CHAPTER – 1

INTRODUCTION

1.1. NOVEL DRUG DELIVERY SYSTEMS

In 21st century, the pharmaceutical industry is caught between the downward pressure on prices and the increasing cost of successful drug discovery and development.

In the form of a novel drug delivery systems, an existed drug substances can get a new live, increasing market value, and patent protection period extending.

A significant increase in approval of novel drug delivery systems in the fast few years, and this is expected to continue at an impressive growth rate in the future.

The scale of drug delivery products is worth of at more than $22 billion in worldwide, and this growth is expected to continue into the present century.

Novel drug delivery systems can include that is based on physical mechanisms and based on Bio-chemical mechanisms. Physical mechanisms which includes controlled drug delivery systems are dissolution, diffusion, electro transport and osmosis. Bio-chemical mechanisms include Gene therapy, Monoclonal antibodies, Liposome, Vector substances and drug-polymer complex.

A novel drug delivery system is a system that offer multiple drug delivery forms.

1) Oral drug delivery systems,
2) Nasal and pulmonary drug delivery systems,
3) Parenteral drug delivery systems,
4) Implant drug delivery systems,
5) Transdermal drug delivery systems,
6) Topical drug delivery systems,
7) Protein and peptide drug delivery systems.

1.2 ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS¹⁹

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed for controlled release systems, the oral route of administration has by far received the most attention with predict to research on physiological and drug constraints as well as design and testing of products. This is because there is more flexibility in dosage form design for the oral route than other routes.

The most common and popular route for delivering drug in controlled manner or conventional way is known oral route. Historically, oral route of drug administration is predominant route and convenient route for drug delivery. The reasons for selection of oral route include easy of administration and well known gastrointestinal physiology offering flexibility in drug design as dosage forms in different ways. Oral route of drug administration requires least aseptic constraints and their easy manufacturing.

Solid dosage forms (i.e. tablets and capsules) are the majorly administered through oral route before the advances introduced in drug delivery technology. In the last two decades development in drug
delivery technology is rapid and many oral novel drug delivery systems invented.

In spite of tablets, capsules, solutions, emulsions and suspensions, they are more superior to the oral conventional formulations. The aid of drug development is to increase safety and efficacy of therapy when administered to patients. In such a way many pharmaceutical industries challenged, optimization of drug properties and the way in which they are delivered from different dosage forms.

Novel oral drug delivery systems are controlled release dosage forms and targeting dosage forms, due to GIT act as barrier for systemically acting drugs and as target site for local action purpose. Generally controlled drug delivery systems delivered drug in controlled manner for systemic absorption and no specified particular area in GIT. While in targeted preparations show their action in a specified area or tissue of the GIT (e.g.: colon, duodenum etc). Targeting systems are either controlled release or in burst at the specific area of the GIT. A new generation in oral drug delivery technology is osmotic activated systems, have recently entered into the market through regulatory approval. All formulations for systemic delivery through oral route of administration, independent of mode of delivery (immediate or controlled release) and the design of dosage form (either solid or liquid), must be developed within the characteristics of gastrointestinal physiology. Therefore fundamental understanding of GI physiology, pharmacokinetics, pharmacodynamics and formulation design, are plays an important role in achieve a systemic approach to
the successful development of an oral pharmaceutical drug delivery systems.

**Table 1.1: Characteristics of the intestinal regions**

<table>
<thead>
<tr>
<th>Section</th>
<th>Length</th>
<th>Secretion quantity/day</th>
<th>pH</th>
<th>Chyme (pH)</th>
<th>Retention time (hr)</th>
<th>Absorption area (m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth</td>
<td>10 cm</td>
<td>1-2 L</td>
<td>Saliva 5-8.5</td>
<td>---</td>
<td>10-20 sec</td>
<td>0.02</td>
</tr>
<tr>
<td>Esophagus</td>
<td>20 cm</td>
<td>Mucus</td>
<td></td>
<td></td>
<td>10-30 sec</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>25 cm</td>
<td>Empty stomach 50-100ml &amp; after meals 2-3 L</td>
<td>Gastric fluid 1-1.5</td>
<td>3-5</td>
<td>0.5-3 hr</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>Small intestine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>25-30 cm</td>
<td>0.7-1.5 L</td>
<td>Pancreatic juice 7.5-8.4</td>
<td>6-6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>2 m</td>
<td>0.6 L</td>
<td>Bile 6.1-8.6</td>
<td>6-8</td>
<td>6-8</td>
<td>100</td>
</tr>
<tr>
<td>Ileum</td>
<td>3 m</td>
<td>2-3 L</td>
<td>Mucosal secretion 7.6 L Reabsorption of water 7 L</td>
<td>6-8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>1.2-1.5 m</td>
<td>Reabsorption of water 0.3 - 1 L</td>
<td>---</td>
<td>6 – 7</td>
<td>10 or 5-4 cm/hr</td>
<td>0.5 – 1</td>
</tr>
<tr>
<td>Rectum</td>
<td>12-20 cm</td>
<td>---</td>
<td>Rectal mucus 7.2-7.4</td>
<td>---</td>
<td></td>
<td>0.04-0.07</td>
</tr>
</tbody>
</table>

