in a tablet by using the portion of the gums, together with the third component, with the tablet coating. The system combines xanthane and locust bean gums mixed with dextrose. These system facilitated to form a gel in the presence of water. However, is the rate of water penetration to the system is controlled by drug release. (Fig. 9).

9) PULSY Technology

This technology is having one immediate release and two delayed release by using soluble and insoluble coating materials. It is measured a significant step for improving recent antibiotics treatment regimens. The technology was delivered drug in parallel concomitant pulses corrected the flaws in anti-infective therapy. Exposing the bacteria to rapid antibiotic pulses within the first hours of initial dosing was found to have the potential to cripple the natural protection mechanisms of bacteria, eliminating them more efficiently and effectively than conventional anti-infective therapy regimens. The Moxatag tablet having the drug amoxicillin has been formulated for infections, that is capable in killing of bacteria exposed to antibiotics to reduces the period of therapy.
10) PORT Technology
The Programmable Oral Release Technologies system is composed of gelatin capsule coated with cellulose acetate as semipermeable membrane that contains an immediate drug release drug and in soluble plug as well as an osmotic agent along with second portion of drug for timed release (Figure 11). The poorly water soluble drugs can be coated with solubilizing agent to control release from the medicaments. Encapsulated gelatin is coated with a cellulose acetate as a rate controlling polymer. Upon contact with aqueous media the immediate drug is delivered and water enters into capsule through the semipermeable membrane, which increases the osmotic pressure and results in the ejection of plug after a predetermined lag time. The lag time is regulated by the coating thickness, the second dose is delivered. The compartment can be added according to need.

![Drug Release Mechanism From PORT System](image)

11) EGALET Technology
In this system, one of the delayed release form along with two lag plugs as well as enclosed a plug of active drug in the middle component. The inert plugs where the drug is released, and causes a lag time and shells are made of one slowly biodegradable polymer like ethyl cellulose and Cetostearyl alcohol as a plasticizer like while the matrix plug is a physical mixture of excipients, mainly polymers such as poly ethylene glycol (PEO).
12) Chronotopic Technology

The Technology contains of solid dosage form hydrophilic sellable HPMC coated that drug releases after lag-time, which depending on coating thickness & the polymer viscosity. An additional enteric-coated film is given outer surface of this layer to overcome intra-subject variability in gastric emptying rates also the onset of action is controlled by the thickness and the viscosity grade of HPMC. The system is appropriate for both solid dosage forms like tablets & capsules. The in-vivo & in-vitro showing good correlation with the accurate amount of the hydrophilic retarding polymer and showing appropriate lag times to maintain constant drug release throughout time period. \(^\text{104}\)
13) Three-dimensional printing (Their Form Technology/ 3DP)

This technology subjected to computer-aided design and analogous to an “ink-jet” printer. It is designed through computer as three-dimensional models, before a definite execution of their preparation development. This technique is applicable as chronopharmaceutics in near future. The 3-D printing is a complex oral dosage will be deliver based fabrication methods. The device is complicated internal geometries with different densities, diffusivities, and chemicals. The oral drug delivery devices have been fabricated by using the 3DP process as immediate-extended release dual pulsatory release tablets. The enteric dual pulsatory tablets were consists of one enteric excipient phase into which drug was printed into two portions. During in vitro .two pulses of release with about 4 hrs lag time between pulses.105

14) Controlled-release erodible polymers

In technique the rate of drug release is controlled by the erosion. The Time dependent drug release can be achieved by the thickness of the outer coat. The pulsatile drug-delivery system involving erodible polymers. It shows potential to control a rate of drug release that matches the necessary of the circadian rhythm of a given disease state. This technique designed for ChrDDS applications106.

![Schematic diagram of drug delivery with erodible coating layer.]

15) Controlled-release microchip

It is another method to achieve pulsatile or chronopharmaceutical drug release. which is designed by microfabrication technique. The solid-state silicon microchips are similar to micrometer scale pump, valves, and flow channel to deliver the active medication. It is thin anode membranes covered microreservoirs filled with either chemicals in solid / liquid /gel form. (Fig.15) This technology designed for
INTRODUCTION

ChrDDS with improved manage over drug kinetic release in order to match biological requirement over versatile period of time. The reservoir can contain multiple drugs or additional molecule in erratic dosages. The reservoir along with drug can be capped with material that degrade or allow the molecule to diffused out and the materials that oxidized and dissolved by electric current. The active device can be controlled by a preprogrammed microprocessor. A novel flexible drug delivery chip-like device was effectively intended and fabricated using electrophoretic-based technology to convey a drug-carrying core-shell magnetic nanoparticle into a membrane. It responds a range of release patterns, including sustained release, and burst release, according to the specified maneuver mode of the magnetic field and is suitable to evaluate the feasibility of this newtype of drug delivery chip in anti-epileptic treatment and diabetes, Parkinson’s disease, congestive heart failure, osteoporosis.\textsuperscript{107,108}

