FORMULATION AND EVALUATION OF TAMSULOSIN HYDROCHLORIDE SUSTAINED RELEASE TABLETS

Dissertation

Submitted to

The Tamil Nadu Dr.M.G.R Medical University, Chennai

In partial fulfillment for the award of degree of

MASTER OF PHARMACY

in

PHARMACEUTICS

by

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DEPARTMENT OF PHARMACEUTICS

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OCTOBER-2013

DECLARATION

I hereby declare that this thesis work entitled**" FORMULATION AND EVALUATION OF TAMSULOSIN HYDROCHLORIDE SUSTAINED RELEASE TABLETS"** Submitted to The Tamilnadu Dr.M.G.R Medical university, Chennai was carried out by me in the Department of Pharmaceutics, Ultra College of Pharmacy, Madurai under the valuable and efficient guidance of **Mr.K.Senthil Kumar, M.Pharm.,** Assistant Professor, Department of Pharmaceutics, Ultra college of Pharmacy, Madurai during the academic year Nov 2012- Oct 2013. I also declare that the matter embodied in it is a genuine work and the same has not formed the basis for the award of any degree, diploma, and associateship, fellowship of any other university or institution.

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CERTIFICATE

This is to certify that, the thesis work entitled **" FORMULATION AND EVALUATION OF TAMSULOSIN HYDROCHLORIDE SUSTAINED RELEASE TABLETS "** submitted in partial fulfillment of the requirements for the award of degree of Master of Pharmacy in Pharmaceutics of The Tamil Nadu Dr.M.G.R Medical University, Chennai is a bonafide work carried out by **D.Prawin** and was guided and supervised by me during the academic year Nov 2012- Oct 2013.

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EXAMINERS:

1.

2

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INTRODUCTION

INTRODUCTION

1.1 ORAL DRUG DELIVERY SYSTEMS

The oral route of drug administration is the most important method of administering drugs for systemic effects. Oral route has been the most popular for delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system. It is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route.

Oral dosage forms: There are mainly two types of oral dosage forms.

Those are

1. Solid oral dosage forms
2. Liquid oral dosage forms

Advantages of oral dosage forms:

- Superior flexibility in dosage form design.
- Patient acceptance.
- Safe route of drug administration.
- Minimum potential damage at the site of administration.
- Convenience in administration.

Disadvantages of oral dosage forms:

- Limited solubility of drug.
- Poor permeation across the gastrointestinal tract.
- Oral bioavailability is affected by presystemic metabolism.
- Drug absorption in the gastro intestinal tract.

1.1.1 Solid oral dosage forms: Of drugs that are administered orally, solid oral dosage forms represents the preferred class of product. Tablets and capsules occupies major portion of solid oral dosage forms. The reasons for preference of solid orals are as follows:

- These are less expensive compared to liquid orals because of high manufacturing and shipping costs of liquid orals.
- Drugs are generally more stable both chemically and physically in solid form than in a liquid form and expiration dates tend to be longer.
- Tablets and capsules represent unit dosage forms in which one usual dose of the drug has been accurately placed.

Of the two oral solid dosage forms commonly employed in this country, the tablet and the capsule the tablet has a number of advantages.

1.1.2 TABLETS:

The term tablet derived from the Latin word 'tabuletta' which is associated with the appearance of dosage form, i.e., tablets are small disc like or cylindrical specimens. Tablets are defined as unit solid dosage forms containing one or more active ingredients and prepared either by compression or molding. In addition to medicament(s) tablet also contains inactive ingredients, usually called as excipients. Tablets are the most common type of solid dosage form in contemporary use. These are mainly intended for oral administration. Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use the drug must be released from the tablet, i.e., normally dissolved in the fluids of the mouth, stomach or intestine and thereafter be absorbed into the systemic circulation, by which it reaches its site of action. Alternatively tablets can be formulated for local delivery of drugs.

1.1.3 Properties of tablets:

- Accurate dosage of medicament, uniform in weight, appearance and diameter
- Have the strength to withstand the rigors of mechanical shocks encountered in its production, packaging, shipping and dispensing
- Release the medicinal agents in the body in a predictable and reproducible manner.
- Elegant product, acceptable size and shape.
- Chemical and physical stabilities.

Advantages of Tablets:

- They are unit dosage form, and they offer greatest capabilities of all oral dosage forms for the greatest dosage precision and the least content variability.

- Their cost is lowest of all the dosage forms.
- They are the lightest and most compact of all the dosage forms.
- Product identification is simplest when employing an embossed punch face.
- They lend themselves to certain special release profile products
- They have the best combined properties of chemical, mechanical, and microbiological stability of all the oral forms

Disadvantages of the Tablets:

- Some drugs resist compression in to dense compacts, owing to their amorphous nature or flocculent, low-density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT may be impossible to formulate and manufacture as a tablet.
- Drugs with objectionable organoleptic properties may require coating after compression, which will increase the cost of production.

1.1.4 TYPES AND CLASSES OF TABLETS:

A. Oral tablets for ingestion:
- Compressed tablets
- Multiple Compressed tablets
- Repeat action tablets
- Delayed action and enteric coated tablets
- Sugar coated tablets
- Film coated tablets
- Chewable tablets

B. Tablets used in the oral cavity:
- Buccal tablets
- Sublingual tablets
- Troches and lozenges
- Dental cones

C. Tablets administered by other routes:
- Implantation tablets
- Vaginal tablets (inserts)

D. Tablets used to prepare solutions:
- Effervescent tablets
- dispensing tablets

- hypodermic tablets
- tablet triturates or molded tablets

1.1.5 TABLETTING METHODS:

Tabletting methods are categorized into

- Dry methods
  - Dry granulation
  - Direct compression
- Wet methods
  - Wet granulation

1.2.1 Dry granulation:

Dry granulation processes create granules by light compaction of the powder blend under low pressures. The compacts so-formed are broken up gently to produce granules (agglomerates). This process is often used when the product to be granulated is sensitive to moisture and heat. Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor. Dry granulation equipment offers a wide range of pressures to attain proper densification and granule formation. Dry granulation is simpler than wet granulation, therefore the cost is reduced. However, dry granulation often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet. Dry granulation requires drugs or excipients with cohesive properties, and a 'dry binder' may need to be added to the formulation to facilitate the formation of granules.

1.2.2 Direct compression:

In Direct compression tablets are compressed directly from powder blends of the active ingredient and suitable excipients. No pretreatment of the powder blends by wet or dry granulation procedures is necessary.

1.2.3Wet granulation

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis.

1.2.4 Procedure

- Step 1: The active ingredient and excipients are weighed and mixed.
- Step 2: The wet granulate is prepared by adding the liquid binder–adhesive to the powder blend and mixing thoroughly. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia, and cellulose derivatives such as methyl cellulose, gelatin and povidone.
- Step 3: Screening the damp mass through a mesh to form pellets or granules.
- Step 4: Drying the granulation. A conventional tray-dryer or fluid-bed dryer are most commonly used.
- Step 5: After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size.

1.3.1 MODIFIED RELEASE PROFILES:

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized".

Advantages:

- Obtain extended or prolonged release
- Avoid release in the stomach (enteric coating)
- Target different parts of the GI tract (colon delivery)
- Delay release from the stomach

Disadvantages:

- Release and uptake of the drug can be affected by the passage through the gastro- intestinal track
- Only limited periods of sustained release can be achieved this dependence on where in the GI tract uptake occurs. True sustained release is often difficult to obtain.

Several types of modified-release drug products are recognized.

A. Extended release
- Sustained release
- Controlled release

B. Delayed release

C. Targeted release
- Site specific targeting
- Receptor specific targeting

1.3.2 EXTENDED RELEASE DOSAGE FORMS:

A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate release form. Ex: Controlled release, Sustained release.

a. Controlled release dosage form: An ideal **controlled release system** is the one which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time. Thus unlike conventional immediate release systems, the rate of appearance of drug in the body with such a system is not controlled by absorption process. Following absorption of drug from such a system there is no control over its fate. It differs from sustained release systems which simply prolong the drug release and hence plasma drug levels for an extended period of time (i.e., not necessarily at a predetermined rate)

b. Sustained release dosage form: An ideal **sustained release system** is the one which slowly releases the drug locally or systemically, for an extended period of time, not particularly at a pre determined rate.

1.3.3 DELAYED RELEASE DOSAGE FORMS:

An ideal **delayed release system** is the one which releases a discrete portion of drug at a time or times other than promptly after administration, although one portion may be released promptly after administration. Ex: Enteric coated dosage forms

1.3.4 TARGETTED RELEASE DOSAGE FORMS:

An ideal **targeted drug delivery system** is the one which delivers the drug only to its site of action and not to the non targeted organs or tissues. With this approach control of kinetics of drug release is difficult.

a. Site specific targeting: This refers to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

b. Receptor targeting: This refers to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery

1.3.5 SUSTAINED RELEASE DOSAGE FORMS:

The basic goal of any drug therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time. The design of proper dosage regimen is an important element in accomplishing this goal.