The successful developments of an oral drug delivery system need the scientific frame work of understanding basic aspects include

i. Biopharmaceutical characteristics of the drug,

ii. The anatomy and physiology of GIT, and

iii. Physicochemical properties and model delivery by the dosage form to be designed.
Although, it is impractical to alter biopharmaceutical characters of drug to be delivered by chemical modifications, such as synthesis of an analog, medically undesirable to modify the anatomy and physiology of GIT, the design of controlled release oral dosage form with optimization of dosage form characteristics with GIT characteristics could provide some opportunity to rationalize the systemic drug delivery with maximum therapeutic benefits.

The term “controlled release oral dosage form” is not new those people working in various fields of pharmaceutical R&D. Really, approximately 30 years ago, the USFDA published regulatory requirements for controlled release systems. From last decades there has also been an increase in the use of controlled release products.

In the searching of oral controlled release drug administration, potential challenged areas include

1. Proper delivery system developed for therapeutically effective rate to desirable site for direction required for optimal treatment.

2. Change or alteration of GI transit time leads to drug delivery to a target site or to the vicinity of an absorption site and prolongation in drug delivery.

3. Reduction of hepatic first pass metabolism via bypass or minimization of extent.\textsuperscript{2}
1.2.1 Advantages\textsuperscript{19}

1) Reduction in dosing frequency easily acceptance of patient.
2) Loss of drug can be reduced by targeting.
3) Decreasing GI side effects and toxicological effects.
4) Fluctuation in plasma drug level minimized.
5) Better patient compliance.
6) Convenient to administration compared to other routes of administration.
7) Stability of drug can be increased.
8) Uniform drug effect achieved.
9) Delivery of drug in the vicinity of site of action.
10) Maintenance of optimal and effective dosage levels for long action.

1.2.2 Disadvantages\textsuperscript{19}

There are some disadvantages also encountered in controlled oral drug delivery systems. They are

1) It is an expensive process.
2) Poor in vitro-in vivo correlation.
3) Dose dumping occurred due to polymer burst action at a particular site.
4) It is difficult to terminate the toxicity by withdrawal process.
1.3 NEED OF CONTROLLED ORAL DRUG DELIVERY SYSTEMS

Controlled release of active ingredients from oral dosage forms may be required for the following reasons,

- Avoidance of undesirable local side effects.
- Local treatment of diseases of GI tract.
- Protection of active ingredients against the influence of digestive fluids.
- Influencing the pharmacokinetics of active ingredients.

1.4 CLASSIFICATION OF ORAL CONTROLLED RELEASE SYSTEMS

The majority of oral controlled release drug delivery systems depends on, diffusion, dissolution or a combination of diffusion and dissolution mechanisms to produce slow release of drug. Depending upon the manner of drug release these systems are classified as

1. Dissolution controlled release systems
2. Diffusion controlled release systems
3. Dissolution and diffusion controlled release systems
4. Ion exchange resins
5. pH independent formulations
6. Osmotic controlled release systems
7. Altered density release systems
8. Prodrugs
9. Delayed release systems
1.4.1 Dissolution controlled release systems

A drug with a poor dissolution rate will yield an inherently controlled blood drug level. The preparation of controlled release products of highly water soluble drugs by reducing dissolution rate by

- Preparing an appropriate salt derivatives,
- By coating the drug with a slowly dissolving material or
- By incorporation into a tablet with a slowly dissolving carrier.