16) GeoClock® Technology

The technique is designed where the hydrophilic matrix core was as coated. The coating adjusted to the core by hydration process and the surface area to be minimized. In the presence of dissolution medium the barrier layers swells and converted to gel. This gelling layer to control drug release which is a acts as a modulating membrane. The erodible surface removed by the dissolution fluid. The maximum planar the core surface is exposed to environment with increasing time on erosion\textsuperscript{109} The technology is designed in such manner that consists of a coated solid dosage form and lipidic barriers, consists of carnauba wax and bees’ wax along with a
hydrophilic surfactants as polyoxyethylene sorbitan monooleate which improves adhesion to the core. When it comes in the contact with dissolution medium, the dispersion may be rehydrated or redisperses. The lag time could be controlled by changeable the film thickness. So the time required for rehydration, the core releases drug immediately. This technology showing reproducible results in-vitro and in-vivo. This technology are better appropriate for water-soluble drug.\textsuperscript{109}

\begin{center}
\includegraphics[width=\textwidth]{image.png}
\end{center}

**Epileptic Seizure**

A seizure may be explained as a disruption of consciousness which is followed by alteration in motor, sensory, or also in behavioural activity as a repeated paroxysmal disorder of cerebral function which is featured as instant attacks of consciousness in appropriate behaviour occurred due to abnormal excessive release of cerebral neuron.\textsuperscript{110}

The word ‘fit’ is used to describe an epileptic seizure. Epilepsy is defined as a condition characterized by a reappearance of seizures. A patient should not be described as having epilepsy until a second non-febrile seizure occurs. The following is a broad account of the classification of seizures, or epileptic syndromes based on the International League Against Epilepsy (ILAE).\textsuperscript{111}

Seizures can be classified according to different indication or group of symptom, duplicate precious part of cerebral hemisphere where the seizure arises. Most usual neurological disorder after stroke that appears in humans.\textsuperscript{112}
Antiepileptic drug concentrations can be used to assess patient compliances, predict the safety of a dosage alter and to evaluate the potential for side effects for the antiepileptic drug as well as to identify patients who do not respond to therapy. As stated, the concentration should be individualized for each patient and should reflect a concentration that prevents occurrence of seizures with a minimum of side effect. 113

The interval between changes in dose, the time to steady state, the estimation of loading dose, an estimation of a maintenance dose, expectation of drug interactions and the pharmacodynamics responses, may be altered by age, renal failure, liver dysfunction, other drugs interference, low albumin and other factors. These variables should be taken into consideration in therapeutic drug monitoring (TDM) of antiepileptic drugs. 114

Monotherapy is the ideal approach for antiepileptic drug treatment. The ideal response is manage of seizures with no side effects; however, this may not occur in all patients. Therefore, when an antiepileptic drug is started an endpoint should be set. If the patient achieves cessation of his or her seizures with no or tolerable side effects, the therapeutic objective has been reached. Polytherapy is indicated only if the patient has failed two or more drugs as single agent. Patients on polytherapy may be changed to monotherapy. Also, antiepileptic drug therapy may be discontinued in many patients after a sustained period of no seizures. This is a long term goal, as there should be at least two to four seizure-free years before the antiepileptic drug is discontinued; however, antiepileptic drugs do not necessary have to be given for life. 115

A therapeutic goal in the treatment of epilepsy is to control the seizures with no or minimal side effects. These drugs have differing side effect profiles and this would be measured during selecting the initial drug of choice. 116

Choice of antiepileptic. 117

- After taking decision to treat, the option of antiepileptic drug is to determine mainly by its effectiveness against type of seizures experienced and its potential adverse effects.
- Monotherapy is preferable to a multiple-drug regimen, so treatment is begun with a single drug, followed by increase in the dose gradually until the seizures are brought under control or adverse effects become unacceptable.
- If treatment with the initial drug fails, it is preferable to attempt substitute single first-line antiepileptics prior to giving combinations of the
drugs. It has been recommended for the practical purposes of a patient should be measured to have the refractory epilepsy, if the seizure control is not obtained with the successive trials of well tolerated antiepileptics.

- The exchange from one antiepileptic to another should be made carefully, withdrawing the first drug only when the new regimen has been largely established.
- If combinations are essential in intractable cases, regimens should avoid the inclusion, where ever possible, of sedating drugs such as the barbiturates or benzodiazepines drugs with different modes of action should be chosen for combined therapy to reduce the risk that adverse effects will be additive many antiepileptics interact with each other through the complex mechanisms and the dosage adjustments may be required to sustain plasma concentrations within the therapeutic range; the plasma monitoring may be advisable with the combination therapy.

- To control pharmacokinetic interactions, or in cases of suspected toxicity or non adherence.
- If trials of combination therapy do not construct worthwhile benefits, treatment should revert to the regimen (monotherapy or combination) that has been provide the most suitable balance of both the seizure control and the adverse effects.

- The monotherapy with the first or second choice antiepileptic without developing intolerable adverse effects. The remaining 30 to 40% will have epilepsy that is difficult to control from the start, although some of these patients will respond to the combination therapy.

**MODE OF ACTION**

- Anti epilepsy drugs that inhibits the neuronal discharge
- Reduces cell membrane permeability to ions, principally voltage-dependent sodium channels which are responsible for inmost current that generates an action potential. Cells that are sacking cyclically at high frequency are blocked preferentially , that permits discrimination between epileptic and physiological activity
INTRODUCTION

- Enhance the activity of γ-aminobutyric acid, the principal inhibitory transmitter of the brain, the result is increased membrane permeability to chloride ions, which reduce cell excitability.