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to

identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

Advantages:
The several advantages of a sustained drug delivery system over a conventional dosage from are-

- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of dose administered.
- Reduction in health care cost though improved therapy release conventional dosage forms; this may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site-specific absorption etc.,

Disadvantages:-

- Decreased systemic availability in comparison to immediate release conventional dosage forms; this may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site-specific absorption, pH-dependent solubility, etc.
- Poor in vitro-in vivo correlation.
- Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dosage adjustment of drug normally administered in varying

strength.

- Higher cost of formulation.

1.3.6 Selection Criteria of Drug:

- Half-life should be 2-8 hours.
- It should not undergo extensive first –pass metabolism.
- It should be stable in GIT.
- Compounds with high partition coefficient are better to choose.
- Lower limit of solubility of a drug is 0.1 mg/ml.
- Drugs absorbed throughout GIT are better candidates.

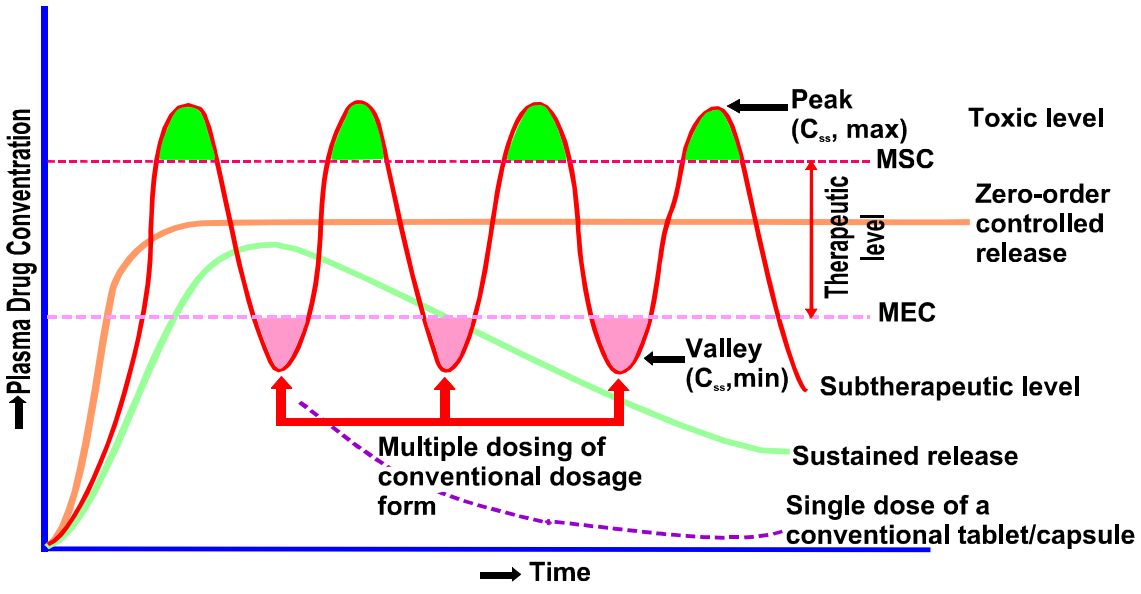


Fig 1: Graphical representation of the coventional and modified release dosage form release profiles

The type of delivery system and route of administration of the drug presented in sustained drug delivery system may depend upon several properties (Bramhankar and Jaiswal, 1995). They are

a. Physicochemical Properties of drugs
b. Biological Factors.
c. Route of drug delivery
d. Target sites
e. Acute or chronic dosing
f. The disease

1.4.1 Physicochemical Properties of Drugs

a. Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general a single dose of 0.5 to 1gm is considered maximum (Nicholas et al., 1987).

b. Ionization, P^{Ka} & Aqueous Solubility

The pH Partition hypothesis simply states that the unchanged form of a drug species will be preferentially absorbed through many body tissues. Therefore it is important to note the relationship between the P^{Ka} of the compound and its absorptive environment. For many compounds, the site of maximum absorption will also be the area in which the drug is least soluble.

For conventional dosage forms the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of the intestine. For sustained release formulations much of the drug will arrive in the small intestine in solid form. This means that the solubility of the drug is likely to change several orders of magnitude during its release.

Compounds with very low solubility are inherently controlled, since their release over the time course of a dosage form in the GIT will be limited by dissolution of the drug.

The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1mg/ml (Fincher et al., 1968). Thus for slightly soluble drugs, diffusional systems will be poor choice, since the concentration in solution will be low.

For example Tetracycline has maximum solubility in the stomach and least solubility in the intestine where it is maximally absorbed. Other examples of drugs whose incorporation into sustained release systems are limited because of their poor aqueous solubility and slow dissolution rate are digoxin, warfarrin, griseofulvin and salicylamide. Very soluble drugs are also good candidates for the sustained release dosage forms.

c. Partition coefficient

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability. Compounds with very low partition coefficient will have difficulty in penetrating membranes resulting poor bioavailability. Furthermore partitioning effects apply equally to diffusion through polymer membranes.

d. Drug Stability

The drugs, which are unstable in stomach, can be placed in a slowly soluble form and their release delayed until they reach the small intestine. However, such a strategy would be detrimental for drugs that either are unstable in the small intestine (or) undergo extensive gut wall metabolism, as pointed out in the decrease bioavailability of some anticholinergic drugs from controlled /sustained release formulation. In general the drugs, which are unstable in GIT environment poor candidates for oral sustained release forms.

e. Protein Binding

It is well known that many drugs bind to plasma proteins with a mostly recirculated and not eliminated. Drug protein binding can serve as depot for drug producing a prolonged concomitant influence on the duration of drug action. Since blood proteins are release profile, especially if a high degree of drug binding occurs.

1.5.1. Biological Factors

a. Biological Half-Life

Therapeutic compounds with half-life less than 8 hrs are excellent candidates for sustained release preparations. Drugs with very short half-life (less than 2 hrs) will require excessively large amounts of drug in each dosage unit to maintain controlled effects. Thus forcing the dosage form itself to become too large to be administered. Compounds with relatively long half-lives, generally greater than 8 hrs are not used in the sustained release dosage forms, since their effect is already sustained and also GI transit time is 8-12 hrs (Jantzen et al., 1996). So the drugs, which have long -half life and short half- life, are poor candidates for sustained release dosage forms.

Some examples of drug with half-lives of less than 2 hours are ampicillin, cephalexin, cloxacillin, furosemide, levodopa, penicillin G and propylthiouracil. Examples of those with half-lives of greater than 8 hours are dicumarol, diazepam, digitoxin, digoxin, guanethidine, phenytoin and warfarin.

b. Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained release product. Drugs which are absorbed by specialized transport process (carrier mediated) and drug absorption at special sites of the gastrointestinal tract (Absorption Window) are poor candidates for sustained release products.

c. Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained-release system for that drug. As long as the location, rate and extent of metabolism are known and the rate constant(s) for the process (es) are not too large, successful sustained-release products can be developed.

There are two factors associated with the metabolism of some drugs; however that present problems of their use in sustained-release systems. One is the ability of the drug to induce or inhibit enzyme synthesis; this may result in a fluctuating drug blood level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Examples of drugs that are subject to intestinal metabolism upon oral dosing are hydralazine, salicylamide, nitroglycerine, isoproterenol, chlorpromazine and

levodopa. Examples of drugs that undergo extensive first-pass hepatic metabolism are propoxyphene, nortriptyline, phenacetine, propranolol and lidocaine.

Drugs that are significantly metabolized especially in the region of the small intestine can show decreased bioavailability from slower releasing dosage forms. This is due to saturation of intestinal wall enzyme systems. The drugs should not have intestinal first pass effect and should not induce (or) inhibit metabolism are good candidates for sustained release dosage form.

1.6. TECHNIQUES FOR PREPARING SUSTAINED RELEASE FORMULATIONS:

1.6.1 Based on drug modification:

a. Complex formation: The rate of dissolution of solid complex in biological fluids and rate of dissociation o complex in the solution are considered and they depend upon PH and composition of gastric and intestinal fluids.

b. Drug adsorbate preparation: In this product is insoluble. Drug availability is determined by rate of disabsorption.

c. Prodrug synthesis: They are inactive and need enzymatic hydrolysis for regeneration, Solubility, absorption rate of prodrug must be lower than parent drug.

d. Ion exchange resins: They are water insoluble, cross linked polymers containing salt forming groups. The drug is bound to the resin by using chromatographic column or by prolong contact. Drug release from this complex depends on PH and property of resin

1.6.2 Based on dosage form modification:

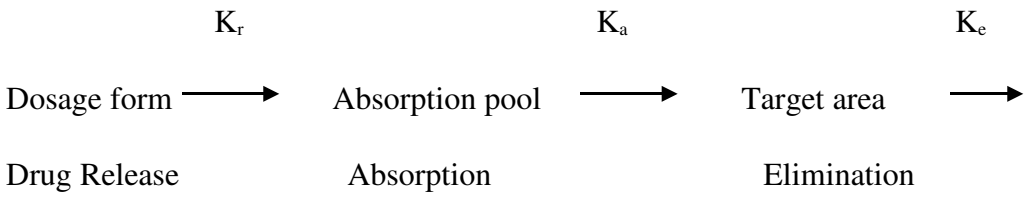
a. Microencapsulation: It is a process in which tiny particles are surrounded by uniform coating (microcapsule) or held in a matrix polymer (microsphere)

b. Barrier coating: In this one quarter of granules are in non sustained form for sudden drug release, remaining part are coating for sustained release.