The principle dissolution control is as follows

\[ J = -D \frac{dc}{dx} \]

Where \( J \) is flux

\( D \) is diffusion coefficient and

\( \frac{dc}{dx} \) is concentration gradient from the solid surface to the bulk solution.

If the concentration gradient is linear and layer thickness is \( h \),

\[ \frac{dc}{dx} = \frac{(C_b - C_s)}{h} \]

Where \( C_s \) is concentration of the solid surface, and

\( C_b \) is concentration in the bulk solution.

The common formulations depending on dissolution to determine release rate of drug fall into two categories:

I. Encapsulated dissolution systems

II. Matrix dissolution systems

Encapsulated dissolution systems prepared by application of coating on particles or granules of drug with varying thickness of slowly soluble polymers or by microencapsulation.
Matrix dissolution devices are prepared by compressing the drug with a slowly dissolving polymer carrier into a tablet by congealing or aqueous dispersion methods.

**1.4.2 Diffusion controlled release systems**

In this systems release rate of drug is depend on its diffusion through a water insoluble polymer. Two types of diffusion devices are available. They are reservoir devices and matrix devices. The release of drug from the reservoir device is explained by Fick’s first law

\[ J = -D \frac{dC}{dx} \]

Where \( J \) is flux of drug across a membrane, 
\( D \) is diffusion coefficient over a distance \( x \). 
Depending on the device, equation of drug release will vary.

In matrix devices, rate of drug release is dependent on rate of drug diffusion but not dissolution. Drug release from these devices can be explained by higuchi’s equation.

**1.4.3 Dissolution and diffusion controlled systems**

The main characteristic is that the drug reservoir is surrounded with a partially soluble layer. The part of dissolution membrane allow to diffusion of the drug through pores in the polymer membrane. The drug release from these systems explained by following equation:

\[ \text{Release rate} = AD(C_1 - C_2)/l \]

Where \( A = \text{Surface area} \),

\[ D = \text{Diffusion coefficient} \]
L = Diffusion path length

$C_1 =$ Concentration of drug in the system

$C_2 =$ Concentration of drug in the dissolution medium.

1.4.4 **Ion exchange resins**

This principle has been used for a long time in analytical and protein chemistry. It is an attractive one of controlled drug delivery because drug release characteristics related to the ionic charges of the resin containing drug and should therefore be less susceptible to environmental conditions like enzyme content and pH at the site of absorption. Drug release can be modified by application of coating on the drug-resin complex.

1.4.5 **pH independent formulations**

The GI tract presents different features that are not fond in other routes of drug administration. The variable nature of the chemical environment throught the GIT is a constraint on dosage form design. Indeed, drugs administered orally would encounter a spectrum of pH ranging from 1 to 1.6. The pH dependency of drug release from controlled release formulations has been demonstrated by study of papaverine hydrochloride.

1.4.6 **Osmotically controlled release systems**

In these systems, osmotic pressure provides the driving force that produce constant drug release. This system is prepared by applying a semi permeable membrane around an osmotically active drug core or osmotically inactive drug core in combination with
osmotically active salt. A delivery orifice made on the system by a high speed – mechanical drill.

1.4.7 Altered density controlled release systems

The GI transit time varies depends on person. In most human subjects, it is the range of 8 to 62 hrs has been found. The specific density of these subunits is found to be a more significant factor than their diameter in influencing their GI transit time, specifically; increasing density from 1 to 1.6 increases the average transit time from 7 to 25 hrs. This approach helped in design of floating drug delivery systems and swelling systems.

1.4.8 Prodrugs

A prodrug is chemically modified one which will liberate the active pharmaceutical ingredient in the body either enzymatic or hydrolytic cleavage. The main objective of a prodrug for oral administration is to increase absorption rate or to reduce local side effects.(i.e. GI irritation by aspirin).

1.4.9 Delayed release systems

The development of these systems involves release of drug only at a specific site in the GIT. The drugs formulated in such a systems include

i. Known to cause gastric distress,

ii. To sensitive of gastric juice or intestinal enzymes,

iii. Absorption occurs at a specific intestinal site or

iv. To localization at a specific GIT site.
The most common ones are intestinal release systems and colonic release systems.

