

# Need for alfuzosin hydrochloride extended release tablets biology essay

[Science](#), [Biology](#)



## **ABSTRACT**

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Controlled drug delivery system for oral dosage forms offer greater advantages in minimizing the dosage frequency and thereby the toxicity and improves the patient compliance. These novel drug delivery system control the release of drug by diffusion or erosion or osmosis etc. The present study was to develop stable and robust formulations of Alfuzosin Hydrochloride ER tablets 10mg and controlled release tablets of Citicoline 1000 mg. Alfuzosin Hydrochloride is used to reduce the symptoms of benign prostatic hyperplasia (BPH). Citicoline is useful in the treatment of ischemic stroke, head trauma and neurodegenerative disease. Design of controlled release drug delivery systems for highly soluble drugs is challenging to pharmaceutical scientists. Various techniques have been proposed in the design of controlled release systems of these moieties. Matrix tablets have gained popularity in the designing of controlled drug delivery systems. But it is difficult to control the release of high soluble drugs by simple matrix system. Hence in the present study we aimed in the preparation of matrix dosage forms for alfuzosin and citicoline by using mixture of polymers. In case of alfuzosin we used different combination of hydroxyl propyl methyl cellulose and guar gum. The formulation ALF /10 (combination of guar gum and HPMC K100 M) showed comparable results with respect to in vitro and in vivo tests, when compared with commercial reference formulation (UROXATRAL). In case of citicoline we used combination of hydrophilic and hydrophobic polymers. Citicoline controlled release tablets were prepared by wet granulation method using non aqueous granulation fluid. The

formulation CTC/14 (Eudragit RSPO- 12.5 % W/W and tablet coated with Eudragit RLPO) showed comparison results with respect to in-vitro tests, when compared with marketed formulation (STROLIN- OD) and also proven controlled drug release when compared with respect to in-vivo studies. Both the formulations (ALF/10 & CTC/14) were fitted in to zero order, first order, Higuchi's, Peppas & Korsmeyer kinetics with fickian model diffusion mechanism. They followed first order kinetics with diffusion mechanism. Both the formulations were evaluated stability studies and they are proven stable at accelerated conditions of  $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$  &  $75\% \pm 5\% \text{RH}$  for 3 months.

## **NEED FOR ALFUZOSIN HYDROCHLORIDE EXTENDED RELEASE TABLETS**

Alfuzosin is a quinazoline derivative belongs to class of alfaadrenoreceptor antagonists, 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, chest pain, orthostatic hypotension, drowsiness, asthenia, tachycardia, drymouth, pruritus, oedema, skin rashes and upper respiratory tract infections if present in a larger concentration in GIT. Alfuzosin 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.

## **NEED FOR CONTROLLED RELEASE DOSAGE FORM OF CITICOLINE:**

Citicoline is widely used as cerebroprotectant and nutraceutical agent in the world wide. Citcoline is derived from cytidinetriphospate 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. Citcoline helps in increase acetylcholine levels in the brain. Citcoline has minor sideeffects 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 citcolineto avoid fluctuations in plasma concentrations, enabic absorption, associated GIT disturbances and improve patient acceptance.

## **CHAPTER – 1**

### **1. 1. NOVEL DRUG DELIVERY SYSTEMS: 1**

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. Oral drug delivery systems, Nasal and pulmonary drug delivery systems, Parenteral drug delivery systems, Implant drug delivery systems, Trans dermal drug delivery systems, Topical drug delivery systems, Protein and peptide drug delivery systems.

## **1. 1. 1BENEFITS OF NOVEL DRUG DELIVERY SYSTEMS:**

Improvement of patient acceptance of treatment. Allowing patients to receive medications as out patients. Controllable drug release provides especially for sensitive drugs. Technologies for self - assembles.

Improvement in patient compliance. Reduction of adverse reactions.

Materials for nanoparticles those are biocompatible and biodegradable.

Improved out comes. Reduction of the treatment cost. Reduce fluctuations of plasma - drug levels.

## **1. 2 ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS: 19**

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 gastro intestinal 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

### Section

### Length

### Secretion quantity/day

### pH

### Chyme (pH)

### Retention time (hr)

### Absorption area(m<sup>2</sup>)

Mouth 10 cm  
1-2 L  
Saliva 5-8. 5

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10-20 sec  
0. 02  
Esophagus 20 cm  
Mucus 10-30 sec  
Stomach 25 cm  
Empty

stomach 50-100ml & after meals  
2-3 L  
Gastric fluid 1-1. 5  
3-50. 5-3 hr  
0. 1-0.

2  
Small intestine  
Duodenum 25-30 cm  
0. 7-1. 5 L  
Pancreatic juice 7. 5-8. 4  
6-6.

56-8100  
Jejunum 2 m  
0. 6 L  
Bile 6. 1-8. 6  
6-8  
Ileum 3m  
2-3 L  
Mucosal secretion 7.

6  
Reabsorption of water 7 L  
6-8  
Colon 1. 2-1. 5 m  
Reabsorption of water 0. 3 - 1

L

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6 - 7  
10 or 5-4 cm/hr  
0. 5 - 1  
Rectum 12-20 cm

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Rectal mucus 7. 2- 7. 4



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0. 04-0. 07The successful development of an oral drug delivery system need the scientific frame work of understanding basic aspects include3Biopharmaceutical characteristics of the drug, The anatomy and physiology of GIT , andPhysicochemical 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 includeProper delivery system developed for therapeutically effective rate to desirable site for direction required for optimal treatment. 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. Reduction of hepatic first pass metabolism via bypass or minimization of extent. 2

### **1. 2. 1 ADVANTAGES:**

Reduction in dosing frequency easily acceptance of patient. Loss of drug can be reduced by targeting. Decreasing GI side effects and toxicological effects. Fluctuation in plasma drug level minimized. Better patient compliance. Convenient to administration compared to other routes of administration. Stability of drug can be increased. Uniform drug effect achieved. 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:**

There are some disadvantages also encountered in controlled oral drug delivery systems. They are it is an expensive process. Poor in vitro-in vivo correlation. Dose dumping occurred due to polymer burst action at a particular site. 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 Dissolution controlled release, Diffusion controlled release, Dissolution and diffusion controlled release, Ion exchange resins, pH independent formulations, osmotic controlled release, Altered density formulations, Prodrugs, Delayed release systems.

### **1. 4. 1 DISSOLUTION CONTROLLED RELEASE: 8**

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  $J = -D (dc/dx)$  Where  $J$  is flux,  $D$  is diffusion coefficient and  $dc/dx$  is concentration gradient from the solid surface to the bulk solution. If the concentration gradient is linear and layer thickness is  $h$ ,  $dc/dx = (C_b - C_s)/h$  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: Encapsulated dissolution systems, 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: 19**

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  $J = -D \frac{dC_m}{dx}$  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: Release rate =  $\frac{AD(C_1 - C_2)}{l}$  Where A= surface area, D= Diffusion coefficient, l= Diffusion path length, C<sub>1</sub>= Concentration of drug in the system, C<sub>2</sub>= Concentration of drug in the dissolution medium.

### **1. 4. 4 ION EXCHANGE RESINS: 4**

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 found in other routes of drug administration. The variable nature of the chemical environment through the GIT is a constraint on dosage form design. Indeed, drugs administered orally would encounter a spectrum of pH ranging from 1 to 7. The pH dependency of drug release from controlled release formulations has been demonstrated by study of papaverine hydrochloride.

#### **1. 4. 6 OSMOTICALLY CONTROLLED RELEASE:**

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 PRODUGS:**

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 Known to cause gastric distress, To sensitive of gastric juice or intestinal enzymes, Absorption occurs at a specific intestinal site or 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: 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 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 maybe granulated prior to compression.

### **1. 5. 1 ADVANTAGES OF MATRIX TABLETS:**

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

### **1. 5. 2 DISADVANTAGES OF MATRIX TABLETS:**

The release rate can be effected by various factors like food, GI transit time, etc  
The matrix must be removed from the body after releasing the drug  
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 systems drug dispersed in a matrix or encapsulated.