C.Matrix embedding: Drug is dispersed in a matrix of retardant material which may be encapsulated or compressed in a tablet.

1.6.3 Release Rate and Dose Consideration:

The conventional dosage forms include solutions, capsules, tablets, emulsions, etc. These dosage forms can be considered to release their active ingredients into an absorption pool immediately.



The absorption pool represents a solution of the drug at the site of absorption.

Where

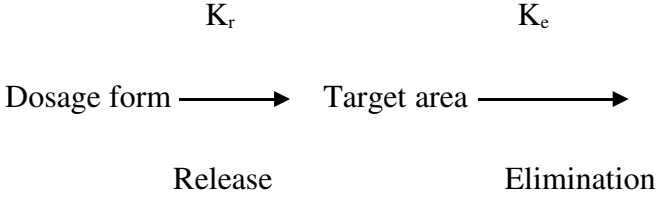
K_r= First order rate constant for drug release.

K_a=First order rate constant for drug absorption.

K_e=First order rate constant for overall drug elimination.

For immediate release dosage forms $K_r >>> K_a$ or alternatively absorption of drug across a biological membrane is the rate-limiting step in delivery of the drug to its target area.

For non-immediate release dosage forms, $K_r <<< K_a$, that is, release of drug from the dosage form is the rate limiting step. This cause the above kinetics scheme to reduce to



Thus, the effort to develop a delivery system that releases drug slowly must be directed primarily at altering the release rate by affecting the value of K_r.

The ideal goal in designing a controlled-release system is to deliver drug to the desired site at a rate according to needs of the body, i.e. a self-regulated system based on feedback control but this is a difficult assignment.

1.7 BENIGN PROSTATIC HYPERPLASIA (BPH):

Benign prostatic hyperplasia (BPH) also known as benign prostatic hypertrophy (technically a misnomer), benign enlargement of the prostate (BEP), and adenofibromyomatous hyperplasia, refers to the increase in size of the prostate. It is common for the prostate gland to become enlarged as a man ages. Doctors call this condition benign prostatic hyperplasia (BPH), or benign prostatic hypertrophy.

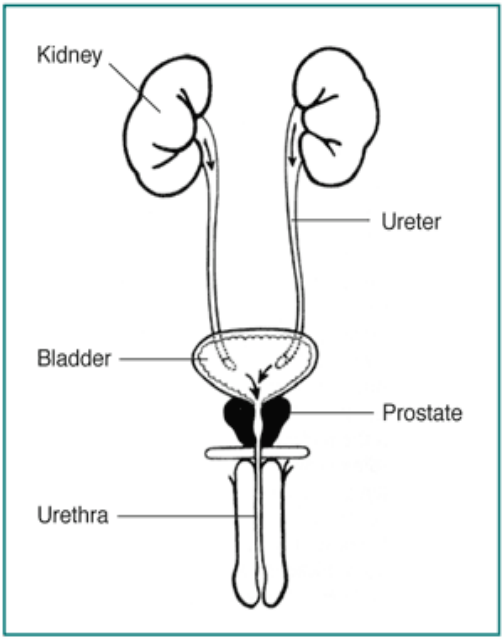


Fig 2: Normal urine flow.

As a man matures, the prostate goes through two main periods of growth. The first occurs early in puberty, when the prostate doubles in size. At around age 25, the gland begins to grow again and the Second growth phase often results year later in Benign prostatic hyperplasia (BPH).

Why BPH Occurs:

The cause of BPH is not well understood. No definite information on risk factors exists. For centuries, it has been known that BPH occurs mainly in older men and that it doesn't develop in men whose testes were removed before puberty. Throughout their lives, men produce both testosterone, an important male hormone, and small amounts of estrogen, a female hormone.

As men age, the amount of active testosterone in the blood decreases, leaving a higher proportion of estrogen. Studies done on animals have suggested that BPH may occur because the higher amount of estrogen within the gland increases the activity of substances that promote cell growth.

Another theory focuses on dihydrotestosterone (DHT), a substance derived from testosterone in the prostate, which may help control its growth. Most animals lose their ability to produce DHT as they age. However, some research has indicated that even with a drop in the blood's testosterone level, older men continue to produce and accumulate high levels of DHT in the prostate. This accumulation of DHT may encourage the growth of cells. Scientists have also noted that men who do not produce DHT do not develop BPH.

Symptoms:

The symptoms of BPH vary, but the most common ones involve changes or problems with urination, such as a) a hesitant, interrupted, weak stream b) urgency and leaking or dribbling c) more frequent urination, especially at night**.** The size of the prostate does not always determine how severe the obstruction or the symptoms will be. Some men with greatly enlarged glands have little obstruction and few symptoms while others, whose glands are less enlarged, have more blockage and greater problems.

Treatment:

Men who have BPH with symptoms usually need some kind of treatment at some time.. The results of their studies indicate that early treatment may not be needed because

the symptoms of BPH clear up without treatment in as many as one-third of all mild cases. Instead of immediate treatment, they suggest regular checkups to watch for early problems. If the condition begins to pose a danger to the patient's health or causes a major inconvenience to him, treatment is usually recommended.

REVIEW OF LITERATURE

2.1 REVIEW OF LITERATURE

T.S. Nithiyananthan, et al., (2009) has performed "Prolonged, sustained or extended release systems, release the active ingredient slowly than conventional dosage forms similarly administered. Tamsulosin is selective, potent and competitive α1 – adrenoreceptor antagonist. It has a greater affinity for the α1A – receptor subtype and is indicated to treat uretheral stone symptoms associated with benign prostatic hyperplasia. In the present work, attempt was made to develop and once daily sustained release matrix tablet of Tamsulosin hydrochloride. Hydroxy propyl methyl cellulose was used as a hydrophilic matrix polymer. The formulation showed acceptable pharmacotechnical properties and HPLC assay requirements.

Tsuda Y, et al., (2010) has performed Population pharmacokinetics of tamsulosin hydrochloride in paediatric patients with neuropathic and non-neuropathic bladder. Pharmacokinetics and Non-Clinical Safety Department, Nippon Boehringer Ingelheim Co., Ltd, Hyogo, Japan. Tamsulosin is available on prescription as a modified release capsule in the US (Flomax), and in most European countries for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). The pharmacokinetics of tamsulosin hydrochloride (Hydrochloric acid) have been extensively studied in adults

Chang HS, et al., (2009) has performed Assessment of patient-reported outcome of patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and treated with Tamsulosin Hydrochloride in Korea. To evaluate the effect of tamsulosin 0.2 mg once daily in treatment of patients with benign prostatic hyperplasia (BPH) using the new subjective assessment of patient-reported outcomes and the lower urinary tract symptoms (LUTS) outcome score (LOS).

Van Hoogdalem, et al., (1997) has performed Disposition of the selective alpha1A-adrenoceptor antagonist tamsulosin in humans: comparison with data from interspecies scaling. Tamsulosin-Hydrochloric acid is an alpha1A-adrenoceptor antagonist that is mainly eliminated by metabolism in animals and humans and is highly bound to alpha1-acid glycoprotein in blood plasma. The disposition of the compound (0.4 mg as modified-release granules in a capsule) was determined in male volunteers, using intravenous (iv) infusion of tamsulosin-Hydrochloric acid (0.125 mg over 4 h) as reference treatment for the assessment of absolute oral bioavailability.

Nieminen T, et al., **(2005)** has performed Effects of adrenoceptor blocking drugs on cardiovascular responsiveness to passive orthostasis: a placebo-controlled double-blind study. To compare the acute effects of the beta-blocker propranolol (CAS 525-66-6), beta + alpha1-blocker carvedilol (CAS 72956-09-3) and alpha1-blocker tamsulosin (CAS 106463-17-6) on the cardiovascular responses to passive orthostasis.

Prosnitz RG, et al.,(1999) has performed, Tamsulosin palliates radiation-induced urethritis in patients with prostate cancer: results of a pilot study. A pilot study was performed to determine the effectiveness of Flomax (Tamsulosin Hydrochloride) in the management of acute radiation urethritis in prostate cancer patients undergoing conformal external beam radiation therapy (RT). Potential predictors of response to Flomax were evaluated.

Sudoh K, et al., (1996) has performed Effect of tamsulosin, a novel alpha 1-adrenoceptor antagonist, on urethral pressure profile in anaesthetized dogs. The effect of tamsulosin(YM617,(R)(-)-S-[2-[[2-(o-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide Hydrochloric acid), a potent and selective alpha 1-

adrenoceptor antagonist, was examined on urethral pressure profile (UPP) and mean arterial blood pressure (MBP) in pentobarbital anaesthetized male dogs.