1.5 MATRIX TYPE ORAL CONTROLLED DRUG DELIVERY SYSTEMS\textsuperscript{5-7}

Matrix type drug delivery systems releases drug by both dissolution as well as diffusion controlled mechanisms. Drug release from the system depends on different solubility properties of drug dispersed in polymers. One of the simplest method involves the fabrication of sustained release dosage forms involve the direct compression of blended drug, polymer and additives. To develop tablet formulation in which the drug is dispersed in a matrix of the polymer. In another way drug and polymer may be granulated prior to compression.

1.5.1 Advantages of matrix tablets

1. Minimize the local and systemic side effects
2. Improvement efficacy in treatment
3. Minimization of drug accumulation
4. Improvement the bioavailability of the some drugs
5. It is a versatile and low cost
6. Reducing toxic effects by slowing absorption
7. Increase stability of drug by protection from hydrolysis
8. The ability to provide special effects

1.5.2 Disadvantages of matrix tablets

1. The release rate can be effected by various factors like food, GI transit time, etc
2. The matrix must be removed from the body after releasing the drug.

3. The drug release rate vary with square root of time.

### 1.5.3 Classification of matrix tablets

Matrix drug delivery systems broadly divided into two classes are:

- **Reservoir type matrix systems** – in this system drug release controlled with membrane.
- **Monolithic matrix systems** – in this system drug dispersed in a matrix or encapsulated.

### 1.5.4 Depending on the type of polymer

Matrix tablets classified into following types:

#### 1.5.4.1 Lipophilic matrices (Plastic matrices)

This concept was first discovered in 1959. In method of oral sustained release systems, drug is blended with polymer and compressed into a tablet. In fact sustained release produced by the dissolved drug has diffused through a network of channels of matrix. The rate controlled step involves liquid penetration into the matrix. E.g.: Polyvinyl chloride (PVC), Polyethylene (PE), Ethyl cellulose (EC), Acrylate polymers and their copolymers.

#### 1.5.4.2 Wax matrices

These are prepared by using lipid waxes and their derivatives. In this system, release of drug occurred through pore diffusion and erosion. Release characteristics are more sensitive to digestive fluids than to insoluble polymers matrix.
E.g.: Carnauba wax with stearyl alcohol or stearic acid is commonly used.

1.5.4.3 Hydrophilic matrices

These are widely employed in oral controlled drug delivery system due to their flexibility. The drug is formulated into gelatinous capsules or in tablets, polymers with high gelling capacities. In fact a matrix means mixing of one or more drugs with a polymer that leads to swelling when exposed to liquid environment. Commonly used polymers are as follows

Natural or semi synthetic polymers include agar-agar, alginates, molasses, carob gum, and polysaccharides such as mannose, galactose and chitosan, modified starches.

Cellulose derivatives are Hydroxylpropylmethyl cellulose (HPMC), Methyl cellulose 400&4000cps, Hydroxyethyl cellulose (HEC), and Sodium carboxymethyl cellulose (NaCMC). Polymers of acrylic acid, carbopol-934 commonly used.

1.5.4.4 Mineral matrices

The polymers extracted from seaweed species for system development. E.g.: Alginic acid obtained from brown sea weeds by using alkali.

1.5.4.5 Biodegradable matrices

These consist of polymers those comprised of monomers through cross linking between functional groups in the back bone. These are biodegraded into oligomers by metabolically with the
help of enzymes. E.g.: Proteins, Polysaccharides, Polylacticacid, Polyglycolicacid etc.

1.5.5 Depending on porosity of matrix\textsuperscript{15-18}

Matrix systems also classified according to its intrinsic character i.e. porous nature. They are

- **Micro porous system**: Size range of pores is 50 to 200Å slightly larger than diffusant molecule size.
- **Macro porous system**: Size range of pores is 0.1 to 1micrometers, which is larger than diffusant molecule size.
- **Non porous system**: There is no pores and drug diffuse through the network of matrix.

The present work is planned to prepare and evaluate novel drug delivery systems of highly soluble drugs alfuzosin hydrochloride and citicoline using hydrophilic and hydrophobic polymers. Alfuzosin is indicated for treatment of BPH. Citicoline is used in the treatment of neurodegenerative disorders like alzheimer’s disease, parkinson’s disease and head injuries with improve patient mental ability.