### **1. 5. 4 DEPENDING ON THE TYPE OF POLYMER: 9-14**

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 net work 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 systems 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 hydroxyl propyl methyl cellulose (HPMC), methyl cellulose 400&4000cps, hydroxyl ethyl cellulose (HEC), and sodium car boxy methyl 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: 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)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 its 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 hyper tropic 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 dihydro testosterone. 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 straining 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 intakeSchedule toilet visitsManage constipationReview 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**

PROBLEMSOLUTIONPatient taking Alfa-blocker still symptomatic after 2 weeks. Patients should be advised that it may take 2-6 weeks before symptomatic treatment relief is seen. Patient taking an alfa -adrenoceptor blockers complaints of cardiovascular adverse effects such as dizziness, syncope, palpitations, tachycardia or angina. 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 or using more uroselective drugs such as tamsulosin. Sexual dysfunction. Decreased libido or impotence can occur in patients taking finasteride and dutasteride. Abnormal ejaculation can be caused by alpha-blockers. Tamsulosin in particular can cause a dry climax (retrograde ejaculation). Patients should be forewarned when discussing treatment options. Patients taking finasteride notice breast enlargement. Unilateral or bilateral gynecomastia is a frequently reported side effect with finasteride and patients need to be counseled accordingly when discussing treatment options. Patients taking finasteride or dutasteride who have a sexual partner who is pregnant. Exposure to semen should be avoided as both drugs can cause abnormalities to genitalia in a male fetus. The patient should be advised to use a condom.

## **1. 6. 2 Pharmacological classification of Drugs: 22-23**

1. 6. 2. 1 Alpha1 adrenergic blockers: which decrease tone prostatic/bladder neck muscle. The contraction of prostate gland's smooth muscle occurs by stimulation of adrenergic neurons via alpha1 receptor. There are three subtypes present, alpha1a, alpha1b and alpha1d. The alpha1a is the dominant receptor in prostate gland which is present 70%. Tamsulosin has a selectivity to alpha1a & alpha1b 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 5-alpha-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 5 $\alpha$ -reductase. E. g.: Finasteride, dutasteride etc.

### **Table 1. 3: Marketed drugs available used for the treatment of BPH**

CLASSIFICATION DRUG BRAND NAME STERNGTHT1/2 DOSAGE FORM

blockers Terazosin Hytrin 1, 2, 5 & 10mg Capsule  
Doxazosin Cardura 1, 2, 4 & 8mg 22hrs Tablets  
Tamsulosin Flomax 0. 4 & 0.

8mg 13hrs Capsules  
Alfuzosin Uroxatral 10mg 5hrs Tablet  
Silodosin 4 & 8mg capsules  
5 $\alpha$ -reductase

inhibitors Finasteride Proscar 5mg Tablets  
Dutasteride Avodart 0.

5mg Longer Capsule  
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: 24 -26**

'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 millions 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 and 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 brains as in arteriosclerotic and postencephalic 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 Bradykinesia 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  $\beta$ -amyloid, surrounds with debris and dead nerve cells, and is 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 sodium marketed products****S. No****Brand Name****Dosage Form****Strength**

1. CholinervTablet500mg2. CholinervInjection125mg/ml3. Ceeti  
FCTablet500mg4. Cicolin FCTablet500mg5. MetalinTablet500mg6.  
NeurosparkInjection500mg/2ml7. StrolinTablet500mg8.  
CDPSyrup500mg/5ml9. CitistarTablet500mg10. StrocitTablet500mg

**CHAPTRE -2 LITERATURE REVIEW****2. 1 Past work done on Alfuzosin hydrochloride extended release formulation**

Sritharan et al<sup>33</sup> to evaluate the in vivo and in vitro performance of conventional mono lithic matrix tablet compared to three layer tablet. Alfuzosin Hcl Extended release tablets to be taken once daily were formulated with 10 mg Alfuzosin Hcl. The release was extended by using swellable polymers like polyethylene oxide and Hydroxypropyl methylcellulose. Monzurul Amin Roniet al<sup>34</sup> Alfuzosin hydrochloride extended release tablets were formulated as single matrix tablet with hydrophilic (HPMC) and hydrophobic (Ethyl cellulose) polymers. Dissolution data optimized formula was fitted into zero, first order, & Higuchi's release kinetics. Korsmeyer's equation explained that the drug release was followed both diffusion and erosion mechanism in all cases. Madhu E Nicholas et al<sup>35</sup> Alfuzosin HCl extended release matrix tablets were manufactured by wet

granulation method by using hydrophilic polymers (HPMC K 100 M) and hydrophobic polymers (hydrogenated castor oil and ethyl cellulose). The matrix granules were manufactured by mixing the drug with hydrogenated castor oil using binder solution contains ethyl cellulose in different amounts. The dried granules were compressed with HPMC K 100M at optimized concentration of ethyl cellulose. The optimized batch's drug release follows zero order kinetics by anomalous (non-fickian) diffusion. Quan Liu et al<sup>36</sup> Gastro-retentive matrix tablets of Alfuzosin hydrochloride 10 mg designed, characterized and fitted in to zero-order kinetics. Triple layer and bi-layer composite matrices contains polyethylene oxide, hydroxypropylmethyl cellulose, sodium bicarbonate, citric acid and polyvinyl pyrrolidone. The drug release principle follows swelling and erosion. Anroop(et al <sup>37</sup>Alfuzosin hydrochloride controlled-release matrix tablets formulated by direct compression technique using low viscous hydroxyl propyl methylcellulose (HPMC K-100 and HPMC 15cps). The release rate was not highly significant with different ratios of HPMC K-100 and HPMC15cps. Utpal Kumar Sanki et al<sup>38</sup>Hot-melt granulation techniques used for development of Alfuzosin modified release Tablets using mono glycerides and di-glycerides as rate controlling membranes. The optimized formulation was bioequivalent with respect to rate and extends of absorption to the reference formulation.

## **2. 2 Past work done on Alfuzosin hydrochloride analytical methods**

Akhilesh Chandra et al <sup>39</sup>, Simple and sensitive visible spectrophotometric methods were developed to estimate the Alfuzosin hydrochloride with spectroscopic methods (I and II). Method I obeyed Beer's law in the

concentration range of 2-8 µg/mL with maximum absorption at 783 nm. Method II chromogen also obeyed Beer's law in the concentration range of 10-50 µg/mL with maximum absorption at 510 nm. The both methods were validated statistically agreement with the labeled amounts. AdsulePrajakta Vet al, 40 was developed a simple, economical, precise and accurate three UV spectrophotometric method for the determination of Alfuzosin in bulk and formulations. In method A, method B & method C maximum absorbance measured at 244.99 nm, 243.34 - 246.63 nm(AUC) & 235.12 nm (First order derivative). Linearity was observed in the concentration range of 2.5 - 30µg/mL. SafwanAshouret al41 was developed a simple, sensitive and fast spectrophotometric method for the estimation of Alfuzosin hydrochloride in pure form and formulation dosage form by using indicators like bromothymol blue, bromocresol purple, bromophenolblue absorbance measured at 412nm, 407nm and 413nm respectively. The percentage of recovery was 98.80 - 101.33 %. M. Vamsi Krishna et al42 was developed a simple, accurate and precise three spectrophotometric methods for estimation of Alfuzosin hydrochloride in drug substance and tablet formulation. The first method was developed based on reaction between Alfuzosin and ninhydrin in N, N-dimethylformamide medium to produce a colour and measuring the absorbance at 575nm. The second method was developed based on reaction between Alfuzosin with ascorbic acid in to produce colored product which measures absorbance at 530nm. The third method was developed based on reaction of Alfuzosin with p-benzoquinone to form a colored product which measures at 400 nm. All three procedures are validated. Dipti B Patel et al, 43 was developed both RP-HPLC and HPTLC for the estimation of Alfuzosin

hydrochloride in drug substance and in pharmaceutical formulation. In HPLC method the separation was done by using C18 250×4.6 mm, 5µm, water: methanol: acetonitrile (60: 30: 10 v/v) as the mobile phase, flow rate 1.0 mL/min and detection at 245nm. In HPTLC method the separation was by using an aluminium-backed layer of silica gel 60F254, toluene: methanol: triethylamine (3: 1: 0.2 v/v), detection at 245nm over the range of concentration 50-400ng/spot. K. S. Bharathkumar et al<sup>44</sup> a simple rapid and precise reverse phase high pressure liquid chromatography method was developed and the same validated for the determination of Alfuzosin hydrochloride in tablet dosage form. Parameters of method are the flow rate at 1 mL/min, Retention time and injection volume set at 10min and 10µl, with UV detection at 245nm. And the percentage of recovery found to be 98.8 percentage. Mani Ganesh et al<sup>45</sup> an isocratic reversed phase high-performance liquid chromatographic method with ultraviolet detection at 245 nm has been developed for the determination of Alfuzosin hydrochloride in pharmaceutical dosage form. Separation of Alfuzosin developed by using a column Inertsil ODS-3V (15 cm x 0.46 cm, 5µm) at ambient temperature (25 ±2°C) using Acetonitrile: Water: Tetrahydrofuran: Perchloric acid (250: 740: 10: 1) as mobile phase with flow rate of 1 mL/min. The developed method was validated for its selectivity, accuracy, precision and linearity. This method was found to be suitable for the estimation of alfuzosin hydrochloride in bulk drug and formulation. Vandana P. Patil et al, <sup>46A</sup> reverse phase high performance liquid chromatographic method has been developed for the estimation of Alfuzosin hydrochloride in the pharmaceutical formulation using RP-C18 column, Tetrahydrofuran, Acetonitrile and buffer pH 3.50 (1:

20: 80 ) as a mobile phase with flow rate of 1. 5 mL/min and scanned at 254. 0 nm. The method was validated and RSD was found to be less than 2% it reveals that method is accurate.

### **2. 3 Past work done on Alfuzosin hydrochloride Bio analytical methods**

Utpal Kumar Sankiet al, 47The study was to evaluate in vitro-in vivo performance of Alfuzosin modified release tablet in healthy human subjects. The in vivo pharmacokinetic parameters under fasting conditions between test and reference formulations (Uroxatral 10mg extended release tablets) were comparable. The 90% CI, geometric mean ratio (%) and power of C<sub>max</sub>, AUC<sub>0-T</sub>, and AUC<sub>0-Inf</sub> of the fasting study for the test and reference formulation were performed. The developed formulation was safe to use since there were no any adverse events occurred while conduction of the clinical trial on the healthy subjects. Madhura V. Dhokaet al, 48Rapid, precise, accurate, simple, selective, and sensitive high pressure liquid chromatography method (HPLC) and high pressure thin layer chromatography method (HPTLC) methods for the determination of Alfuzosin in human plasma have been developed. HPLC method was developed by using HiQ sil C8 HS column, mobile phase containing mixture of Acetonitrile: Sodium acetate bufferwith n-hexane sulphonic acid salt having pH 4. 0, at the flow rate of 1mL/min and detection was performed at 244nm. The HPTLC separation was developed on the Aluminium plates coated with silica gel 60 F254 using Toluene: Methanol: Triethylamine as mobile phase and found at 244nm with TLC Scanner.

## **2. 4 Past work done on Citicoline sodium formulation**

Katarzyna Swiader et al.<sup>49</sup> the formulation and evaluation of citicoline enteric coated tablets by using wet granulation method. Aqueous dispersion enteric coats showed good physical resistance in hydrochloric acid of pH 1.2 with no drug release for two hours. The coated tablets dissolved rapidly when tablets were removed from acid medium and dropped in the pH 6.8 phosphate buffer. Amol R. Jipkate et al.<sup>50</sup> Citicoline Sustained Release Tablets were prepared by using hydroxypropyl methyl cellulose (HPMC) at different concentrations of matrix system by wet granulation method.

Hydroxypropylmethylcellulose proved as a rate controlling polymer by the diffusion-dissolution controlled mechanism. Note : Very few work has been done on citicoline controlled release drug delivery systems.

## **2. 5 Past work done on citicoline sodium analytical methods**

Neetu Sachan et al.<sup>51</sup> simple, accurate, precise, rapid and low cost method developed for the determination of Citicoline by using double beam UV spectrophotometer, it obeyed Beer Lambert's law at the concentration range of 5-50 µg/ml and maximum absorption at 272 nm. Method was successfully validated in order to verify selectivity, accuracy, linearity and precision. Sagar Suman Panda et al.<sup>52</sup> was developed a novel, precise and accurate method for the estimation of citicoline sodium in tablet dosage form by difference spectrophotometric method. Citicoline sodium shows two different forms that shows different absorption spectra in acidic (0.1M HCL) & basic (0.1M NaOH) medium. The maxima and minima in the difference spectra of citicoline sodium were found to be 239nm and 283nm

respectively. Linearity in the range of 1-50 µg/mL. The percentage recovery from the tablet dosage form was 98.47%. Malipatil S. M et al<sup>53</sup> was developed simple, accurate, precise and sensitive two spectrophotometric methods in UV and visible region for the estimation of citicoline in pharmaceutical dosage form. The method A shows maximum absorption at 272 nm in distilled water. The method B was developed the reaction of 3-methyl-2-benzothiazolin-2-one hydrazone with citicoline sodium in presence of ferric chloride solution to produce a yellow orange product. The maximum absorption shows at 625 nm. Both the methods were obeyed Beer's law in the concentration range of 10-70 µg/ml and 50-250 µg/ml respectively. G. Raveendra babu et al<sup>54a</sup> validated specific and stability indicating method was developed for estimation of citicoline and its related substances in oral drops formulation on reversed-phase liquid chromatographic method. Detection was performed at 280 nm and the validation data showed that method is specific, sensitive and reproducible for assay and related substances. Sonali O. Uttarwar et al<sup>53</sup> Method was developed for estimation of citicoline on reverse phase liquid chromatography in citicoline sustained release tablets. Separation was achieved by using column hypersil BDS C18 250 × 4.6 mm, 5 µm particle size, buffer: Methanol (98: 2 v/v), flow rate 1.0 mL/min, injection volume was 20 µl and detection at 280 nm.

Developed method was validated for precision, accuracy, specificity, linearity, Robustness, Ruggedness and solution stability. K. Tulasiet al<sup>56</sup> analytical method was developed for the estimation of citicoline from dosage form by using isocratic reverse phase high performance liquid chromatography method, ammonium acetate and methanol used as a mobile phase, Colum



C18, 250mm×4.6mm, 5µm, run time 10 min, flow rate 0.8 mL/min, injection volume 20 µL detection at 270nm. Linearity was observed in the range of 0.2 - 200 µg/mL. The RSD for precision was found to be less than 2.0 %.

RaveendraB. Ganduriet al57a stability indicating liquid chromatographic citicoline sodium assay method was developed from injection formulation. Citicoline was separated from the dosage form by using cosmosil C18250×4.6 mm, 5µm, phosphate buffer and methanol (95.0: 5.0%v/v), flowrate 1.0 mL/min, injection volume 20µL, runtime 25 min and detection wavelength 276nm. The accuracy and precision of the method was found to be 98.30 % and RSD less than 1.0 % respectively. Sanjay Suraniet al58a accurate, simple, specific, and precise spectrophotometric method for the estimation of citicoline sodium in drug substance and tablets. Solvent used were 0.1N Sodium hydroxide and double distilled water, with a absorption maxima of 272 nm. A linear relationship in the range of 5 to 55 µg/mL with a correlation coefficient was found 0.998.

## **2.6 Past work done on citicoline tablets Bio analytical methods**

Keguang Chen et al59 Developed and validated a simple, rapid HPLC Method for the determination of uridine (i. e. a Metabolite of citicoline) in human plasma. Uridine was extracted from plasma by simple precipitation Method, amoxicillin used as internal standard. Uridine separation was carry out by using C18 100×4.6mm, 2.6µ column, mobile phase of 0.05 M phosphate buffer adjusted pH to 3.5 - methanol (98: 2 v/v) and flow rate 0.8mL/min. The standard calibration curve of uridine was linear over a concentration range of 0.02 - 2.0 µg/ mL. The relative bioavailability of citicoline sodium

tablets was 92.7%. The citicoline tablet and capsules are bioequivalent. Amlan Kanti Sarkar et al. (6) developed and validated a simple, rapid high performance liquid chromatography-tandem mass spectrometry method for the determination and pharmacokinetic investigation of choline (active metabolite of citicoline). Metformin used as an internal standard, mobile phase of methanol-water (9:1 v/v). The standard calibration curves were linear over the range of 0.05 - 5 µg/mL.