Ozkan SA, et al., (2003) has performed Voltammetric investigation of TamsulosinThe electrooxidative behavior and determination of Tamsulosin Hydrochloride (TAM), one of the alpha (1) -adrenoceptor antagonist, on a glassy carbon disc electrode were investigated for the first time by using cyclic, linear sweep, differential pulse (DPV) and square wave voltammetry (SWV). TAM showed an irreversible oxidation behavior at all pH values and buffers studied

García-Sáinz, et al., (1996) has performed Coexpression of alpha 1A- and alpha 1B-adrenoceptors in the liver of the rhesus monkey (Macaca mulatta).The alpha 1-adrenoceptors present in the liver of rhesus monkeys was characterized using [3H]prazosin. This radioligand binds to monkey liver membranes with high affinity (KD 0.33 nm) to a moderately abundant number of sites (97 fmol/mg of protein). These sites were characterized pharmacologically, by binding competition, observing two affinities for most ligands. These data strongly suggest that Macaca mulatta liver cells coexpress alpha 1A- and alpha 1B-adrenoceptors. Expression of the mRNA for these receptors was confirmed by reverse transcriptase-polymerase chain reactions.

Jeong-Soo KIM, et al., (2007) has performed "Statistical Optimization of Tamsulosin Hydrochloride Controlled Release Pellets Coated with the Blend of HPMCP and HPMC" The objective of the present study was to evaluate three coating parameters for the application of a blend of HPMCP and HPMC in ethylcellulose aqueous dispersions (Surelease®) in order to obtain controlled release of tamsulosin hydrochloride.. In addition, the dissolution profiles of the controlled release pellets coated with the optimized formulation were similar to those of the commercial Product.

Min-Soo Kima, et al., (2007) has performed," Development and optimization of a novel oral controlled delivery systemfor tamsulosin hydrochloride using response surface methodology" The purpose of this study was to develop and optimize oral controlled-release formulations for tamsulosin hydrochloride using a combination of two cellulose ester derivatives, hydroxypropyl methylcellulose (HPMC) and hydroxypropyl

methylcellulose phthalate (HPMCP), with Surelease®as a coating material. A three-factor, three-level Box-Behnken design was used to prepare systematic model formulations. The response surface methodology (RSM) and multiple response optimizations utilizing the polynomial equation were used to search for the optimal coating formulation

Masaki Ando (2006) et al has performed, . "Development and evaluation of a novel dry-coated tablet technology for pellets as a substitute for the conventional encapsulation technology" Pellet formulations as represented by multiparticulate systems are often contained in hard capsules. OSDRC-technology employs a double-structure punch (center punch and outer punch) allowing for dry-coated tablets to be assembled in a single run. The results revealed that thinner outer punches are not always better for filling small tablets with large amounts of pellets..We considered this to be due to the friction between the pellets and punch wall. We concluded that OSDRC-technology could be applied to capsule-like forms containing pellets _50 wt% through an unconventional approach.

Boyapally H, et al., (2009), Developed and release mechanism of diltiazem Hydrochloric acid prolonged release matrix tablets using HPMC and cocluded that the developed drug delivery system provided prolonged drug release rates over a defined period of time. DIL tablets prepared using dry mixing and direct compression and the core consisted of hydrophilic and hydrophobic polymers such as hydroxyl propyl methyl cellulose (HPMC) and eudragits RLPO.

Hiremath PS, **et al., (2008),** developed oral controlled release matrix tablet formulations of isoniazid using hydroxypropyl methylcellulose and confirmed that the release rate of the drug from the HPMC matrices is highly influenced by the drug/HPMC ratio and viscosity grade of the HPMC. Also, the effect of compression force and release media was found to be significant on the release profiles of isoniazid from HPMC matrix tablets. The release mechanism was found to be anomalous non-Fickian diffusion in all the cases. The formulations were found to be stable and reproducible.

Meyyanathan SN, et al.,(2007) Formulated and evaluated dextromethorphan hydrobromide sustained release tablets by wet granulation using hydroxypropyl methyl cellulose (HPMC-K-100 CR) The studies indicated that the drug release can be modulated by varying the concentration of the polymer and the fillers. A complete cross-over bioavailability study of the optimized formulation of the developed sustained tablets and marketed immediate release tablets was performed on six healthy male volunteers. The extent of absorption of drug from the SR tablets was significantly higher than that for the marketed dextromethorphan hydrobromide tablet because of lower elimination rate and longer half-life.

SCOPE

OBJECTIVE,

& PLAN OF WORK

3. SCOPE, OBJECTIVE, AND PLAN OF WORK

3.1 SCOPE:

Tamsulosin Hydrochloride is primarily used for benign prostatic hyperplasia, but is sometimes used for the passage of kidney stones by the same mechanism of smooth muscle relaxation via alpha antagonism. Benign prostatic hyperplasia (BPH) also known as benign prostatic hypertrophy or benign enlargement of the prostate (BEP), and adenofibromyomatous hyperplasia, refers to the increase in size of the prostate in middle-aged and elderly men. Tamsulosin Hydrochloride capsules and tablets are available in market in the form of sustained release dosage form. Further the sustained release tablet formulation in Europe and Japan markets are available as patented OCAS (Oral Controlled Absorption System) dosage form. The patent of OCAS is claiming an advantage of absorption of drug in the colon part of GIT, by extending the drug release more than 24 hours, without having any food effect against the available capsule form which releases the drug within 12 hrs. Further due to the concerns with the usage of

different polymer matrices which were covered in valid patents on formulation of Tamsulosin Hydrochloride sustained release dosage form; the requirement of identification of a Non-Infringing route was forced. Hence our scope of the current work is to prepare a Matrix formulation of Tamsulosin Hydrochloride sustained release tablets which will not infringe any valid patents and match to the reference product *In-vitro* release profile.

3.2. OBJECTIVE

The objective of the present study is to:

- To Formulate Tamsulosin Hydrochloride sustained release matrix tablets which is Non-Infringing to available sustained release dosage form in the market.
- To compare formulated tablets with marketed tablets.
- Evaluation of the formulated product.
- Decrease the cost of dosage form as compared to marketed products.
- Provide a better control of plasma drug levels for greater efficacy and safety.
- To improve patient compliance.

- A greater selectivity of pharmacological activity.

3.3. PLAN OF WORK

- Literature survey
- Reference product evaluation
- Preformulation studies
- Drug and Excipients compatibility studies.
- Process selection.
- Formulation of Tamsulosin Hydrochloride sustained release matrix tablets
- Evaluation of tablets
- Stability Evaluation

MATERIALS AND METHODS

4.1 MATERIALS

Table 1: Chemicals used

S.No	Ingredients	Manufacturer	Category
1	Tamsulosin Hydrochloride	Rachem pharma ltd	Alpha blocker in treatment of BPH
2	Dibasic calcium phosphate dihydrate (Di-TAB)	Innophos	Diluent
3	Amino Methacrylate copolymer Type- A (Eudragit RL PO)	Evonik Degussa	Polymer
4	Methacrylic acid copolymer Type-A (Eudragit L100)	Evonik Degussa	Polymer

5	Hydrogenated vegetable Oil (Lubritab)	JRS pharma	Polymer
6	PVPK-30 (Povidone)	ISP	Binder
7	PEG 20000	Clariant Inc, USA	Polymer
8	Stearic acid	BASF, Germany	Lubricant
9	Magnesium stearate	Ferro	Lubricant
10	Iso propyl alcohol	Rachem	Solvent
11	Opadry white	Colorcon	Coating material
12	Purified water	Rachem	Solvent

4.2 INSTRUMENTS USED

Table 2: Instruments used

S.No	Ingredients	Manufacturer	Category
1.	Weighing balance	Sartorius	CP225D
2.	Analytical balance	Essae DS-852	DS-852
3.	Tray dryer	Millennium equipments Pvt Ltd	METD-6G
4.	Tablet compression machine	Rimek(karnavathi)	D tooling
5.	Friabilator	Electrolab	EF-2(USP)
6.	Hardness tester	Electrolab	EH01
7.	Dissolution test system	Electrolab	TDT-14L

8.	Mechanical stirrer	Vision labs	NA
9.	HPLC	Schimadzu	LC2010CHT

4.3 DRUG PROFILE

Tamsulosin Hydrochloride is primarily used for benign prostatic hyperplasia, but is sometimes used for the passage of kidney stones by the same mechanism of smooth muscle relaxation via alpha antagonism. Benign prostatic hyperplasia (BPH) also known as benign prostatic hypertrophy or benign enlargement of the prostate (BEP), and adenofibromyomatous hyperplasia, refers to the increase in size of the prostate in middle-aged and elderly men.

Generic Name **:** Tamsulosin Hydrochloride

Synonyms **:** Tamsulosin

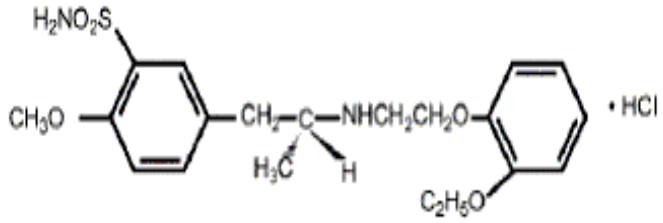
Chemical name **:** (-)-(R)-5-[2-[[2-Ethoxyphenoxy)ethyl]amino]propyl]-2- Methoxybenzenesulfonamide monohydrochloride

Drug Class : Selective Alpha-1 Adrenergic blocking agents.