1.6 INTRODUCTION TO BENIGN PROSTATIC HYPERPLASIA (BPH) \textsuperscript{21}

BPH is a non neoplastic growth of cells within prostate gland. Benign prostatic hyperplasia (BPH) is also known as Benign prostatic hyper trophy. BPH is most common in aged men. It does not cause to prostate cancer. Age is the major factor for occurring BPH.

An estimated histological only 3.5% of men have BPH symptoms below 50 years but 50% of men have BPH by age of 51-60 years and
75% by age of 80 years, reach 90% over the age of 80 years. BPH becomes clinically significant in now a days due to BPH is the 4th disease of commonly noticed among patients greater than 50 years, after diabetes mellitus, obesity, cardiovascular disease and hypertension.

In this, prostate gland is affected means it’s size increased by multiplication of cells. Prostate gland is one of the important glands in male reproductive system. Prostate gland consists of two parts includes secretion (glandular) part and muscular part. The size of the prostate gland vary with age, at birth has size of pea. Prostate gland grows slowly before puberty, when it begins rapid growth occurred and reaches adult size of walnut, in the early 20 years. Prostate can be divided into lobular inner zone and an external layer. The hypertropic changes found in the inner zone that leads to BPH.

Prostate growth occurs in two ways, first type, cells multiply around the urethra and second type middle lobe growth. It leads to squeezing of urethra and patient feels like difficult to urinate. If begins the growth of prostate it continues until medical treatment started. The causes of growth of prostate gland linked with aging and accumulation of dihydrotestosterone. The average size of prostate in BPH patients observed as over 100 gms.

Most commonly encountered symptoms in BPH are clarified into two classes include irritative symptoms and obstructive symptoms. Irritative symptoms include frequency of urination; urgency and nocturia are also collectively known as failure of urine storage.
Obstructive symptoms include haematuria i.e. blood in the urine, weak urine stream due to decreased force and pushing or staining to begin urination, dribbling, hesitancy in initiation of micturition, sensation of incomplete emptying are also collectively known as failure to empty the bladder. The urinary obstruction caused by BPH has a static and dynamic components.

Approximately 32 million peoples in worldwide with moderate severe symptoms of BPH. The treatment options in the management of BPH includes watchful waiting, medical therapies and surgical interventions.

1.6.1 Advice for the management of lower urinary tract symptoms

- Limit fluid consumption before going out and before going to bed (to reduce urinary frequency & nocturia)
- Reduce alcohol and caffeine intake
- Schedule toilet visits
- Manage constipation
- Review medication (including diuretics & other medicines that can affect the urinary symptoms)
- Bladder training (encourage patient to go longer between voiding & increase the volume voided)
- Use distraction techniques (practice breathing exercise & penile squeezing to control symptoms of irritation)
Table 1.2: Common therapeutic problems and proposed management strategies in benign prostatic hyperplasia

<table>
<thead>
<tr>
<th>PROBLEM</th>
<th>SOLUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient taking Alfa-blocker still symptomatic after 2 weeks.</td>
<td>Patients should be advised that it may take 2-6 weeks before symptomatic treatment relief is seen.</td>
</tr>
<tr>
<td>Patient taking an alfa – adrenoceptor blockers complaints of cardiovascular adverse effects such as dizziness, syncope, palpitations, tachycardia or angina.</td>
<td>These side effects are more likely in elderly patients. They are most common after the first dose and reflect the hypotensive effects of the drugs. They can be reduced by titrating the dose are using more uroselective drugs such as tamsulosin.</td>
</tr>
<tr>
<td>Sexual dysfunction.</td>
<td>Decreased libido or impotence can occur in patients taking finasteride and dutasteride. Abnormal ejaculation can be caused by alfa-blockers. Tamsulosin in particular can cause a dry climax (restrograde ejaculation). Patients should be forewarned when discussing treatment options.</td>
</tr>
<tr>
<td>Patient taking finasteride notices breast enlargement.</td>
<td>Unilateral or bilateral gynacomastia is a frequently reported side effect with finasteride and patients need to be counseled accordingly when discussing treatment options.</td>
</tr>
<tr>
<td>Patient taking finasteride or dutasteride has a sexual partner who is pregnant.</td>
<td>Exposure to semen should be avoided as both drugs can cause abnormalities to genitalia in a male fetus. The patient should be advised use a condom.</td>
</tr>
</tbody>
</table>
1.6.2 **Pharmacological classification of drugs**\(^{22-23}\)