## **CHAPTER -3 DRUG –EXCIPIENT PROFILE**

### **3. 1 Drug profile:**

3. 1. 1 Alfuzosin Hydrochloride: 61-63

#### **Synonyms**

Uroxatral, Mittoval, Xatral and Urion

#### **IUPAC Name**

N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl] tetrahydro-2-furancarboxamide.

#### **Therapeutic Category**

In treatment of benign prostatic hypertrophy

#### **Description**

White or almost white crystalline powder.

#### **Molecular weight**

425.91

## **Empirical formula**

C<sub>19</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub>. HCl

## **CAS No**

81403 - 68-1

## **Structure**

UROXATRAL® (alfuzosin HCl) Structural Formula Illustration

## **Melting point**

225°C - 240°C

## **PKa**

8. 13

## **Solubility**

Freely soluble in water, practically insoluble in dichloromethane and sparingly soluble in alcohol.

## **Mechanism of action**

Alfuzosin is an uroselective agent, which binds to prostatic  $\alpha_1$ -receptors and blocked results relaxation of prostate smooth muscle, bladder neck leads to reduction of BPH symptoms subsequently improves urine flow with decrease of hypertensive events. Alfa adrenergic receptors belong to Gq-protein coupled receptor family, upon activation of a G protein leads to activation of phospholipase C (PLC). PLC cleaves into phosphatidylinositol<sub>4</sub>, 5-bisphosphate (PIP<sub>2</sub>) and diacylglycerol (DAG). PIP<sub>2</sub> causes increase inositoltriphosphate (IP<sub>3</sub>), these interacts with calcium channels

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subsequently changes calcium content in the cell and triggers other effects like muscle contraction etc.

## **Pharmacokinetics**

### **Absorption**

Under fasting condition Absorption is lower 50%.

### **Distribution**

3. 2 L/kg, healthy male middle-aged volunteers.

### **Metabolism**

Hepatic, extensive metabolism by the liver.

### **Excretion**

Only 11% of the administered dose excreted unchanged in the urine.

### **Protein binding**

Binding of plasma protein is 82% to 90%.

### **Half life**

Plasma half-life 10 Hrs.

### **Dose & Dosage form**

10 mg & Tablet

## **2. 1. 2 Citicoline Sodium: 64-65**

### **Synonyms**

CDP-choline, Difosfocin, Acticolin, Brassel, Ceraxon and Neuroton

## **IUPAC Name**

Cytidine 5'-(trihydrogen diphosphate) P'-[2-(trimethylammonio) ethyl] ester inner salt.

## **Category**

Neuroprotective agent, In treatment of ischemic stroke and head trauma.

## **Description**

White, crystalline, spongy, hygroscopic powder

## **Molecular weight**

510. 31(Sodium Salt), 488. 32 (Base)

## **Empirical formula**

C<sub>14</sub>H<sub>25</sub>N<sub>4</sub>NaO<sub>11</sub>P<sub>2</sub>

## **CAS NO**

33818-15-4

## **Structure**

Citicoline sodium Structure

## **Melting point**

259°C-268°C

## **pKa**

4. 4

## **Solubility**

Freely soluble in water but in soluble in organic solvents.

## **Mechanism of action**

Citicoline rapidly absorbed from oral administration via hydrolysed into cytidine and choline, distributed to liver via portal circulation. Choline enters into metabolic pathways resulting involved in the synthesis of CDP-choline and phosphatidyl choline. Cytidine enters into the neuclic acid (RNA) formation and remaining unmetabolised one distributed throughout body tissues undergoes further metabolism.

## **Pharmacokinetics**

### **Absorption**

It is rapidly absorbed in the gastrointestinal tract. Plasma level peak in a biphasic manner i. e. at 1 hr after ingestion followed by a 2nd larger peak at 24 hours post -dosing .

### **Distribution**

### **Metabolism**

It is metabolized in the gut wall and liver

## **Excretion**

---

## **Protein binding**

---

## **Half-life**

56 hours for CO<sub>2</sub> and 71 hours for urinary excretion.

## **Dosage form**

Tablet& Injection

## **Dose**

500 -2000mg

## **Packaging and storage**

Store in room condition

## **3. 2 POLYMER AND EXCIPIENT PROFILES:**

### **2. 2. 1 Guar Gum: 66**

#### **Synonyms**

Meyprofin, Galactose, Meyprogat, jaguar gum.

#### **Description**

Guar gum having a bland taste, odourless, white to yellowish powder.

#### **CAS NO**

9000-30-0

## Structure

[http://t2.gstatic.com/images?q=tbn:](http://t2.gstatic.com/images?q=tbn:ANd9GcRhaj6nvRvR0cQazviH8svwfcs1UjvfSzMyc-z_5Fk0RQT8cecO6w)

[ANd9GcRhaj6nvRvR0cQazviH8svwfcs1UjvfSzMyc-z\\_5Fk0RQT8cecO6w](http://t2.gstatic.com/images?q=tbn:ANd9GcRhaj6nvRvR0cQazviH8svwfcs1UjvfSzMyc-z_5Fk0RQT8cecO6w)

## Category

Suspending agent, tablet binder and disintegrate, Viscosity increasing agent.

## Applications

Used in preparation of sustained release matrix tablets as a release controlled agent.

## pH Value

5.0 - 7.0 (1% aqueous dispersion)

## Solubility

Practically insoluble in organic solvents, guar gums disperse and swell almost immediately to form a high viscous, thixotropic solution in hot water and cold water.

## Viscosity

4.86 Pas for 1% w/v dispersion.

## Storage condition

Guar gum powder should be stored in a well closed container in a cool and dry place.



## 2. 2. 2 Hydroxypropyl Cellulose: 67

### Synonyms

Klucel, Methocel, Nisso HPC, Hydroxy propyl ether.

### Description

Hydroxypropyl Cellulose is a tasteless, odourless, and white to slightly yellow colored powder.

### CAS NO

9004-64-2

### Structure

<http://t1.gstatic.com/images?q=tbn:>

ANd9GcRwfsUgUCjS8UTXOyGlnDclwD7xfH7H9BkZtdGRCKEk\_NOEJMye

### Melting point

Chars at 260°C to 275°C, soften at 130°C.

### Category

Tablet binder, suspending agent, coating agent, thickening agent and stabilizing agent.

### Applications

Used in tablet manufacturing as a binder, film coating and extended release matrix former. 15-35% w/w HPMC may be used to produce extended release tablets.

## **pH Value**

5.0 – 8.5 (1% aqueous solution)

## **Solubility**

Freely soluble in water below 38°C, forming a clear, smooth, colloidal solution. Insoluble in hot water. Soluble in polar organic solvents such as dimethyl formide.

## **Viscosity**

Wide range of hydroxypropyl Cellulose grades are available having the different viscosity range.

## **Storage condition**

Store in a well closed container in a cool place.

## **2. 2. 3 Hypromellose: 68**

### **Synonyms**

Hydroxypropyl methyl cellulose, Methocel, Metolose, HPMC, Tylopur, Benecel MHPC.

### **Description**

Hypromellose is an odourless tasteless, and white or creamy white granular or fibrous powder.

### **CAS NO**

9004-65-3

## Structure

<http://upload.wikimedia.org/wikipedia/commons/thumb/9/94/Hypromellose.png/200px-Hypromellose.png>

## Melting point

Chars at 225 - 230°C, brown at 190 - 200°C. Glass transition temperature 170°C -180°C

## Category

Rate controlling polymer for sustained release, suspending agent, coating agent, stabilizing agent, Viscosity- increasing agent

## Applications

It is widely used in oral, topical & ophthalmic pharmaceutical formulations. At higher concentration it can be used in extended release formulations.

## pH Value

5.5 - 8.0 (1% aqueous solution)

## Solubility

Practically insoluble in organic solvents. Soluble in cold water.

## Viscosity

Different grades are available in the market.

## Storage condition

Hypromellose powder should be stored in a well closed container in a cool and dry place.

## 2. 2. 4 Povidone: 69

### Synonyms

Plasdone, Kollidone, Polyvidone and Polyvinylpyrrolidone

### Description

Povidone is a white to creamy white colored, fine, almost odourless, hygroscopic powder.

### CAS NO

9003-39-8

### Structure

<http://t1.gstatic.com/images?q=tbn:>

ANd9GcR9xzrSQhNj8czGLLEKGkocGeUfbFiZdJ78bT9ZaK81bKhAu2Bh

### Melting point

Soften at 150°C.