- Inhibits excitatory neurotransmitters e.g. glutamate

Patients may conscious during some seizure variants. A convulsion specifically denotes motor involvement. It excludes extracebral causes such as syncope and the episodic psychiatric syndromes. It is not a disease, but rather a condition in which a patient suffers from a complex set of syndrome.

The anticonvulsant drug therapy is to reduce the seizure frequency and the sternness within a structure of an satisfactory level of side effect. This goal may be realized by removing the underlying cause, increasing the seizure threshold, or preventing the synchronous extend of impulses once the threshold is exceeded. Efficacy depends on many elements, like the type of seizure and patient’s age at onset, choice of drug, and the clinical pharmacology and the pharmacokinetics of the drug. Complete seizure control may not always be possible. Generally, the severity of epilepsy will partly determine the drug response. All indicated anticonvulsants should be tried in conjunction with the serum drug level determination. When the correct seizure diagnosis is made and the correct drug is administered in correct amount, many seizures considered to be drug resistant can be brought under control. The principal causes for treatment failure are patient noncompliance, selection of an appropriate dosages to attain the essential serum concentrations based on the individualized pharmacokinetics.\textsuperscript{120}

When monotherapy unsuccessful, the choice of antiepileptic drugs used for treatment seizure. The choice of antiepileptic drugs will determine the risk-benefit measurement by the patient. The acute toxic severity or teratogenicity for females which can effect option of drug remedy to maximum degree by the patient.\textsuperscript{121}

It is needed to build up appropriate dosage forms to permit the safety, efficacy and suitable of bioactive compound to patient. It is necessary to one active ingredient (regardless of a small-molecular wt. ‘anicient’ one or a new ‘biopharmaceutical’ one such as therapeutic peptides, proteins or antigens) is one part of the drug administered to the patient and the formulations which render the drug discoveries and pharmacological researches to clinical practices.\textsuperscript{122}
Drugs can be administered through different routes, however, between all route of administrations, oral one is more convenient for administering drugs for systemic effect, as easy of administration by manufacturing and dosage adjustments. The parenteral route is not routinely used because of difficulty in self administration and hence hospitalization may be required. Topical route is newly developed and is employed for only few drugs like nitroglycerine, scopolamine for systemic effect. This route has limitations in its capability to permit effective drug absorptions for systemic drug action. Parenteral administration is employed in case of emergency and where the dosage form is senseless or cannot be swallow. However it is possible that minimum ninety percent of all drug used to produce systemic effect are administered by oral route only. Oral route of drug administration is acceptable orally as solid dosage form represents the chosen classes of product.

Tablets are the unit dosage forms that contains accurately an usual dose of drug. The liquid oral dosage form are generally designed to have one medication in 5-30 ml. These dosage measurements are usually error by factors ranging from 20-50 percent if drug is administered by patient itself. Tablet may vary in shape and differ to a great extent in size and weight in accord on quantity of therapeutic substances and the projected mode of administrations.

### Classification of Seizures, their characteristics, & drugs employed in management

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Seizure Characteristics</th>
<th>Effective Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Generalized</td>
<td>Tonic rigidity of extremity, followed by clonic mass clonic jerking for several minutes, Urinary incontinence, Supor follows, Onset at any age</td>
<td>Phenytoin, Phenobarbital, Primidone, Carbamazepine</td>
</tr>
<tr>
<td>a. Grandmal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Simple absence</td>
<td>Sudden loss of consciousness up to 30 seconds can occur hundreds of times a day, Characteristic 3/sec spike -wave EEG pattern, Clonic jerking of eyelids but no motor activity, Onset between 3-10 years of age; rare in adult</td>
<td>Ethosuximide, Trimethadione, Clonazepam, Valproic acid</td>
</tr>
<tr>
<td>c. Myoclonic</td>
<td>Sudden, violent contractions of extremities, With or without loss of consciousness, Often occurs after awakening or before retiring, Often in combination with other seizure types; Age of onset 5-20 years</td>
<td>Phenobarbital, Clonazepam, Valproic acid</td>
</tr>
<tr>
<td>d. Atonic/Akinetic</td>
<td>Sudden loss of muscle tone lasting 10-60 seconds, EEG shows a slow spike -wave pattern; Often due to organic brain disease; Age of onset 1-5 years</td>
<td>Diazepam, Clonazepam</td>
</tr>
<tr>
<td>e. Infantile spasms</td>
<td>Myoclonic jerks with abrupt flexion/extension of limbs or whole body. Patients mostly mentally retard; high voltage, Slow waves are predominant in EEG; Age of onset 1-5 years</td>
<td>Diazepam, Clonazepam, Phenobarbital</td>
</tr>
</tbody>
</table>
INTRODUCTION

A Seizure is an alteration of consciousness that might be accompanied by a change in behavior or motor, autonomic or sensory activity. Patients may be conscious during some seizure variants. A convolution specifically denotes motor involvement. It excludes extracebral causes such as syncope and episodic psychiatric syndromes. It is not a disease, but rather a condition in which a patient suffers from a complex set of syndrome.