1.6.2.1 **α\(_1\) adrenergic blockers**: Which decrease tone prostatic /bladder neck muscle. The contraction of prostate gland’s smooth muscle occurs by stimulation of adrenergic neurons via alfa\(_1\) receptor. There are three subtypes present, α\(_{1a}\), α\(_{1b}\) and α\(_{1d}\). The α\(_{1a}\) is the dominant receptor in prostate gland which is present 70%. Tamsulosin has selectivity to α\(_{1a}\) & α\(_{1b}\) adrenoceptors and well tolerated drug. When compared with tamsulosin or doxazosin alfuzosin shows higher selectivity for the prostate gland.

E.g.: Prazosin, Terazosin, Alfuzosin, Doxazosin and Tamsulosin.

1.6.2.2 **5α-reductase inhibitors**: Which arrest growth/reduce size of prostate. The important androgen that play major role in the development of prostate is dihydrotestosterone. Testosterone converted into dihydrotestosterone in presence of an enzyme 5α-reductage.

E.g.: Finasteride, dutasteride etc.

**Table 1.3: Marketed drugs available used for the treatment of BPH**

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>DRUG</th>
<th>BRAND NAME</th>
<th>STERNGTH</th>
<th>(T_{1/2})</th>
<th>DOSAGE FORM</th>
</tr>
</thead>
<tbody>
<tr>
<td>α – blockers</td>
<td>Terazosin</td>
<td>Hytrin</td>
<td>1,2,5&amp;10mg</td>
<td>--</td>
<td>Capsule</td>
</tr>
<tr>
<td></td>
<td>Doxazosin</td>
<td>Cardura</td>
<td>1,2,4&amp;8mg</td>
<td>22hrs</td>
<td>Tablets</td>
</tr>
<tr>
<td></td>
<td>Tamsulosin</td>
<td>Flomax</td>
<td>0.4&amp;0.8mg</td>
<td>13hrs</td>
<td>Capsules</td>
</tr>
<tr>
<td></td>
<td>Alfuzosin</td>
<td>Uroxatral</td>
<td>10mg</td>
<td>5hrs</td>
<td>Tablet</td>
</tr>
<tr>
<td></td>
<td>Silodosin</td>
<td>--</td>
<td>4&amp;8mg</td>
<td>--</td>
<td>capsules</td>
</tr>
<tr>
<td>5α -reductase inhibitors</td>
<td>Finasteride</td>
<td>Proscar</td>
<td>5mg</td>
<td>--</td>
<td>Tablets</td>
</tr>
<tr>
<td></td>
<td>Dutasteride</td>
<td>Avodart</td>
<td>0.5mg</td>
<td>Longer</td>
<td>Capsule</td>
</tr>
</tbody>
</table>
Alfuzosin Hydrochloride shows higher selectivity for the prostate when compared with tamsulosin and doxazosin. It has suitable half life (5hrs) for controlled release dosage form and shows rapid onset of action with good tolerability. Alfuzosin reduces BPH effectively and gives sustained beneficial effect on quality of life. It also has least effect on the ejaculatory function compared with other drugs which are used in the treatment of BPH.19-23

Note: Alfuzosin Hydrochloride here after, it will be termed as Alfuzosin in the further discussion.

1.7 INTRODUCTION TO CEREBROVASCULAR DISEASE

“Cerebrovascular” word was combination of two words which is ‘cerebro’ and ‘vascular’.Cerebro means large part of the brain and Vascular means blood vessels (i.e. Arteries and veins), finally cerebrovascular refers to the flow of blood to the brain.

Cerebrovascular disease is the disorders of the brain,which is affected with bleeding or ischemia of the cerebral blood vessels. Cerebrovascular disease includes stroke, aneurysms, vascular malformations and stenosis (i.e.Carotid stenosis, intracranial and vertebral stenosis).

Cerebrovascular disease is general life threatening neurological disorder, stroke is a leading cause of serious long term disability, which is the 3rd leading cause of death in the world. As per the world health organization 15000000 people suffer with stroke per annum, out of this 5 million people are death and another 5 million people are
disabled permanently. Brain does not store oxygen but it receives 25% of body’s oxygen. It is necessary supply of oxygen to brain cells for healthy and function properly. So, needs blood supply continuously to the brain, which occurred via arteries namely carotid arteries and basilar artery.