### Category

Tablet binder, disintegrant, dissolution aid.

### Applications

Used as a tablet binder in wet granulation process.

### pH Value

3. 0 – 7. 0 (5% aqueous solution)

### Solubility

Freely soluble in water and acids. Practically in soluble in ether.

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## **Viscosity**

Different viscosity grade materials are available in the market.

## **Storage condition**

Povidone should be stored in a airtight closed container in a cool, dry place.

## **2. 2. 5 Starch, Pregelatinized: 70**

### **Synonyms**

Starch 1500G, Lycatab C, Compressible starch, Unipure LD.

### **Description**

Pregelatinized starch is a white to off white colored powder, occurs as a coarse to fine, odourless, slight characteristic taste.

### **CAS NO**

9005-25-8

### **Structure**

<http://upload.wikimedia.org/wikipedia/commons/thumb/2/21/Amylose2.svg/270px-Amylose2.svg.png>

### **Melting point**

----

### **Category**

Tabletbinder, tablet and capsulediluentand disintegrant,.

### **Applications**

Used as a tablet diluentbinderand Disintegrant in granulation process.

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**pH Value**

4.5 - 7.0 (10% aqueous dispersion)

**Solubility**

In cold water slightly soluble to soluble, practically insoluble in organic solvents.

**Viscosity**

8 - 10 cP (2 % w/v aqueous dispersion)

**Storage condition**

Pregelatinized starch should be stored in an airtight closed container in a cool, dry place.

**2.2.6 Ammonio methacrylate Copolymer, Type A (Eudragit RLPO): 74****Synonyms**

Acrylate, ammonium methacrylate copolymer, Eudragit RLPO

**Description**

Eudragit RLPO is a white fine powder with a slight amine like odour.

**CAS No**

33434-24-1

**Structure**

[http://eudragit.evonik.](http://eudragit.evonik.com/product/eudragit/SiteCollectionImages/other/norm_land_rl-po.jpg)

[com/product/eudragit/SiteCollectionImages/other/norm\\_land\\_rl-po.jpg](http://eudragit.evonik.com/product/eudragit/SiteCollectionImages/other/norm_land_rl-po.jpg)

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## **Melting point**

Glass transition temperature at 70°C.

## **Category**

Tablet release controlling agent, Film former, tablet diluent.

## **Applications**

Used to form water insoluble film coats for controlled release products.

## **Solubility**

Soluble in acetone, alcohols(i. e. organic solvents).

## **Storage condition**

Eudragit should be stored in a airtight closed container in a cool, dry place.

## **Synonyms**

Acryl-EZE, Kollicoat MAE, Eudragit, polymeric methacrylates.

## **Description**

Eudragit RSPO is a white fine powder with a slight amine like odour.

## **CAS Register Number**

33434-24-1

## **Structure**

[http://eudragit.evonik.](http://eudragit.evonik.com/product/eudragit/SiteCollectionImages/other/norm_land_rs-po.jpg)

[com/product/eudragit/SiteCollectionImages/other/norm\\_land\\_rs-po. jpg](http://eudragit.evonik.com/product/eudragit/SiteCollectionImages/other/norm_land_rs-po.jpg)

## **Category**

Tablet binder, diluent & Film former.

## **Applications**

Used to form water insoluble film coats for sustained release products.

## **Melting point**

Glass transition temperature at 65°C

## **Solubility**

Soluble in organic solvents such as acetone, alcohols, in soluble in water.

## **Storage condition**

Eudragit RSPO should be stored in an airtight closed container in a cool, dry place.

## **2. 2. 7 Ammonio methacrylate Copolymer, Type B (Eudragit RSPO): 75**

## **2. 2. 8 Microcrystalline Cellulose: 71**

## **Synonyms**

Avicel PH, Pharmacel, Celphere, Fibrocel, Vivapur.

## **Description**

Microcrystalline cellulose is a white, tasteless, odourless powder.

## **CAS Register Number**

9004-34-6



## Structure

[http://upload.wikimedia.org/wikipedia/commons/thumb/0/07/Cellulose\\_Sessel.svg/260px-Cellulose\\_Sessel.svg.png](http://upload.wikimedia.org/wikipedia/commons/thumb/0/07/Cellulose_Sessel.svg/260px-Cellulose_Sessel.svg.png)

## Category

Tablet and capsule diluent, suspending agent, tablet disintegrate.

## Applications

Cellulose used in diluent / binder agent in oral tablets and used in wet granulation and direct compression process.

## Melting point

Chars at 260°C to 270°C

## Solubility

Practically insoluble in water,

## Storage condition

Material should be stored in a well closed container in a cool and dry place.

## 2. 2. 9 Colloidal Silicon Dioxide: 72

### Synonyms

Aerosil, fumed silica, Wacker HDK, Cab-O-sil.

### Description

Colloidal silicon dioxide is a bluish white colored, tasteless, odourless, nongritty amorphous powder.

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## **CAS Register Number**

7631-86-9

## **Structure**

[http://apps.kemi.se/flodessok/floden/kemamne\\_eng/gif/kiseldioxid.gif](http://apps.kemi.se/flodessok/floden/kemamne_eng/gif/kiseldioxid.gif)

## **Category**

Adsorbent, anti-caking agent, Glidant, tablet disintegrant.

## **Applications**

Improve the flow properties of dry powder such as tableting.

## **PH Value**

3.5 - 4.4 (4%w/v aqueous dispersion)

## **Solubility**

Practically insoluble in inorganic solvents.

## **Storage condition**

Colloidal silicon dioxide should be stored in a well closed container.

## **2.2.10 Magnesium Stearate: 73**

### **Synonyms**

Magnesium octadecanoate, octadecanoate.

### **Description**

Magnesium stearate is a white colored, very fine, light white, tasteless, odourless, nongritty amorphous powder.

## **CAS Register Number**

557-04-0

## **Structure**

[http://upload.wikimedia.](http://upload.wikimedia.org/wikipedia/commons/thumb/8/87/Magnesium_stearate.png/250px-Magnesium_stearate.png)

[org/wikipedia/commons/thumb/8/87/Magnesium\\_stearate.png/250px-](http://upload.wikimedia.org/wikipedia/commons/thumb/8/87/Magnesium_stearate.png/250px-Magnesium_stearate.png)

[Magnesium\\_stearate.png](http://upload.wikimedia.org/wikipedia/commons/thumb/8/87/Magnesium_stearate.png/250px-Magnesium_stearate.png)

## **Category**

Tablet and capsule lubricant.

## **Applications**

Improve the flow properties of powder such as tableting and capsules.

## **Solubility**

Practically in soluble in inorganic solvents, slightly soluble in warm ethanol and benzene.

## **Storage condition**

Magnesium stearate should be store in a well closed container.

## **CHAPTER -4**

### **Objective and Plan of Work**

The objective of the present work to carry out the development of the controlled drug delivery systems for Alfuzosin Hydrochloride by using Hydroxypropyl methylcellulose (HPMC K100 M), Eudragit RLPO, Guar Gum 8000cps and for Citicoline by using Hydroxypropylmethyl Cellulose (HPMC K100 M) , Hydroxypropyl Cellulose (HF) , Eudragit RSPO, Eudragit RLPO. To

<https://assignbuster.com/need-for-alfuzosin-hydrochloride-extended-release-tablets-biology-essay/>

achieve the above mentioned objective the research work planned in four Phases

1. Identification and sourcing of raw materials.
2. Pre-formulation Studies:  
Alfuzosin Hydrochloride : Solubility studies  
Drug - Polymer interaction studies by DSC, FTIR. Development of analytical procedure for dissolution by UV method. Development of analytical procedure for estimation of drug content by HPLC method.  
Citicoline Monosodium : Solubility studies  
Drug - Polymer interaction studies by DSC, FTIR.
  - a) Development of analytical procedure for dissolution by UV method.
  - b) Development of analytical procedure for estimation of drug content by HPLC method.
3. Formulation development  
Formulation and evaluation of Alfuzosin hydrochloride extended release tablet  
To develop formulations by using different polymers with different concentrations. To evaluate the developed formulation for their physical and chemical properties. To study the in vitro drug release of the different formulations. To conduct the stability studies of the optimized formulation.  
Formulation and evaluation of citicoline controlled release Tablets  
a. To develop different formulations by using different polymers with different concentrations. b. To evaluate the developed formulation for their physical and chemical properties. c. To study the in vitro drug release of the different formulations d. To conduct the stability studies of the optimized formulation
4. In vivo Studies: To conduct in vivo pharmacokinetic study of the optimised Alfuzosin extended release tablets in suitable animal model. To conduct in vivo pharmacokinetic study of the optimised Citicoline controlled release tablets in suitable animal model.