Molecular weight : 444.98

Molecular formula : $C_{20}H_{28}N_2O_5S$ •Hydrochloric acid

Chemical structure **:**



Description : Tamsulosin Hydrochloride is a white crystalline powder.

Solubility : It is sparingly soluble in water and methanol, slightly soluble in glacial acetic acid and ethanol and practically insoluble in ether.

Melting point : Melts with decomposition at approximately at 230^0C

Route of administration : Oral

Oral dose : 0.4mg

BCS Classification : Class I (High solubility- High permeability)

Bioavailability : 100% oral

Half life : 9-13 hrs in healthy individual

14-15hrs in patients with BPH

Protein Binding : 94–99% (mainly to α_1-acid glycoprotein)

Time to peak concentration : 4 to 5 hours under fasting conditions

DESCRIPTION: Tamsulosin is a selective antagonist at alpha-1A and alpha-1B-adrenoreceptors in the prostate, prostatic capsule, prostatic urethra, and bladder neck. At

least three discrete alpha1-adrenoceptor subtypes have been identified: alpha-1A, alpha-1B and alpha-1D; their distribution differs between human organs and tissue. Approximately 70% of the alpha1-receptors in human prostate are of the alpha-1A subtype. Blockage of these receptors causes relaxation of smooth muscles in the bladder neck and prostate.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION:

Tamsulosin, a highly selective alpha-1_A adrenergic antagonist.Alpha-1 adrenoceptor subtypes are Alpha-1A, Alpha-1B and Alpha-1D. The messenger RNA expressionof Alpha-1A,Alpha-1D subtypes are predominant in the prostate and in the base and neck of the urinary bladder.

Post synaptic alpha 1_A blockade leads to:

- Smooth muscle relaxation of prostate, bladder neck and the urethra. Alpha blocker improves the dynamic component of subvesical obstruction due to benign prostatic hyperplasia.
- Resulting in decreased urinary outflow resistance.

PHARMACOKINETICS:

Absorption

Tamsulosin is well absorbed after oral administration under fasting conditions. Tamsulosin Hydrochloride exhibits linear kinetics following single and multiple dosing, with achievement of steady state concentrations by the fifth day of once-a-day dosing.

Food

Food delays time to peak plasma concentration by about 2 hours. When administered under fasting conditions, bioavailability and peak plasma concentration are increased by 30 and 40–70%, respectively, compared with fed state.

Distribution

Appears to distribute into extracellular fluids in humans. In animals, distributed into kidney, prostate, liver, gallbladder, heart, aorta, and brown fat, with minimal distribution into brain, spinal cord, and testes.

Tamsulosin hydrochloride is extensively bound to plasma proteins (94%-99%),primarily alpha 1 acid glycoprotein, with linear binding over a wide concentration range.

Metabolism:

Tamsulosin Hydrochloride is extensively metabolised by cytochrome p450 enzymes in the liver. It is indicated that CYP3A4 and CYP2D6are involved in metabolism of tamsulosin. The metabolites undergo extensive conjugation to glucoronide or sulphate prior to renal excretion.

Elimination:

- Excreted in urine (76%) and feces (21%).
- Tamsulosin Hydrochloride undergoes restrictive clearance in humans via relatively low systemic clearance.

INDICATIONS AND DOSAGE:

Tamsulosin is indicated for the alleviation of urinary symptoms in men including a weak or interrupted urinary stream, a feeling that one cannot empty one's bladder completely, urinary hesitancy, urinary frequency, especially at night and urinary urgency, due to benign prostatic hyperplasia or an enlargement of the prostate.

Dosage:

The recommended dose is 0.4 mg once daily 30 minutes after the same meal each day. If a patient fails to respond within 2-4 weeks after initiation of treatment at 0.4 mg/day the dose may be increased to 0.8 mg/day.

If administration is interrupted for several days of therapy the patient should be restarted at 0.4 mg regardless of the dosage they were receiving prior to the interruption.

Usage:

Tamsulosin Hydrochloride is indicated for the treatment of "BENIGN PROSTATIC HYPERPLASIA".

Reduction of urinary obstruction and relief of associated manifestations in Hypertensive patients with symptomatic BPH. Although drug therapy usually is not as effective as surgical therapy, it may provide adequate symptomatic relief with fewer and less serious adverse effects compared to surgery.

Precautions:

- Carcinoma of the prostate
- Intraoperative floppy iris syndrome
- Sulfa allergy
- Drug-drug interactions (cimetidine, warfarin, other alpha 1 blockers)
- Pregnancy category B
- Children – currently not sufficient evidence to support use in children

Contraindications:

Urological contraindications:

- Chronic urinary retention with renal failure
- Recurrent heamaturia due to prostatic enlargement
- Recurrent infections and bladder stones.

Cardiac contraindications:

- Hypertension, Mechanical Heart failure, Congestive heart failure.

Other contraindications:

- Cataract surgery, as this cause an intraoperative floppy iris syndrome.

B. DRUG INTERACTIONS:

Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6.

Concomitant treatment with ketoconazole (a strong inhibitor of CYP3A4) resulted in an increase in the Cmax and AUC of tamsulosin by a factor of 2.2 and 2.8 Concomitant treatment with paroxetine (a strong inhibitor of CYP2D6) resulted in an increase in the Cmax and AUC of tamsulosin by a factor of 1.3 and 1.6, respectively. The effects of concomitant administration of a moderate CYP2D6 inhibitor (e.g., terbinafine) on the pharmacokinetics of Tamsulosin Hydrochloride have not been evaluated

The effects of co-administration of both a CYP3A4 and a CYP2D6 inhibitor with Tamsulosin Hydrochloride tablets have not been evaluated.

Cimetidine:

Treatment with cimetidine resulted in a significant decrease (26%) in the clearance of tamsulosin hydrochloride, which resulted in a moderate increase in Tamsulosin Hydrochloride AUC (44%)

C. Other Alpha Adrenergic Blocking Agents

The pharmacokinetic and pharmacodynamic interactions between Tamsulosin Hydrochloride and other alpha adrenergic blocking agents have not been determined; however, interactions between Tamsulosin Hydrochloride and other alpha adrenergic blocking agents may be expected.

D. PDE5 Inhibitors

Caution is advised when alpha adrenergic blocking agents including Tamsulosin Hydrochloride are co-administered with PDE5 inhibitors. Alpha adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension.

E. Warfarin

A definitive drug-drug interaction study between Tamsulosin Hydrochloride and warfarin was not conducted. Results from limited in vitro and in vivo studies are inconclusive.

F. Nifedipine, Atenolol, Enalapril

Dosage adjustments are not necessary when Tamsulosin Hydrochloride is administered concomitantly with nifedipine, atenolol, or enalapril.

G. Digoxin and Theophylline

Dosage adjustments are not necessary when a Tamsulosin Hydrochloride is administered concomitantly with digoxin or theophylline.

4.4 EXCIPIENTS PROFILE

4.4.1Eudragit RLPO:

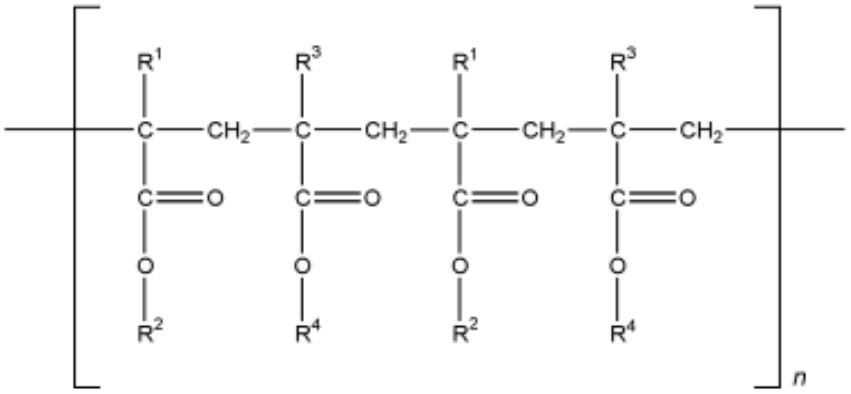
Synonyms

Polymeric methacrylates.

Description

Fine white powder with slightly amine-like odor.

Structural Formula



Chemical Name

Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethylmethacrylate

Functional categories

Polymer for developing sustained release matrix tablets and sustaining films.

Density

0.390 g/cm^3 (bulk)

Incompatibilities: Coagulation may be caused by soluble electrolytes, pH changes, some organic solvents and extremes of temperature.

Stability and storage

Dry powder polymer forms are stable at temperatures less than 30°C and should be stored in a tightly closed container at less than 30°C.

4.4.2 Eudragit L100:

Non proprietary names:

BP : Methacrylic acid ethyl acrylate copolymer (1 : 1)

USPNF : Ammonio methacrylate copolymer

Methacrylic acid copolymer

Synonyms:

Acryl-EZE; Acryl-EZE MP; Eastacryl 30D; Eudragit; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; polymeric methacrylates.