The anticonvulsant drug therapy is to reduce seizure frequency and sternness within a structure of an satisfactory level of side effect. This goal may be realized by removing the underlying cause, increasing the seizure threshold, or preventing the synchronous extend of impulses once the threshold is exceeded. Efficacy depends on many factors, such as the type of seizure and patient’s age at onset, the choice of drug, and the clinical pharmacology and pharmacokinetics of the drug. Complete seizure control may not always be possible. Generally, the severity of epilepsy will partly determine the drug response. All indicated anticonvulsants should be tried in conjunction with serum drug level determination. When the correct seizure diagnosis is made and the correct drug is administered in correct amount, many seizures considered to be drug resistant can be brought under control. The principal causes for treatment failure are patient noncompliance, selection of an appropriate dosages to attain essential serum concentrations based on individualized pharmacokinetics.

The choice of antiepileptic drugs that start as monotherapy and aims to aid the choice of treatment if monotherapy fails. The choice of one AED will be determined by an patient risk-benefit measurement in which the most effective drug for an individual patient. That AED would have the lower risk of significant harm. It is the risk of chronic toxic effects or teratogenicity for women that may affect the option of drug remedy to the maximum degree.

<table>
<thead>
<tr>
<th>Seizure Type</th>
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<th>Effective Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>II. Partial</td>
<td>Manifestations variable depending on site of lesion; convulsions confined to a single limb. Muscle group: no impairment of consciousness; Consciousness; Sensory disturbances occur. EEG shows spiking at the site of the focus; Onset at any age.</td>
<td>Primidone, Carbamazepine, Clobazamide, Valproic acid</td>
</tr>
<tr>
<td>a) Simple seizure (focal or jacksonian seizures)</td>
<td>Confused behavior, with involuntary, Purposeless, repetitive motor activity; accompanied by autonomic manifestations and loss of consciousness; seizures last several minutes, but patients have no recall of attacks; EEG spiking is present in the temporal lobe; control is difficult. Onset at any age.</td>
<td>Carbamazepine, Primidone, Phenytoin</td>
</tr>
<tr>
<td>b) Complex partial seizures (Psychomotor epilepsy)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
It is needed to build up appropriate dosage forms or drug delivery systems to permit the effective, safe and reliable purpose of these bioactive compounds to the patient. It is important to realize that one active ingredient (regardless of whether this is a small-molecularweight ‘classical’ drug or a modern ‘biopharmaceutical’ drug like a therapeutic peptide, protein or antigen) is one part of the medicine administered to the patient and the formulation of the drug into a dosage form or drug delivery system that translates drug discovery and pharmacological research into clinical practice.\textsuperscript{122}

Drugs can be administered through different routes, however, among all the routes of administration, oral route is more convenient for administering drugs for systemic effect, as easy of administration by manufacturing and dosage adjustments. Parenteral route is not routinely used because of difficulty in self administration and hence hospitalization may be required. Topical route is newly developed and is employed for only few drugs like nitroglycerine, scopolamine for systemic effect. This route has limitations in its ability to allow effective drug absorption for systemic drug action. Parenteral administration is employed in case of emergency and in which the dosage form is comatose or cannot be swallow. However it is possible that at least 90 % of all drugs used to produce systemic effect are administered by oral route only. Oral route of drug administration is acceptable orally as solid dosage form represents the preferred class of products. The follows reasons are

Tablets are the unit dosage forms in which one usual dose of drug has been accurately placed. The liquid oral dosage forms are usually designed to contain one medication in 5-30 ml. Such dosage measurements are usually error by a factor ranging from 20-50 %, when the drug is self- administered by patient. Tablets may vary in shape and differ to a great extent in size and weight depending on the amount of therapeutic substance and the projected mode of administration\textsuperscript{123}

**Tablet dosage form**

Tablets are defined as unit solid dosage preparations each having a single dose of 1 or more active medicament along with additives and elicited by compression homogenous volume of particles. This dosage form is used mainly for systemic drug delivery as well as for local drug action. For systemic effect the drug must be released from tablet to dissolve in oesophageal fluid and absorbed into systemic circulation to reach the site of action.
Tablets are popular dosage form because of the advantages, afforded both to the concern of the manufacturer for economy for the preparation and the stability of dosage form, ease in packing, shipping and dispensing and for the patient, the accuracy of dosage, compactness, portability, taste and easy of administration. Tablets may also be coated to regulate the drug release.\textsuperscript{124}

1.4.2 Advantages of tablets\textsuperscript{125}

- They are easy to administer as well as elegant in the appearance.
- They an accurate and stable dose precision and the least content variability.
- Their cost is lowest among all other oral dosage forms.
- They may provide ease of swallowing with least tendency for hang up above the stomach.
- The coated tablets such as enteric or delayed release products provided that tablet disintegration is not rapid, so release profile products are stable for the different diseases.
- They are having the combined properties of chemical, mechanical and microbiological stability of all the oral forms.
- One of the major advantages of tablet over capsules is that the tablet is essentially “tamperproof dosage form”.