## CHAPTER -5

### 5. Development and Evaluation of Alfuzosin Hydrochloride Extended Release Tablets

#### 5.1 Materials and Equipments

**Table 5. 1: List of materials used in research work**

##### **Name of the Material**

##### **Manufacturer**

Alfuzosin Hydrochloride Dr. Reddys laboratory, Hyderabad, India. Doxazosin Mesylate Clearsynth labs , India. Microcrystalline Cellulose( Avicel PH-101) FMC Bio Polymer, Ireland. Ammonio Methacrylateco-polymers (Eudragit RLPO) Evonik industries, Germany. Povidone(PVP K-30) ISP Sales (UK) Limited. Partially Pregelatinized Starch (Starch 1500) Colorcon , Goa Hypromellose (Methocel K100M) Dow chemical company Gaur Gum 8000 cps Lucid Colloids, Colloidal Silicon Dioxide Evonik industries, Germany. Magnesium Stearate Ferro corporation, Cleveland. Acetonitrile (AR Grade) Merck Specialties Pvt. Ltd, Mumbai. Triethylamine (AR Grade) Merck Specialties Pvt. Ltd, Mumbai. Potassium dihydrogen Orthophosphate (AR Grade) Merck Specialties Pvt. Ltd, Mumbai. Hydrochloric acid (AR Grade) Merck Specialties Pvt. Ltd, Mumbai. Sodium hydroxide Pellets S. D Fine Chemicals Ltd., Mumbai, India. Orthophosphoric acid (AR Grade) Merck Specialties Pvt. Ltd, Mumbai. Potassium coated EDTA Tubes Merck specialities Pvt. Ltd, Male Rabbits weighing 2.8 - 3.2 Kg Sree venkateswara enterprise, Bangalore , India

## Table 5. 2: List of equipments used in the research work

### Equipment Name

### Manufactured By

Electronic Weighing BalanceMettler Toledo (AB104), Germany. Rapid mixer granulatorDiasonaHot air ovenInnovative instrumentsDouble cone blenderShakthi engnering , AhemadabadSievesJayant Scientific Ind., BombayCompression Machine (8 Station)Cadmach, AhemadabadDigital Vernier CalipersMitutoyo (CD-8CSX), China. Friability ApparatusElectrolab EF - 2W, Mumbai. Hardness TesterDr. Schleuniger (6D), Germany. Dissolution ApparatusTDT-08L, Electrolab, Mumbai. SonicatorPower sonic 505, India. HPLCWaters, Japan. FT-IRPerkin Elmer, Vortex MixerSpinex, India. Stability ChamberMack, Mumbai. DSCDSC21, Mettler Toledo, USA. UV visible spectrophotometerAnalytikjena Specord 210Overhead 3-blade medium duty stirrerRemi stirrer, Mumbai, India. CyclomixerRemi Instruments, Mumbai, India. Multifuge CentrifugerHeraus, Germany.

## 5. 2 ANALYTICAL METHODS

There are several reported methods for the estimation of alfuzosin hydrochloride available in the literature, those are UV, Colorimetry, HPLC &LC-MS methods. In the present investigation we have develop a modified Ultraviolet spectroscopic method for the estimation of alfuzosin hydrochloride for dissolution samples\*. HPLC method was developed for estimation of drug content (Assay)\*. The analytical methods(i. e dissolution and assay)of alfuzosin hydrochloride extended release tablets not published in official pharmacopeia.(i. e IP, BP&USP)\* The methods was developed on

the basis of development and validation of UV spectrophotometric method for estimation of alfuzosin by Adsule Prajakta V et al for dissolution samples and New RP HPLC method development and validation of assay for alfuzosin in tablet dosage form by K. S. Bharathkumar et al for uniformity of content and assay samples. A new HPLC method was developed and validated for the estimation of alfuzosin in rabbit plasma.

### **5. 2. 1 METHOD DEVELOPMENT:**

The solubility of the Alfuzosin hydrochloride was tested in different dissolution media like 0. 01N HCl, pH 4. 5 Acetate buffer, pH 6. 8 phosphate buffers , pH 10. 0 phosphate buffer and Purified water. Based on the solubility data dissolution media 0. 01N HCl was selected as media with 900mL of volume, maintained at  $37 \pm 0. 5^{\circ}\text{C}$  and USP Apparatus-II (Paddle). Samples were collected at appropriate time intervals from dissolution vessels and diluted the samples and measured the absorbance at 245nm using UV-Visible spectrophotometer and calculated using standard calibration curve.

#### **5. 2. 1. 1 Standard calibration curve of Alfuzosin hydrochloride:**

##### **5. 2. 1. 1. 1 Preparation of 0. 01N HCl:**

8. 5mL of Hydrochloric Acid was diluted with water to 10 Litres.

##### **5. 2. 1. 1. 2 Preparation of standard stock solution:**

25. 0 mg of Alfuzosin HCl weighed in to 50ml volumetric flask and made up the volume with 0. 01N HCl. 2ml of this solution further diluted to 100ml with 0. 01N HCl.

### **5. 2. 1. 1. 3 Preparation of standard Calibration Curve:**

From the standard stock solution serial dilution were done to obtain solutions ranging from 0. 5µg/mL to 6. 0µg/mL, i. e. from 10% to 120% with respect to sample concentration. The absorbance of above solutions was measured at wavelength of 245nm using UV-Visible spectrophotometer (Analytikjena Specord 210), against dissolution media as blank. The absorbance values of standard curve was represented in table 5. 3 and a graph was plotted of concentration v/s absorbance which was shown in Fig. 5. 1

### **Table 5. 3: Standard Calibration curve values of Alfuzosin Concentration in µg/mL**

#### **Absorbance**

0. 50. 06911. 00. 13542. 00. 27613. 00. 42015. 00. 68826. 00. 8281Slope0. 1381Intercept0. 0001Correlation Coefficient1. 000The linear equation was  $y = 0. 1381 x - 0. 0001$  Where x is concentration and y is the peak absolute area. The correlation coefficient was  $r = 1. 000$ , indicating good linearity.

### **Figure: 5. 1 Standard Calibration curve of Alfuzosin HCl**

## **5. 2. 2 ASSAY BY HPLC:**

### **5. 2. 2. 1 METHOD DEVELOPMENT**

Different columns, mobile phases, flow and column temperatures were tested in the development of the analytical method. C-8 and C-18 columns of the same length, different lengths and diameters were also tested and pH of buffer variations from 3. 0 to 6. 5 were also tested by keeping all parameters and conditions were constant (0. 8 mL/min., injection volume of 20µL,



temperature at 25°C). Then the mobile phases with different buffer concentrations and organic content were also tested by keeping the all parameters and conditions were constant. Finally we got the good chromatographic peak with more than 5000 theoretical plates, tailing factor of less than 2.0 and Relative standard deviation of less than 2.0% for six replicate standard injections.

### **5.2.2.1.1 Preparation of Dilute Orthophosphoric acid:**

9. 3mL of 82%-Ortho phosphoric acid was diluted to 100mL with water.

### **5.2.2.1.2 Preparation of Buffer:**

2. 72g of Potassium dihydrogen phosphate weighed and transferred into a beaker containing 1000mL of water. Sonicated to dissolve and 2.0mL of Triethylamine was added and mixed well. pH of the solution was adjusted to  $3.0 \pm 0.05$  with diluted orthophosphoric acid. Solution was filtered through 0.45 $\mu$  membrane filter.

### **5.2.2.1.3 Preparation of mobile phase:**

Prepare and degassed the mixture of buffer and acetonitrile in theratio of 75:25%v/v. Diluent: Mobile phase was used as diluent.

### **5.2.2.1.4 Chromatographic conditions:**

Column : C18, 150×4.6mm 5 $\mu$  or equivalentFlow rate : 0.