A stroke is the result of loss of oxygen supply to the brain due to reduction of blood flow to the brain parts. Stroke can be caused by blockage and subsequently bleeding, of a blood vessel in the brain. Nearly 90% of strokes are ischemic type. In olden days nearly 2000 years ago, stroke was called ‘apoplexy’, common term applied to suddenly struck down with paralysis.

**1.7.1 Types of stroke**

There are mainly two types of major strokes and minor ones are transient ischemic attacks and silent strokes.

- Ischemic stroke
- Hemorrhagic stroke

**1.7.1.1 Ischemic stroke**

It arises from blockage of blood supply to the specific part of the brain. In which three categories are present,

- Thrombotic stroke is caused by blood clot forming in blood vessel or in the brain and disrupting blood flow to the specific part of the brain.
- Embolic stroke occurs when blood vessel supplying the blood to the brain is blocked by circulating debris (embolus) such as when clots form on artificial heart valves.
• Lacunar stroke, which cause weakness, clumsiness and emotional variabilities.

1.7.1.2 Hemorrhagic stroke

Strokes caused by blood vessel breaking and leaking blood into the brain. In which also two types are present,

• Intracerebral hemorrhage occurs when a blood vessel ruptures within the brain and leaks the blood into the around the tissues. High blood pressure is the primary cause to hemorrhage type stroke. In which observed symptoms are loss of consciousness, nausea, vomiting or severe headache.

• Subarachnoid hemorrhage is usually occurred by an aneurysm. A bulge in a wall of blood vessel, bursting in a large artery near the delicate membrane surrounding the Brain. In which symptoms include worst head ache of the patient, vasospasm when blood vessels irritated by excess blood and narrow in size. This leads to insufficient blood supply to brain.

1.7.2 Complications

The imbalance of cognitive abilities, speech, coordination, perception and paralysis. Depending on the damaged part, symptoms will be varied.

Eg: 1. Damage of right hemisphere causes paralysis of left side of the body.

2. Damage of cerebellum leads to problem with balance and coordination.
3. Brain stem damage leads to involuntary “life support” functions such as breathing and heart rate causes death.

1.7.3 Factors for stroke

There are two types of factors affect the stroke, they are

- Non modifiable factors
- Modifiable factors.

Non modifiable factors: Age, gender, race, ethnicity and genetics. Modifiable factors: blood pressure, excess fibrinogen, high low density lipophilic cholesterol, insulin resistance/glucose in tolerance and sleep apnea.

1.8 PARKINSON’S DISEASE (PD) 27-28

Parkinson’s disease is a neurological disorder in which movement, muscle control and balance can be affected by loss of dopaminergic neurons in the brain. It is a part of motor system disorders, which related with the loss of dopamine-producing cells of the brain. The dopamine related motor disorders commonly known as Parkinsonism. Parkinson’s disease generally occurs over the age of 50 years.

Parkinsonism is usually idiopathic but can arise from ischemic changes in the brain as in arteriosclerotic and postencephatic Parkinsonism. Parkinson’s disease occurs by cells destruction in the substantia nigra of brainstem and loss of neurotransmitter i.e. dopamine in corpus striata (caudate and putamen). Nerve cells of substantia nigra send out fibers gray and white bands of the brain both sides.
Dopamine loss or deficiency in the brain cells particularly in substantia nigra pars compacta, is primary cause to parkinson’s disease, which is one of the important catecholamine neurotransmitter, control movement, coordination and memory. Most common symptoms encountered in parkinson’s disease are

✓ Bradykinetia means poverty of movement and slowness,
✓ Muscular rigidity,
✓ Resting tremor means abates during voluntary movements.
✓ Disturbances of falling and gait,
✓ Difficulty in swallowing
✓ No expression in the face.

1.9 ALZHEIMER’S DISEASE (AD) 29-32

Alzheimer’s disease is a neurodegenerative disorder in which progressively irreversible destroys of brain cells. It is not a infection, but most common cause of dementia. Dementia is a condition which affects 10% of those over the age of 65 and 20% over the age of 75. The exact cause of Alzheimer’s disease is not known until now.