1.4.3 Disadvantages of tablets\textsuperscript{125}

i. Certain drugs like amorphous, hygroscopic and low density are difficult to compress the tablet.

ii. Drugs with poor solubility and wetting, slow dissolution properties, during the tableting.

iii. Tablets are unsuitable for drugs having bitter taste which are sensitive to the environmental condition.

iv. Tablets are slow rate of onset action when compared to the parenteral dosage form.

v. The novel drug delivery system is preferred over tablets when the drugs undergo hepatic first pass metabolism.

vi. Tablets are difficult to be swallowed by children & serious ill patient.
INTRODUCTION

Excipients used in the formulation of tablets

Excipients are inert substances that are used as diluents or vehicles with drug to develop formulations. In the pharmaceutical industry which includes various subgroups comprising additives or fillers, binders or adhesives, disintegrants, lubricants, glidants, flavors, colors and sweeteners. All of these should meet the certain standards as follows:

a) They must be uniform weight, size and attractive in appearance
b) Tablets should be sufficient strength and must be resistant to shocks, fractures and erosion during its manufacture, transport..
c) They must be physical and chemical stability throughout its shelflife.
d) The tablets should free from any incompatibilities
e) They must not affect with the bioavailability of the drug.

To assure that no excipient interferences with the exploitation of the drug, the formulator must sensibly and critically assess combinations of the drug with each of the intended excipients and must as certain compliance of each ingredient with present principles and regulations. The screening of drug-excipient and excipient-excipient interactions should be carried out routinely in pre formulation studies. Determination of the optimum drug-excipient compatibility determined by DSC, FTIR, & XRD studies.

Formulation of chronotherapeutic dual delivery

Generally, the biphasic delivery system are devise to discharge the drug at two diverse rates or in two different timeperiods: they are either fast/slow or slow/fast. A fast/slow discharge schemedelivers a preliminary rupture of drug release subsequently a constant rate of release over fixed period of time. This system is used usually when maximumrelief requires to be attained rapidly, and is succeeded by asustained release phase to refrain reputation of administrations.

In general, traditional controlled dosage form slow the discharge of therapeutic systemic level and do not deliver a quick onset of actions. For change drug release the surface area exposed to a fluid can be controlled by the accumulation of barrier layers to one or both side of dosage form. However the multilayer system for attaining a
constant release rate from a tablet without a biphasic release of drug. When a constant rate for drug release does not effect completely therapeutic level, the fast/slow discharge system may be an other mode. This biphasic release system can be accomplished by applying an instant release layer to the conventional layered matrix tablet.\textsuperscript{130}

For obtaining fast/slow drug delivery system, established a two-layer tablet that extended discharge of piretanide for eight hours; β-cyclodextrin used in the fast releases layer, whereas ethylcellulose and hydroxypropyl methylcellulose were used for sustained releaselayer. Similar fashion (compressed two-layer tablet) also implemented to get a biphasic release of drug. The rapid release layer enclosed asuper disintegrating agent (cross-linked sodium starch glycolate) to enhance drug release rate. The delay release layer consisted of an HPMC matrix tablet.\textsuperscript{131}

A different way to attaining rapid/slow drug delivery includes the application of a compressed core as in Figure. It consist of a sustained release tablet, that coated by compression over entire surface with a fast-disintegrating formulation. The drug was in both core tablet and outer powder layer. From the viewpoint of manufacturing, this technique is an eye-catching substitute to productions of multilayer dosage form, as additional layer are adhering to pre-compressed layers in process of double-layer or multilayer tableting may tough. Moreover, due to this system employ traditional manufacturing approaches, it is more satisfactory to industry.

\[ 
\text{Excipient + Drug} \quad \rightarrow \quad \text{Core Tablet} \quad \rightarrow \quad \text{Compressed Core Tablet System} \\
\text{(Immediate release granules)} \quad \text{(Sustained release tablet)}
\]

Mechanism of quick/slow drug release from chronof ormulation techniques
So appropriate association of the rapid and constant release phases would be permit optimization of the rapid and slow-dose fraction for the purpose of drug pharmacokinetic and metabolism.\textsuperscript{132}

To regulate drug discharge (i.e., in extended release component of biphasic system), in core tablet as sustained release agents ethylcellulose and hydroxypropyl methylcellulose were used. In matrix drug release systems, features of matrix-forming agent show a significant act in discharge tools of drugs. Amongst hydrophilic polymer, hydroxypropyl methylcellulose is one of the carrier most usually employed in the formulation of oral controlled drug delivery system, due to its capability to swell on gelification as comes contact to water. The gel develops a viscous layer, standing as a protective barrier to both influx of water and efflux of the drug in the solution.\textsuperscript{133}

On contrary, inert polymers like ethylcellulose can aid as an substitutes for the swelling polymers by forming inert matrices, with non physiological exploit, constant at various pH values and moisture levels, and regulate diffusion of the drug in direction of the surface of the matrix before to discharge.

**Granulation Techniques**\textsuperscript{141}

1. *Wet granulation*

The conception of wet granulation is used as a conventional process for tablet formulation, generally to reduce the bitterness of active drug with water insoluble materials. In this method, the material to be granulated, generally in powder forms, were wetted with an aqueous composition of a granulating agent to form agglomerates. This agglomerated product is afterwards dried and milled to reduced size in suitable form.