8ml/minDetection : 245nmInjection volume : 20 $\mu$ LColumn temperature:

AmbientRun time : 10min

### **5. 2. 2. 1. 5 Standard preparation:**

50. 0mg of Alfuzosin Hydrochloride standard weighed accurately and transfer into a 200. 0ml volumetric flask, dissolved and diluted with diluent. 5. 0ml of this solution was transferred in to 100ml of volumetric flask, dilute to volume with diluent and mixed well.

### **5. 2. 2. 1. 6 Sample preparation:**

20 tablets were weighed and determined the average tablet weight in mg. Tablets were crushed into fine powder. Weighed the sample equivalent to 10. 0mg of Alfuzosin Hydrochloride and transferred it into individual 200ml volumetric flask with the aid of 120ml diluent. Solution was sonicated for 15min, dissolved and diluted to volume with diluent. Portion of sample was centrifuged for about 15min prior to dilution. 5. 0ml of sample solution was transferred into individual 20. 0ml volumetric flask, made up the volume with diluent and mix well.

### **5. 2. 2. 2 METHOD VALIDATION:**

The system suitability linearity, accuracy and precision of the method were validated. The specificity of test method by HPLC demonstrated that the excipients from tablets do not interfere with the analytic peak. The linearity of the method was tested in the concentration range 1. 26µg/mL to 15. 08µg/mL (10. 0% to 120. 0%). For accuracy of the method, standard drug was spiked from 70. 0% to 130. 0% and recovery was found to be 99. 2% to 100. 9% and RSD 0. 8%. The precision of the method was checked were found to be relative standard deviation 0. 9%.

**Table 5. 4: Linearity****Concentration in %****Concentration in µg/ml****Peak Area**

101. 26402135202. 51839456405. 031690564607. 54258415410012.

56412589112015. 085023154Intercept13707Slope331585Correlation

Coefficient

**0. 999****Figure 5. 2: Alfuzosin assay Linearity graph****Table 5. 5: Accuracy/recovery****Level****Actual weight added in mg****% in mg recovery****% recovery**

70%7. 027. 0099. 7100%10. 049. 9699. 2130%12. 9813. 10100. 9

**Mean****99. 9****SD**

0. 8

**RSD****0.8****Table 5.6 Precision****S. No.****% Assay**

199.02101.0399.0499.5598.6699.0

**Avg**

99.4

**SD**

0.86

**% RSD**

0.9

**Figure 5.3: Alfuzosin Assay Standard****Uniformity of drug content test**

Ten tablets were selected randomly, weigh the tablet individually and place it into individual 200ml volumetric flask with the aid of 120ml diluent.

Solution was sonicated for 15min, dissolved and diluted to volume with diluent. Portion of sample was centrifuged for about 15min prior to dilution.

5.0ml of sample solution was transferred into individual 20.0ml volumetric flask, made up the volume with diluent and mix well and inject to the HPLC System as followed as per assay method. (4.2.2)

## **5. 3 Pre-formulation**

### **5. 3. 1 Solubility Analysis:**

The solubility of Alfuzosin Hydrochloride was determined in different media as follows. 0. 01N HCl pH 4. 5 Acetate buffer pH 6. 8 phosphate buffer pH 10. 0 phosphate buffer Purified Water Excess amount of the drug was weighed and transfer to 50 ml volumetric flasks. To each of the volumetric flasks above mentioned media were added and shaken well. The volume was made up to volume with same media the samples were kept in constant water bath shaker for 24 hours at temperature of 37 °C. After 24 hours the samples were removed from bath, equilibrated for 1 hr. then the samples were filtered through 0. 45 µm filter. The dissolved drug was measured using UV visible spectrophotometer at 245 nm after suitable dilutions.

### **5. 3. 2 Compatibility Studies:**

#### **5. 3. 2. 1 Differential Scanning Calorimetry:**

Differential Scanning Calorimetry of active ingredient and polymers were studied to investigate the compatibility of the both materials when mixed together by observing any changes occur in melting points of the drug. The test was performed at a rate of 5°C min<sup>-1</sup> from 25°C to 300°C temperature range under nitrogen flow of 25 ml min<sup>-1</sup> using differential scanning calorimeter.

#### **5. 3. 2. 2 Fourier Transform Infra-Red (FT-IR) spectral analysis:**

Fourier-Transformed Infrared (FT-IR) spectrums of Alfuzosin Hydrochloride with HPMC , Guar gum, Eudragit RLPO and Povidone K-30 performed

individually and in combinations at range of 400 to 4000  $\text{cm}^{-1}$  and the resolution was 1  $\text{cm}^{-1}$  using Fourier Transform Infrared (FTIR) spectrophotometer, (Perkin Elmer, spectrum-100, Japan )using the KBr disk method (2 mg sample in 200 mg KBr). This spectral test was used to check the compatibility of Alfuzosin Hydrochloride with the selected polymers. The spectrums were shown in Fig. 5. 15 to 5. 31.

## **5. 4 Preparation of Matrix Tablets:**

### **5. 4. 1 Preparation of matrix tablets containing Alfuzosin Hydrochloride**

The wet granulation technique was chosen to prepare matrix tablets. The compositions of the formulations were given in Table 4. 7. Matrix tablets were prepared using below technique. Step1. Required quantity of Alfuzosin Hydrochloride, retardant (HPMC K100 M or Guar gum 8000 cps or Eudragit RLPO) and other excipients (Microcrystalline Cellulose (AVCEL PH 101, Pregelatinized Starch and Povidone) were weighed and sifted through 40# sieve. Step 2. Step1 material was mixed in rapid mixing granulator (RMG) for 15min and blend was granulated using purified water as the granulating agent. Step 3. The wet granules were sifted through 14 # sieve and dried in hot air oven at inlet temperature of  $60 \pm 5^\circ\text{C}$  till the moisture comes below 3%w/w. Step 4. The dried granules were sieved through 20 # sieve and lubricated with Magnesium stearate and colloidal silicon dioxide (previously shifted through # 40 mesh) for about 5 min in a double cone blender. Step 5. The lubricated granules were compressed into tablets using 8. 8 mm round shaped with standard concave punches.

**Table 5. 7: Composition of matrix tablet containing Alfuzosin Hydrochloride****Name of ingredient****mg/tablet****ALF/01****ALF/02****ALF/03****ALF/04****ALF/05****ALF/06****ALF/07****ALF/08****ALF/09****ALF/10****ALF/11****ALF/12**

Alfuzosin HCL10. 0010. 0010. 0010. 0010. 0010. 0010. 0010. 0010. 0010.

0010. 0010. 00Microcrystalline Cellulose Avicel PH 101158. 00245. 50204.

0090. 50187. 00134. 00204. 00194. 00194. 00184. 00174. 00104.

00Eudragit RLPO120. 00

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Povidone K -309. 00



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Starch 1500

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15. 00

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Hydroxypropyl methyl cellulose K100M

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100. 00150. 00100. 00105. 00100. 00110. 00115. 00150. 00Guar gum 8000  
cps

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40. 0080. 00180. 00

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-

30. 0035. 0040. 0040. 0045. 0080. 00Purified

WaterQSQSQSQSQSQSQSQSQSQSQSQSCollodial silicone dioxide

---

1. 502. 001. 50

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2. 002. 002. 002. 002. 002. 002. 00Magnesium Stearate3. 003. 004. 003.

003. 004. 004. 004. 004. 004. 004. 004. 00

## **Tablet Weight**

**300.00**

**300.00**

**300.00**

**300.00**

**300.00**

**300.00**

**350.00**

**350.00**

**350.00**

**350.00**

**350.00**

**350.00**

## **5.5 Evaluation of Tablets**

### **5.5.1 Evaluation of physical parameters for granules**

#### **5.5.1.1 Flowability:**

Flowability of lubricated granule were tested by using Bulk density, Tap density, Compressibility, Hausner's ratio and Angle of repose. Formulas are as below. Bulk Density = Weight of the powder (g) / Untapped volume (ml) Tapped Density = Weight of the powder (g) / Final tapped volume (ml)

## Compressibility Index (%)

= (Tapped Density - Bulk Density) × 100 / Tapped Density  
 Hausner's Ratio = Tapped Density / Bulk Density

## Angle of repose:

Take funnel stand with smooth base, keep the funnel and adjust the funnel height such a way that the distance between the powder pile and funnel should be approximately 2-4 cm. keep the graph paper on base, hold the funnel orifice, pore the powder and leave the orifice to fall down. Find the height (H) of the cone of powder and circle of the powder carefully. Find out the angle of repose using following equation: Where,  $\alpha$  is angle of the repose." H" is height of the powder cone" R" is radius of the circle.