Chemical name and CAS registry no. :

Poly(methacrylic acid, methyl methacrylate) 1 : 1 ; [25806-15-1]

Empirical formulae and molecular weight:

Methacrylic acid–ethyl acrylatecopolymer (1 : 1) is a copolymer of methacrylic acid and ethylacrylate having a mean relative molecular mass of abou250 000. The ratio of carboxylic groups to ester groups is about1 : 1. It may contain suitable surfactants such as sodium dodecylsulfate or polysorbate 80. The ratio of carboxylic acid to ester groups is about 1 : 1.

Functional category:

Eudragit L 100-55 is an alternative to Eudragit L 30 D-55 which is used as an enteric coating film former for solid-dosage forms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5. It is commercially available as a redispersible powder Acryl-EZE and Acryl-EZE MP which are designed for enteric coating of tablets and beads, respectively. Eastacryl 30 D, Kollicoat MAE 30 D, and Kollicoat MAE 30 DP, are aqueous dispersions of methacrylic acid–ethyl acrylate copolymers. They are also used as enteric coatings for solid-dosage forms.

Description:

Several different types of eudragit L100 are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60: 40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent. Eudragit L-100 and Eudragit S-100 are white free-flowing powders with at least 95% of dry polymers.

Typical properties:

Acid value: 300-330

Alkali value: 23.9-32.3

Density (bulk): 0.390 g/cm^3

Density (tapped): 0.424g/cm^3

Solubility: soluble in acetone and alcohols and in intestinal fluids from P^H 6

Viscosity (dynamic): 100-200 mpas

Stability and storage conditions:

Dry powder polymer forms are stable at temperatures less than 30ºC. Above this temperature, powders tend to form clumps. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30 ºC. Dispersions should be stored at temperatures between 5 and 25 ºC.

Incompatibility:

Coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature. Dispersions of Eudragit L 30 D, RL 30 D, L 100-55, and RS 30 D are incompatible with magnesium stearate.

Safety:

Polymethacrylate copolymers are widely used as film-coating materials in oral pharmaceutical formulations. They are also used in topical formulations and are generally regarded as nontoxic and nonirritant materials. A daily intake of 2 mg/kg body-weight of Eudragit L100 may be regarded as essentially safe in humans.

Applications:

Eudragit L, S and FS types are used as enteric coating agents because they are resistant to gastric fluid. Different types are available that are soluble at different pH

values: e.g. Eudragit L is soluble at pH > 6; Eudragit L 30 D-55 is used as an enteric coating film former for solid-dosage forms.

4.4.3. Di Calcium Phosphate Di Hydrate:

Nonproprietary Names:

BP: Calcium hydrogen phosphate

USP: Dibasic calcium phosphate

Chemical Name and CAS Registry Number:

Dibasic calcium phosphate dihydrate [7789-77-7]

Empirical Formula and Molecular Weight

$CaHPO_4.\ 2H_2O$ - 172.09

Category:

Tablet and capsule diluents

Synonym:

Di- TAB

Description:

It is a white, odorless, tasteless powder or crystalline solid. Tablets produced with Di-calcium phosphate do not disintegrate readily.

Properties:

Angle of Repose: 28°.3´

Bulk density: 0.87 gm/cm^2

Tapped density*:* 0.93 gm/cm^2

Solubility*:*

Practically insoluble in water

Stability and Storage:

It is a non-hygroscopic, relatively stable material. Stored in a well-closed container, cool, dry place.

Incompatibility:

It is incompatible with tetracycline antibiotics, Indomethacin

Applications:

Dibasic calcium phosphate dihydrate is widely used in tablet formulations both as an excipient and as a source of calcium and phosphorus in nutritional supplements.

It is one of the more widely used materials, particularly in the nutritional/health food sectors.

It is also used in pharmaceutical products because of its compaction properties, and the good flow properties of the coarse-grade material.

Dibasic calcium phosphate dihydrate is abrasive and a lubricant is required for tableting, for example about 1% w/w of magnesium stearate or about 1% w/w of sodium stearyl fumarate is commonly used.

Two main particle-size grades of dibasic calcium phosphate dihydrate are used in the pharmaceutical industry.

The milled material is typically used in wet-granulated, roller-compacted or slugged formulations.

The ‘unmilled’ or coarse-grade material is typically used in direct-compression formulations. Dibasic calcium phosphate dihydrate is non hygroscopic and stable at room

temperature. However, under certain conditions of temperature and humidity, it can lose water of crystallization below 100°C.

Dibasic calcium phosphate dihydrate is also used in toothpaste and dentifrice formulations for its abrasive properties.

4.4.4. Lubritab:

Non proprietary names:

BP : Hydrogenated vegetable oil

JP : Hydrogenated oil

USPNF : Hydrogenated vegetable oil

Synonyms:

Hydrogenated cottonseed oil: Akofine; Lubritab; Sterotex.

Hydrogenated palm oil: Softisan 154.

Hydrogenated soybean oil: Lipovol HS-K; Sterotex HM

Chemical name and CAS registry no:

Hydrogenated vegetable oil [68334-00-9]

Empirical formulae:

$R_1COOCH_2—CH(OOCR_2)—CH_2OOCR_3$

where R_1, R_2, and R_3 are mainly C_{15} and C_{17}.

Functional category:

Tablet and capsule lubricant; tablet binder

Description:

Hydrogenated vegetable oil is a mixture of triglycerides of fatty acids. The two types that are defined in the USPNF 23 are characterized by their physical properties; Hydrogenated vegetable oil type I occurs in various forms, e.g. fine powder, flakes, or pellets. The color of the material depends on the manufacturing process and the form. In general, the material is white to yellowish-white with the powder grades appearing more white-colored than the coarser grades.

Typical properties:

Density (tapped): 0.57 g/cm^3

Melting point: 61–66°C

Particle size distribution: 85% < 177 mm, 25% < 74 mm in size

Average particle size is 104 mm.

Solubility: soluble in chloroform, petroleum spirit, and hot propan-2-ol; practically insoluble in water.

Stability and Storage Conditions:

Hydrogenated vegetable oil type I is a stable material; typically it is assigned a 2-year shelf-life. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with strong oxidizing agents.

Safety:

Hydrogenated vegetable oil type I is used in food products and oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant excipient.

Applications:

- Hydrogenated vegetable oil type 1 is used as a lubricant in tablet and capsule formulations. It is used at concentrations of 1–6% w/w, usually in combination with talc.
- It may also be used as an auxiliary binder in tablet formulations.
- Hydrogenated vegetable oil type I is additionally used as the matrix-forming material in lipophilic-based controlled-release formulations;
- It may also be used as a coating aid in controlled-release formulations.
- Hydrogenated vegetable oil type I is used as a viscosity modifier in the preparation of oil-based liquid and semisolid formulations
- In the preparation of suppositories, to reduce the sedimentation of suspended components and to improve the solidification process

In the formulation of liquid and semisolid fills for hard gelatin capsules.

4.4.5. Stearic Acid:

Nonproprietary Names

BP : Stearic acid

JP : Stearic acid

PhEur : Acidum stearicum

USPNF : Stearic acid

Synonyms

Cetylacetic acid; Crodacid; E570; Edenor; Emersol; Hystrene; Industrene; Kortacid 1895; Pearl Steric; Pristerene; stereophonic acid; Tegostearic.

Chemical Name and CAS Registry Number

Octadecanoic acid [57-11-4]

Empirical Formula and Molecular Weight

$C_{18}H_{36}O_2$ 284.47 (for pure material)

The USPNF 23 describe stearic acid as a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$). In the USPNF 23, the content of stearic acid is not less than 40.0% and the sum of the two acids is not less than 90.0%. The USPNF 23 also contains a monograph for purified stearic acid; see Section 17. The PhEur 2005 contains a single monograph for stearic acid but defines stearic acid 50, stearic acid 70, and stearic acid 95 as containing specific amounts of stearic acid ($C_{18}H_{36}O_2$);

Functional Category: Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant; although it may also be used as a binder or in combination with shellac as a tablet coating. It has also been suggested that stearic acid may be used as a sustained-release drug carrier. In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation of creams. The partially neutralized stearic acid forms a creamy base when mixed with 5–15 times its own weight of aqueous liquid; the appearance and plasticity of the cream being determined by the proportion of alkali used. Stearic acid is used as the hardening agent in glycerin suppositories. Stearic acid is also widely used in cosmetics and food products.

Description

Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor and taste suggesting tallow.

Stability and Storage Conditions

Stearic acid is a stable material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Stearic acid is incompatible with most metal hydroxides and may be incompatible with oxidizing agents. Insoluble stearates are formed with many metals; ointment bases made with

stearic acid may show evidence of drying out or lumpiness due to such a reaction when compounded with zinc or calcium salts. A number of differential scanning calorimetry studies have investigated the compatibility of stearic acid with drugs. Although such laboratory studies have suggested incompatibilities, e.g. with naproxen, they may not necessarily be applicable to formulated products. Stearic acid has been reported to cause pitting in the film coating of tablets coated using an aqueous film-coating technique; the pitting was found to be a function of the melting point of the stearic acid.