Dementia is a group of symptoms associated with deterioration in cognitive processes like memory, thinking and language ultimately effect on behavior. The neurofibrillary tangles which are made up of protein called as tau, leading to destruction of nerve cells subsequently form the protein called β-amyloid, surrounds with debris and dead nerve cells, and core of the plaque causes the brain shrink. The neurotransmitter acetylcholine level in the brain of Alzheimer’s patient much low, plaques and tangles are greater.
Symptoms of Alzheimer’s disease depend on the patient, there are mild, moderate and severe symptoms.

- Milder ones are forgetfulness, mood swings and speech problems.
- Moderate ones are delusions, difficulty performing spatial tasks, disturbed sleep, disorientation etc.
- Severe ones are dysphasia, weight loss, complete loss of short-term and long-term memory, difficulty changing position or moving from place to place etc.

**Table 1.4: Citicoline marketed products**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Brand Name</th>
<th>Dosage Form</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Cholinerv</td>
<td>Tablet</td>
<td>500mg</td>
</tr>
<tr>
<td>2.</td>
<td>Cholinerv</td>
<td>Injection</td>
<td>125mg/ml</td>
</tr>
<tr>
<td>3.</td>
<td>Ceeti FC</td>
<td>Tablet</td>
<td>500mg</td>
</tr>
<tr>
<td>4.</td>
<td>Cicolin FC</td>
<td>Tablet</td>
<td>500mg</td>
</tr>
<tr>
<td>5.</td>
<td>Metalin</td>
<td>Tablet</td>
<td>500mg</td>
</tr>
<tr>
<td>6.</td>
<td>Neurospark</td>
<td>Injection</td>
<td>500mg/2ml</td>
</tr>
<tr>
<td>7.</td>
<td>Strolin</td>
<td>Tablet</td>
<td>500mg</td>
</tr>
<tr>
<td>8.</td>
<td>CDP</td>
<td>Syrup</td>
<td>500mg/5ml</td>
</tr>
<tr>
<td>9.</td>
<td>Citistar</td>
<td>Tablet</td>
<td>500mg</td>
</tr>
<tr>
<td>10.</td>
<td>Strocit</td>
<td>Tablet</td>
<td>500mg</td>
</tr>
</tbody>
</table>

**Note:** Citicoline Sodium here after, it will be termed as Citicoline in the further discussion.
1.10 NEED FOR ALFUZOSIN EXTENDED RELEASE TABLETS

Alfuzosin is a quinazoline derivative belongs to class of α adrenoreceptor antagonist, used in the effective treatment of Benign Prostatic Hyperplasia through oral administration, selectivity for a post synaptic alfa-1 adrenoceptor of the prostate gland. The recommended daily dose of Alfuzosin hydrochloride is 2.5 to 10mg in divided doses 2 to 3 times a day. The drug causes gastrointestinal disturbances such as nausea, gastric pain, diarrhea, dizziness, fatigue and headache. Rarely syncope, palpitations, chestpain, orthostatic hypotension, drowsiness, asthenia, tachycardia, dry mouth, pruritus, oedema, skin rashes and upper respiratory tract infections if present in a larger concentration in GIT. Alfuzosin hydrochloride has a short half life of 5hrs.

Because of above mentioned reasons controlled release formulation of alfuzosin hydrochloride is designed. These systems improve the efficacy, reduces the frequency of administration and also reduces the toxicity and adverse effects.

1.11 NEED FOR CONTROLLED RELEASE DOSAGE FORM OF CITICOLINE

Citicoline is widely used as cerebroprotectant and nutraceutical agent in the world wide. Citicoline is derived from cytidinetriphosphate reaction with phospocholine, act as intermediate for phospotidyl choline which is an important chemical substance in the brain cells. Citicoline used widely in the treatment of neurodegenerative disorders
especially in trauma, Alzheimer’s and Parkinson’s disease. It is used in doses of 500, 1000, 2000 and 3000mg once or twice daily oral administration. Head injuries and ischemic stroke requires continuous therapy or prolonged administrations of Citicoline from few days to years due to severity of diseases. Citicoline helps in increase acetylcholine levels in the brain. Citicoline has minor side effects of gastric disturbances like stomach pain and diarrhea. The common preparations of citicoline are tablets, injections and solution forms available in the market. Controlled release formulations are needed for Citicoline to avoid fluctuations in plasma concentrations, enablc absorption, associated GIT disturbances and improve patient acceptance.