## Table 5. 8: Experimental consideration for Compressibility Index, Hausner Ratio and Angle of Repose

### Flow Property

### Compressibility Index

### Hausner Ratio

### Angle of Repose

Excellent  $\leq 10$  1. 00-1. 11 25-30 Good 11-15 1. 12-1. 18 31-35 Fair 16-20 1. 19-1. 25 36-40 Passable 21-25 1. 26-1. 34 41-45 Poor 26-31 1. 35-1. 45 46-55 Very poor 32-37 1. 46-1. 59 56-65 Very, Very poor  $> 38 > 1. 60 > 66$

## **5. 5. 2 Evaluation of physical parameters for Tablets**

### **5. 5. 2. 1 Uniformity of Weight:**

Ten tablets were selected randomly from each batch and weighed individually and determine the average weight, then check for weight variation. The average weight of tablet with % deviation as per Indian pharmacopeia was represented in table

### **Table 5. 9: Average weight of tablet with % deviation as per Indian Pharmacopeia.**

#### **Average weight of Tablet**

#### **% Deviation**

80 mg or less  $10^{\circ}$  80 mg and  $<250$  mg  $7.5^{\circ}$  250 mg  $5.0$

### **5. 5. 2. 2 Thickness:**

Thickness of the tablets were checked using digital Vernier clipper by placing the tablet in between the two jaws.

### **5. 5. 2. 3 Hardness:**

Hardness is main criteria for tablets and should have enough to withstand mechanical stress like coating, packaging, shipment, and handling by the consumer. The crushing strength test of tablet diametrically was performed on 10 tablets from each formulation by using Dr. Schleuniger, Hardness tester.

### **5. 5. 2. 4 Friability:**

The friability test is to evaluate the ability of the tablet to withstand abrasion in coating, packaging, handling and shipping. Friability of each formulation

tested using 20 tablets was determined using a Roche type friability tester. 20 tablets were weighed, transferred to friabilator and performed the test with 100 rotations at speed of 25 rpm. After completion of rotations tablets were removed, dedusted and weighed. Friability of tablet should not be more than 1.0%. Friability percentage was calculated using the following equation: % Friability = (initial weight - Final weight) / initial weight × 100.

### **5.5.3 Effect of Hardness on dissolution:**

To study the effect of hardness on the tablet formulation, we have compressed the formulation (B. No: ALF/10) at different hardness levels i. e. low hardness (8.1 to 9.3kp), optimum hardness (10.7 to 12.2 kp), high hardness (14.4 to 15.7 kp). The dissolution studies were performed arrive the effect of the hardness on the drug release. All the samples were analysing for in-vitro drug release by using same mentioned method (4.2.1). For comparison, marketed samples also analysed by using same method (4.2.1)

### **5.5.4 Drug content by HPLC:**

Accurately weighed 20 tablets and determined the average tablet weight in mg. Tablets were crushed into fine powder. Weighed the sample equivalent to 10.0mg of Alfuzosin Hydrochloride and transferred it into individual 200ml volumetric flask with the aid of 120ml diluent. Solution was sonicated for 15min, dissolved and diluted to volume with diluent. Portion of sample was centrifuged for about 15min prior to dilution. 5.0ml of sample solution was transferred into individual 20.0ml volumetric flask, made up the volume with

diluent and mix well. Alfuzosin hydrochloride was estimated by HPLC using developed method step: 5. 2. 2.

### **5. 5. 5 In vitro Dissolution Study: (By UV)**

#### **Dissolution Parameters**

Medium

:

0. 01N HClVolume

:

900mLApparatus

:

USP-II (Paddle)Revolutions(RPM)

:

100Temperature

:

37 ± 0. 5° CTime Points

:

1, 2, 3, 6, 12 and 20 hoursLambda √

:

245nm



### 5. 5. 5. 1 Test Solution:

All the bowls were filled with 900 mL of dissolution medium and maintained at  $37 \pm 0.5$  °C. Dropped one tablet in to each dissolution vessel and start the dissolution test. 10. 0 ml of aliquot were withdrawn at specific time intervals and same quantity of fresh dissolution media was replaced. Aliquots were filtered through  $0.45 \mu$  (Millipore) nylon membrane filter. 5ml of this solution was diluted to 10ml with dissolution medium. Samples were estimated by developed method step: 5. 2. 1.

### 5. 5. 5. 2 Statistical approach to difference and similar factor:

The model independent method is most suitable for dissolution profile comparison when 3 to 4 or more dissolution time points are available. Statistical models such as Difference factor (f1) and similar factor (f2) both were constructed for optimised batch and marketed product dissolution profile by using following equations. Difference factor measures the % difference between 2 curves at each time point and the relative error between the two curves, similarity factor is a measurement of % dissolution similarity between the two curves. Difference Factor

$$f1 = \left\{ \frac{\sum_{t=1}^n (R_t - T_t)}{\sum_{t=1}^n R_t} \right\} \times 100$$

Similar Factor

$$f2 = 50 \times \log \left\{ \left[ 1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \right\} \times 100$$

Where, n is number of time points. R(t) is the mean % drug dissolved of Marketed product at time t. T(t) is the mean % drug dissolved of test product. f1 value should be close to 0 (0 to 15) to prove the both the

formulations are not different.  $f_2$  value should be between 50 to 100 to prove the both the formulations are similar.

## **5.5.6 Kinetic modelling system for In-vitro release**

### **5.5.6.1 Zero Order:**

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly (a constant release rate) can be represented by zero order equation. To study the release kinetics, in vitro data of drug release studies were plotted as cumulative amount of percentage drug released versus time. It describes the rate of drug release is independent of the concentration of dissolved substance.  $C = K_0 t$  Where,  $K_0$  is zero-order rate constant expressed in units of concentration/time and  $t$  is the time. Application: This equation can be used to describe the drug dissolution of matrix tablets with low soluble drugs, osmotic systems and transdermal systems,

### **5.5.6.2 First Order:**

This model useful in the determination of drug absorption and/or elimination. Drug release depending on the concentration.  $\log C = \log C_0 - kt/2.303$  Where,  $C_0$  = The initial concentration of drug and  $K$  is first order constant. Application: This equation can be used to describe the drug release in porous matrices those containing water-soluble drugs.

### **5.5.6.3 Erosion model:**

This equation defines the drug release based on erosion alone.  $Q = 1 - (1 - k_3 t)^3$  Where,  $Q$  is the fraction of drug released at time  $t$ ,  $k_3$  is the release rate

constant. Thus, a plot between  $[1-(1-Q)^{1/3}]$  against time will be linear if the release obeys erosion equation.

### **5.5.6.4 Korsmeyer-Peppas model:**

To find the drug release mechanism first 60% drug release data were fitted in Korsmeyer-Peppas model, which described drug release from a polymeric system equation. To study release kinetics, in vitro drug release data was plotted as log cumulative % drug release versus log time.  $M_t / M_\infty = Kt^n$  Where  $M_t / M_\infty =$  a fraction of drug released at time  $t$ ,  $K =$  The release rate constant and  $n$  is the release exponent. The  $n$  value is used to characterize different mechanism of drug release for cylindrical shaped matrices.

### **5.5.6.5 Higuchi's:**

The first mathematical model which describes drug release from a matrix system proposed by Higuchi in 1961. It is applicable for planar systems initially; it was then extended to different geometrics and porous systems.  $Q = KH \times T^{1/2}$   $KH =$  The Higuchi dissolution constant The values of cumulative percentage drug release versus square root of time. Application: This can be used to describe the drug release from matrix tablets with water soluble drugs and transdermal systems.

### **5.6 Stability Studies:**

Stability study of selected formulation was tested according to international conference of harmonization guidelines. The tablets was stored in Alu-Alu blister for 3 months in stability chamber at  $40^\circ\text{C} \pm 2^\circ\text{C}$  &  $75\% \pm 5\% \text{ RH}$ .

Stability samples were tested for Physical, drug content and in vitro dissolution.