Safety

Stearic acid is widely used in oral and topical pharmaceutical formulations; it is also used in cosmetics and food products. Stearic acid is generally regarded as a nontoxic and nonirritant material. However, consumption of excessive amounts may be harmful.

LD50 (mouse, IV) : 23 mg/kg

LD50 (rat, IV) : 21.5 mg/kg

4.4.6 Polyethylene Glycol

Nonproprietary Names

BP : Macrogols

JP : Macrogol 400
Macrogol 1500
Macrogol 4000
Macrogol 6000
Macrogol 20000

Ph. Eur : Macrogols

USPNF : Polyethylene glycol

Synonyms

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

Chemical Name and CAS Registry Number

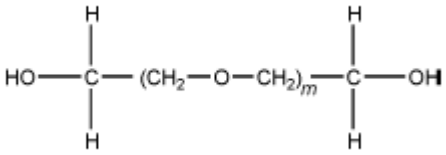
a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

Empirical Formula and Molecular Weight

$HOCH_2(CH_2OCH_2)mCH_2OH$ where m represents the average number of oxyethylene groups.

Alternatively, the general formula

Structural Formula



Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases. Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol. Mixtures of polyethylene glycols can be used as suppository bases, for which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats. Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell. In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms. In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules. However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations, a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75^{0}C. The mass becomes paste like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required. Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol. Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps. In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers. The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of overheating. Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents. It has also been used in insulin-loaded microparticles for the oral delivery of insulin; it has been used in inhalation preparations to improve aerosolization; polyethylene glycol nanoparticles have been used to improve the oral bioavailability of cyclosporine; it has been used in selfassembled polymeric nanoparticles as a

drug carrier; and copolymer networks of polyethylene glycol grafted with poly(methacrylic acid) have been used as bioadhesive controlled drug delivery formulations.

4.4.7. Poly Vinyl Pyrolidone:

Synonyms:

Povidone, polyvidone

Chemical name:

1-Vinyl-2-pyrrolidinon-Polymere

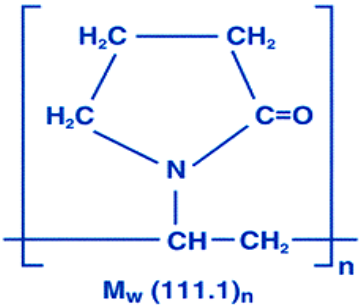
Functional category:

Binder For pharmaceutical products, viscosity increasing agent,

Description:

Fine white amorphous powder which precipitates readily

Chemical structure:



Molecular mass:

2.500 - 2.5000.000 $g \cdot mol^{-1}$

Viscosity: 42000cps

Grades:

Depending up on the cross linking agent, cross linked PVP is divided into three grades

Table 3: Grades of PVP

Cross linked PVP	0.45%	0.20%	1.0%
Viscosity	42000cps	21000cps	6200cps
Nitrogen%	12.3	12.3	12.3
Water%	1.17	0.85	0.44

Melting point: 110-180^{0}C

Density: 1.2g/cm^3

Applications:

- PVP is used as a binder in many pharmaceutical tablets
- PVP is also used in personal care products, such as shampoos and toothpastes, in paints, and adhesives. It has also been used in contact lens solutions and in hair sprays and hair gels
- PVP is a stabilizer and has E number **E1201**. PVPP is **E1202**. It is also used in the wine industry as a fining agent for white wine.

4.4.8. Magnesium Stearate:

Nonproprietary Names:

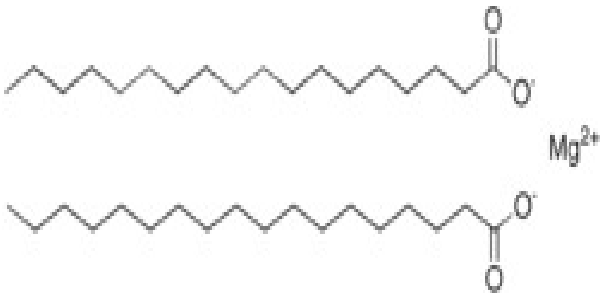
BP : Magnesium stearate

JP : Magnesium stearate

PhEur : Magnesii stearas

USP : Magnesium stearate

Structure:



Synonyms:

Magnesium octadecanoate; stearic acid magnesium salt; octadecanoic acid, magnesium salt.

Chemical Name

Octadecanoic acid magnesium salt

Empirical Formula :

$C_{36}H_{70}MgO_4$

Structural Formula:

$[CH_3(CH_2)_{16}COO]_2Mg$

Functional Category:

Tablet and capsule lubricant.

Description:

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of Stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Typical Properties:

Crystalline forms: high purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk): 0.159 g/cm^3

Density (tapped): 0.286 g/cm^3

Flash point: 250°C

Flow ability: poorly flowing, cohesive powder.

Melting range: 117-150°C (commercial samples)

126-130°C (high purity magnesium stearate).

Stability and Storage Conditions:

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration.

Applications :

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25-5.0%. It is also used in barrier creams.

4.4.9. ISO PROPYL ALCOHOL:

Non proprietary Name

USP- Isopropyl alcohol

BP- Isopropyl alcohol

Functional Categories

USP-Solvent

Other-Local disinfectant.

Synonyms

Isopropanol, alcohol Isopropylieum, petrohol, dimethylcarbinol, 2-propan-2-ol, secondary propyl alcohol.

Chemical Name

2-propranol.

Emperical formula

C_3H_8O

Molecular formula

60.1g/ml.

Description

Transparent, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone and a slightly bitter taste.

Melting point

$88.5^{0}C$

Stability and storage condition

Store in a tight container remote from heat and protected form light.

Incompatibilities

Oxidizing agents like hydrogen peroxide and nitric acid decompose isopropyl alcohlol. It may be slated out form aqueous mixtures by the addition of sodium chloride, sodium sulfate and other salts or by sodium hydroxide.

Applications in Pharmaceutical Formulation

Isopropyl alcohol can be used for pre-operative and skin cleaning and as a disinfectant.

Other uses ingredient in lotions but as marked degreasing properties may limit its usefulness in preparations used repeatedly.

5. METHODOLOGY

5.1 Innovator product evaluation

The project was initiated with innovator product characterization. Procured innovator product FLOMAXTRA XL was evaluated for physical and chemical parameters.

5.2 Preformulation Studies

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first in the rational development of dosage forms.

The use of Preformulation parameters maximizes the chances in formulating an acceptable, safe efficacious and stable product.

Physical properties

For a drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug.

Determination of bulk density and tapped density

Bulk density is the ratio of the weight of a powder to the volume it occupies. It is expressed as gm/ml. Volume occupied by powder includes volume of the solid portion of the particle and voids between the particles. Bulk density is important in determining the size of the containers needed for handling and processing

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density, and tapped density were calculated using the following formulas:

$$\textbf{Bulk density} = W / V_o$$

$$\textbf{Tapped density} = W / V_f$$

Where,

W = weight of the powder

V_0 = initial volume

V_f = final volume

a. Flow Properties:

Irregular flow of powders from the hopper produces tablets with non uniform weights. As respects content uniformity and dose precision cannot be achieved in a production of tablets & capsules. Flow properties depend on particle size shape porosity and density of bulk powder. The flow characteristics are measured by angle of repose

b. Angle of Repose:

Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$$\tan \theta = \frac{h}{r}$$

Where, h = height of pile; r = radius of the base of pile; θ = angle of repose.

Lower the angle of repose better the flow property though the irregular surface of the particles gives higher angle of repose. It can be decreased by the addition of lubricants, of low concentration decreases the angle of repose at high concentration; enhances angle of repose.

Fines (passed through mesh 100) increases angle of repose.

Method: A glass funnel is held in place with a clamp over a glass plate, powder was poured in funnel keeping the orifice blocked. When powder is emptied from funnel, angle of heap to horizontal plane is measured with protector. Height of pile (h) and radius of the base (r) is measured with ruler. Thus the angle of repose is measured.

Table 4: Relationship between angle of repose (θ) & powder flow

S. No	Angle of repose (θ) degrees	Flow
1	< 25	Excellent
2	25-30	Good
3	30-40	Passable
4	40 & above	Very poor

c. Compressibility Index:

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size of a powder.

Table 5: Compressibility Index Range

S. No.	% compressibility index	Flow ability
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair-passable
4	23-35	Poor
5	33-38	Very poor
6	<40	Very Very Poor

Compressibility index were calculated using the formula:

Compressibility index= T.D-B.D/T.Dx100

d. Hausner Ratio:

It indicates the flow property of the powder and measured by the ratio of tapped density to bulk density

Table 6:Hausner Ratio

Hausner ratio	Properties
0 -1.2	Free flowing
1.2 -1.6	Cohesive powder

Hausner ratio=T.D\B.D

Where, T.D= Tapped density, B.D= Bulk density

e. Drug-Excipient Compatibility Study:

For drug-excipient compatibility study, selected excipients are as below

Table 7: List of excipients

S.No	Excipient	Functional category
1	Di-TAB	Diluent
2	Lubritab	Polymer
3	Eudragit RLPO	Polymer
4	Eudragit L100	Polymer
5	Poly ethylene glycol 20000	Polymer
6	Stearic Acid	Polymer
7	Povidone	Binder
8.	Magnesium stearate	Lubricant

The compatibility study was carried out to study the possible interactions between the active pharmaceutical ingredients and several inactive ingredients used in the formulations and the ratio of Drug: Excipients was selected on the basis of the level of excipients will be used in the formulation trials in their highest concentration. Physical mixtures were kept in 40ºC / 75% RH and 60ºC in a 2ml glass vial in exposed condition for 1 month.