![Figure 1: Process principle for formation of agglomerates](image)
Wet granulation is carried out employing a high-shear mixer. This high-shear granulation process is a fast process which is liable for over wetting. Thus, the liquid volume added and the optimal amount is affected by the characteristics of the raw materials. Power consumption of the impeller motor and the impeller torque have been applied to screen the rheological properties of the wet mass during agglomeration and thus, have been used to regulate the end point of water addition.

### Steps involved in wet granulation

**Dry granulation**

In this method compression of the powder mixture is done without using of heat and the solvent. It is the minimum desired of whole method of granulation. The main fundamental steps are by compression formation of a compact of material and then after to mill this compact to get granule. Generally, 2 steps are applied for dry granulation. One is slugging, in which the powder is pre-compressed and milling of ensuing tablet to produce granule. The prime benefits of dry granulation or slugging are that use of minimum equipment and space. It doesn’t require for binder solution, mixing machinery and time taking drying step needed for wet granulation.
Direct compression
The term “direct compression” is defined as the method by which compression of tablet dosage forms are done directly from mixture of powder of API with proper excipient. No pretreatment of the powder mixture by wet or dry granulation technique is essential.

Steps involved in the direct compression method

Certain the applied drug delivery systems performs an important role in regulating pharmacological effect of the drug as it can influence the pharmacokinetic characteristics of the drug and drug action period and afterwards side-effect. The optimum drug delivery systems assures that active drug is accessible at the site of action for right time and interv

Differentiating drug delivery system in accord to their mechanism of drug releases

Alternative systematic which may be employed for the drug delivery systems is in accord to release of drug. Generally, it can differentiate as:

- **Immediate release** – drug is released instantly after administration.
- **Modified release** – drug release only happens after few time of the administration or for a extended duration or to a specific target in body.

Revised release systems may be of as below:

- **Delayed release**: drug is discharged only at some point after the initial administration.
- **Extended release**: extends the release to reduce dosing frequency.
- **Targeted-release systems**: The drug is discharged at or close to the proposed physiologic site of action.
Extended release systems can be again grouped as

- **Sustained release:** The drug is released that attains delay in release of drug about a prolonged duration non specific at a fixed rate.
- **Controlled release:** Thedrug delivery systems from which the drug at a scheduled rate over a extend period of time,

**IMMEDIATE RELEASE ORAL DRUG DELIVERY:**

- Immediate release formulations are designed and developed to disintegrate and discharge drug without presence of any regulating factors like coating or any formulation methods.
- The disintegrating and releasing their medicinal quickly in the g.i. tract.
- A *disintegrant* is a substance in a tablet formulation that enables the tablet to split into very small parts on contact with g.i. fluid.
- Such a quick rupture of the tablet matrix improves tablet particles surface area, hence rate of absorption of the active ingredient is increases & fabricating the wanted therapeutic actions.
- The appropriate choice of disintegrant and its stability of performance are important to development of formulation of instant release tablet. Starch is a universal excipients and also inexpensive, and effective tablet disintegrantion agent.
- A high concentration of starch is required as disintegration for immediate release..

**Role of Superdisintegrants in the manufacturing of immediate release tablets**

Disintegrating agents are used in formulation of tablet and also formulation of hard shell capsule to stimulate penetration of moisture and diffusion of dosage form matrix in dissolution media. Starch is generally must present at level of more than 5 percent to unfavorably affect compatibility, particularly in direct compression. However, intra granular starch in the wet granulations is not as effective as the dry starch.
Mechanism of Superdisintegrants

The tablets disintegration having as four major mechanisms as follows

**Swelling**

Tablets with high porosity display reduced disintegration because of deficiency of acceptable swelling force. This force is used in the tablet with low porosity. When segment of packing is very high, fluid is incapable in penetrating into tablet and again slows down in disintegration.137

**Porosity and capillary action**

Always the first step is disintegrations by capillary action. When the tablet placed in a appropriate aq. media, the media goes into the tablet and exchanges the adsorbed air on the particle, causes diminish the intermolecular bond and split tablet into fine particle. Uptake of water by tablet be governed by on hydrophilicity of the drugs or excipients. For these maintenance of disintegrant of porous structure and reduce interfacial tension toward aq. fluid is essential that aid in disintegration by generating a hydrophilic grid around drug elements.

**Particle repulsive forces**

This mechanism describes the swelling of tablet done by ‘nonswellable’ disintegrant. According to the particle repulsion theory nonswelling particles also make disintegrations of tablet. The electric repulsive force between particles and water repulsion is 2ndary to capillary action.

**Because of deformation**

Throughout tablet compression, the disintegrated particle became deformed and absorb their regular structures after comes contact with water or aqueous media. The swelling capability of starch was enhanced when granules were deformed in compression. That size increase of deformed particles yields spilt of the tablets.

**Characteristics of disintegrant**138

The ideal disintegrant should have the following characteristics:

- Should have poorly soluble
- ShouldPoor gel formation
- Should have better hydration capability
- Shoud have good compressibility and the flow characteristics
- No propensity to formation of complexes with the drugs.
Method of Addition of Disintegrants

Disintegrants are primarily added to tablet granules for producing the tablet in compressed form to split or disintegrate if kept in aq. environment. There are 2 method for incorporate disintegrating agent into the tablet:

- Internal Addition (Intra granular)
- External Addition (Extra granular)
- Partly Internal and External

In the external addition method, before to compression the disintegrant is added to the different size granules with mixing. In internal method, prior wetting the powder mixtures with granulating fluid the disintegration agent is mixed with excipient. Hence disintegrant is combined within the same granule. These methods are employed for some part of disintegrant may added internally & an additional part externally, which gives instant interruption of tablet into before compressed granules also the disintegrating agent within the granules yields more deterioration of granules to active powder particles.  

Factors affecting action of disintegrants

- Percentage of disintegrating agent
- Category and Type of substances
- Combination of disintegrants.
- Concentration of surfactants.
- Hardness of the tablets.
- Nature of Drug substances.
- Mixing and Screening.

After administration, the dosage forms made accordingly are to discharge the drug instantly or minimum as fast as conceivable, that is applicable when a fastest onset action is needed for therapeutic cause. For i.v. injection and infusion onset action is very quick & pharmacological effect may be occurs after route of administration. The reasons are

I. Already drug is in solution, hence usually there is no need of drug to be released from the dosage form.
II. The drug is rightly given into the body, hence there is no possibility of drug permeation by the skin or mucosal membrane, formerly the target organs may attained.

The powders and granules require to dissolve 1st prior to dissolution by drug is released. For tablets at first the tablet disintegrates, if it is of from compressed granules this will initially occur to the levels of granules, from which more disintegration into powder particles & at last drug dissolution happen. Then after drug may either dissolve from usually solid powders or granules in case of hard gelatin or HPMC capsules or may dispersed from the usually liquid, lipophilic content of a soft gelatin capsule. The instant-release dosage forms have an onset action in sequence of min. to hr. The instant-release dosage forms dissolve or disperse drug in a single action that follow 1st order kinetics profile. Which means initially drug is released very fast and then after passes through the mucosal membrane into the body, attaining the highest plasma level ($C_{\text{max}}$) in a least time ($t_{\text{max}}$). Uptake by the mucosal membranes may be due to passivediffusion or by receptor-mediated active transport mechanisms. It is the sum of a 1st-order absorption and a 1st-order elimination process. The resulting function is termed as the Bateman function. Figure 1.2 shows an ideal plasma conc. vs time profile of an instant-release oral dosage form.

![Figure 1.2](image_url)

**FIG:** Idealised plasma conc. VS time profile of an instant release oral dosage form.
INTRODUCTION

Cmax is highest drug plasma concentration. T max is time at which Cmax is reached. The area under the plasma conc. VS time profile is known as AUC and explains total amount of absorbed drug.

The necessary review for immediate-release dosage forms is that time of action of drug is limited to time that conc. of drug is above MEC. If drug is of short biological half-life, time duration may be short, needful constant dosing which leads to short patient compliances and suboptimal therapeutic outcomes.145

Modified release

Dosage forms can be optimized & designed to made modification in release of drug over a certain time or after the dosage form attains the needed site.

Delayed release

Slow release dosage forms may explained as systems that are formulated to discharge active ingredient at a time other than instantly after administration. Delayed release from oral dosage forms can regulate where drug is released.

Slow release systems may applied to guard the drug from degradation in the low pH environment of stomach or to protect stomach from irritation by the drug. In such cases drug release must be delayed till dosage form has attained small intestine. The suitable polymer is required for delay drug release due to lag time achieved. The polymer dissolves at paricular pH, so when the dosage forms get into the low-pH of the stomach to high pH atmosphere of small intestine, the polymer coat dissolves and cause the drug release. The drug release resulting the plasma conc. vs time curve is comparable to that for instant release dosage forms. The optimization of colon-specific drugs and dosage forms may be useful in treatment of local and systemic diseases, along with colorectal cancer and Crohn’s disease. Figure explains an ideal plasma conc. vs time profile of a delayed-release oral dosage form. Tmax (but not Cmax) is highly dependant on gastric emptying times may quite variable.146
**FIG** Idealized plasma concentration versus time profile of a delayed-release oral dosage form compared to an instant-release dosage form. $T_{\text{max,IR}}$ Instant release is time for max. plasma conc. of drug released from an immediate-release dosage form and $T_{\text{max,DR}}$ is time for max. plasma conc. of drug released from a delayed-release dosage form.

**Extended release**

Extended-release systems permit for drug to be free over a prolonged period of time. By extension of the release profile of a drug, the frequency of dosing can be lowered. For instant-release dosage forms the time interval the plasma conc. is in the therapeutic range of the drug can be quite short. Hence constant dosing, with its related compliance issues, is mandatory. This is particularly a concern in chronic diseases when patients require to take the medicine for prolonged durations of time, often for remaining of their life. Extended release may attained using sustained- or controlled-release dosage forms.

**SUSTAINED RELEASE ORAL DRUG DELIVERY:**

- It is the dosage formulation which permits high drug loading, predominantly for active ones with high solubility of water.
- Initially an adequate quantity of drug used to the body to cause anticipated pharmacological action. The remaining amount of drug is released
regularly and need to maintain the max. initial pharmacological activity for
wanted duration of time in excess of time wanted from usual single dose.

- To optimize the biopharmaceutic, characteristics as well as
  pharmacokinetic and pharmacodynamic properties of a drug to use maximized
  through decreasing in side effects and regulate of lowest amount of the drug
  administered for sustained drug delivery system.

- Sustained release means maintainance dose and loading dose required to
  complete the same therapeutic effect.

- The therapeutic amount of drug to the exact site in organ of body to
  attain and also to maintain the wanted drug conc provided for sustained
  drug delivery.

- Oral route used for sustained delivery of drugs higher flexibility in
  dosage form design and comfort of production and cheap low cost.

- The mechanism of this drug delivery was based on dissolution,
  diffusion or a combination to control of drug release.

Advantages:

- Reduction in fluctuation in steady state level and there fore better
  control of disease condition and decreased intensity of local or systemic side
  effect.

- the safety margin of high potency drugs is increased due to better
  control of plasma levels.

- Increased patient compliance and convenience due to less frequent drug
  administration.

- The drug delivery to specific target areas of the body in a specified
  period of treatment.

- Maximum utilization of drug enabling decrease in total amount of
  dose administered

- To administer and monitor patient is reduced in personnel time.
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Considerations for formulation of sustained release formulation:

- If the pure drug has a long half-life, then the drug itself is a sustained one.
- If the pharmacological activity of the active drug is not associated to its blood levels, then the time releasing has no function.
- If the active compound has a short half-life, it requires a huge quantity of effective dose.
- The therapeutic window is required to avoid toxicity.
- First pass clearance
- High therapeutic index
- Required absorption window.

Limitations

- Decreased systematic availability in comparison to immediate release conventional dosage forms due to the insufficient residence time for the complete release.
- Poor in invitro-invivo Correlation.

Requirement for sustained drug release

- Release rate and dose concentration.
- Drug properties like physical–chemical properties like dose size, aqueous solubility, the partition coefficient, the drug stability, and the biological properties like ADME, duration and the therapeutic of action.
- Fabrication of sustained release products.

The rate of drug release over a sustained duration system is maintained. For example, if the dosage form is sustained throughout the gastrointestinal tract, i.e., reduction in $C_{\text{max}}$ and the time period of drug concentration in therapeutic range, that may decrease frequency of dosing. This dosage form can achieve the generally by the use of suitable polymers like EC/HPMC having different grades that are employed either to coat granules or tablets like reservoir systems or to form a matrix in which drug is dissolved or dispersed.
The release kinetics of the drug from these systems may vary:

1. Reservoir systems follow a zero-order kinetics
   (linear release as a function of time).

2. Matrix systems regularly follow Higuchi model
   (linear release as a function of the square root of time.)

The drug conc. at exact sites should be above the MEC and below MTC. This conc. duration is termed as the therapeutic range and illustrating as the drug plasma levels after oral administration of a drug from an instant release dosage form attaining the wanted conc. of a drug is dependant on the frequency of dosing, drug clearance rate, route of administration and the drug delivery system employed.

**FIG:** Drug plasma levels after oral administration of a drug from an instant release dosage form. Therapeutic range is the conc. duration between MEC & MTC. $\Delta t$ is time interval drug is in therapeutic range.
Controlled-release

Controlled-release systems also give a sustained-release profile but, in variation to sustained-release forms, this system made to edge to probably continuous plasma conc., freely to biological circumstance of the applicable site that indicates that they are regulating drug conc. in body, not only to release of drug from the dosage form, as in a sustained-release system. Other difference is that restricted to oral dosage forms whilst controlled-release systems are used in a different of route of administration, including transdermal, oral and vaginal.

These are drug delivery systems in which drug is released in a fixed manner over a set duration of time, so drug release follows zero-order kinetics. The drug release rate from dosage form should be the rate-determining step for absorption of drug. It depends upon the drug conc. in plasma and target site. The controlled-release systems are not essentially target-specific, that means that it do not ‘particularly’ discharge drug to targeting organ. This system is so called as targeted delivery systems that goal to feat the features of drug carrier and drug target to regulate bio-distribution of the drug. Figure shows an ideal plasma conc. vs time profile of a controlled-release dosage  

![Image](image.png)

**FIG** : Ideal Plasma conc. VS time profile of a controlled-release dosage form.

Plasma drug conc. profiles for current tablet / Capsules formulation, a sustained release formulation and zero order controlled release formulation comparision shows in figure
Comparison of controlled, sustained and conventional dosage forms

**Repeated action dosage form**
It is a category of modified drug release which is made to release one dose or drug initially succeeded by a 2nd dose at latter time.

**Prolonged action dosage form**
It is fashioned, drug slowly and provides continuously supply of drug over an extended duration of time.

**Targeted-release dosage forms**
The drug releasing rate is controlled from its delivery system can regulate conc. of plasma drug levels, once drug released there is little regulate over distribution of drug in body. Some little drugs bind entirely to wanted therapeutic target and this can occurs to decreased efficacy and higher toxicity. Drug targeting to regulate release of a drug within body such that the main stream of the dose selectively interrelates at a cellular or subcellular level with target tissue. It is feasible to enhancing the activity and specificity of drug and to decrease its toxicity and side-effects. Drug targeting can be attained by making systems that calmly target sites by applying normal condition of target organ or tissue to direct drug to target site. Rather drugs and specific delivery system can be aggressively targeted in use of targeting groups like antibody to fix to particular receptor on cell.\(^{150}\)