Samples were withdrawn at 2^{nd} and 4^{th} week interval and observed for any change in physical appearance.

f. Fourier Transform Infrared Spectroscopy (FTIR)

Potassium Bromide (KBr) pellet method was employed. KBr was dried in oven at 45 ˚C before analysis. The sample was triturated with KBr and pellet was prepared by setting

the pressure to 100 kg/cm^2 for 2 minutes. The obtained pellet was analyzed in FTIR 8400 S, Shimadzu, Japan. KBr background was obtained initially before analysis of test samples. Test samples were analyzed following the same method.

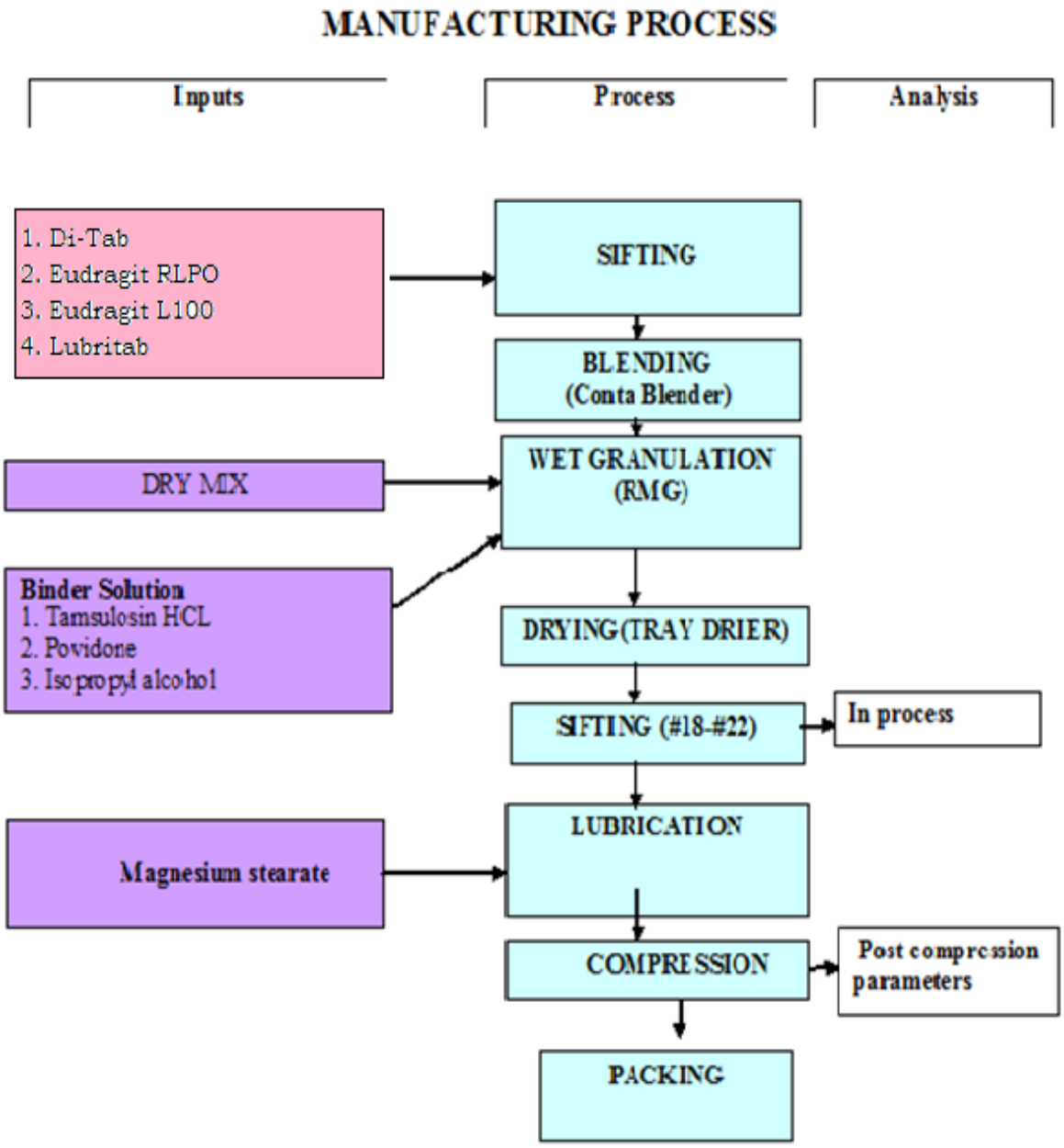


Fig. 3: Manufacturing Process

5.3 FORMULATION DEVELOPMENT:

a. Sifting

Accurately weigh required quantity of dry mix materials and sift through ASTM 30 mesh.

b. Dry mixing

Dry mix the materials geometrically in RMG for 5 minutes.

c. Binder solution

Dissolve Tamsulosin Hydrochloride and Povidone in required quantity of Isopropyl alcohol with the aid of Mechanical stirrer.

d. Granulation

To the dry mix add the binder solution using the impeller speed of 150 rpm and the chopper at 1500 rpm for 3 minutes in RMG.

e. Drying

Dry the granulated mass at inlet temperature of 45^{o}C ±5^{o}C in tray drier to get LOD in the range of 0.5 –1.0%w/w at 50^{o}C using moisture analyzer

f. Size reduction

Reduce the size of the dried granules in Multi mill at medium speed and knife forward direction using 1.5mm Mesh.

g. Lubrication

Lubricate the sized granules with magnesium stearate for 5 minutes.

h. Compression

Compress the lubricated blend with the following specifications

Table 8: Compression specifications

Description	White biconvex shaped tablets
Tooling	8.99 ×6.51 Oval shaped
Hardness	60-75N
Thickness	3.40-4.20mm
Friability	NMT 1% w/w
Uniformity of Weight	± 5% of average weight

Table 9: FORMULATION TRIALS

Ingredients	mg/tablet									
	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Trial 8	Trial 9	Trial 10
Dry Mixing										
Di Tab	154.6	184.6	194.6	189.6	179.6	184.6	184.6	159.6	172.8	163.9
Eudragit RSPO	50	30	25	30	30	35	40	40	40	0
Lubritab	10	10	10	10	10	10	10	10	10	10
Eudragit RLPO	0	0	0	0	20	10	5	0	0	40
Eudragit L100	0	0	0	0	0	0	0	0	0	25
PEG 20000	0	0	0	0	0	0	0	30	15	0
Binder Solution										
Povidone	3	3	3	3	3	3	3	3	3	3
Tamsulosin Hydrochloride	0.404	0.404	0.404	0.404	0.404	0.404	0.404	0.404	0.404	0.404
Stearic acid	0	0	0	0	0	0	0	0	1.8	0
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Lubrication										
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1.2
Eudragit RSPO	0	0	0	0	0	0	0	0	0	0
Eudragit RLPO	25	15	10	10	0	0	0	0	0	0
Film Coating										
Opadry white	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Weight of tablet	250.0	250.0	250.0	250.0	250.0	250.0	250.0	250.0	250.0	250.0

5.4 Evaluation of Tablets:

The following parameters were performed

a. Size and Shape:

The size and shape of tablets can be dimensionally described, monitored, and control. The compressed tablet's shape and dimensions are determined by the tooling during compression process.

b. Weight Variation Test

The test ensures that all the tablets in each batch are of same potency, within reasonable limits. According to the USP weight variation test, 20 tablets were weighed individually and collectively. Average weight per tablet was calculated from the collective weight. Then the weights of the individual tablets were compared with the average weight to determine weight variation. The specification of weight variation limits as per USP is given in following Table.

Table.10: Specifications for weight variation of tablets as per USP

Average weight of tablet	% Deviation
130 mg or less	± 10
More than 130 mg but less than 324 mg	± 7.5
324 mg or more	± 5

The thickness of a tablet was the only dimensional variable related to the process.10 tablets were measured for their thickness and diameter with Vernier calipers. Average thickness and diameter were calculated.

d. Hardness:

Tablet hardness has been defined as the force required breaking a tablet in a diametric compression test. To perform this test, there is a Tablet Hardness is present which is manufactured by ERWEKA. The tablet is placed between two anvils, force is applied to the anvils and the crushing strength that just causes the tablet to break is recorded. Hardness is thus sometimes termed as the tablet crushing strength.

e. Friability:

The friability of tablets is determined by ERWEKA. 20 tablets were taken and weighed. After weighing the tablets were placed in the friabilator and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for 4 minutes dropping the tablets from a distance of six inches with each revolution. After operation the tablets were dedusted and reweighed. Friability is determined by

$$F=100\ (1-W_0/W_t)$$

Where, W_0 = Wt of tablets before friability test.

Wt = Wt of tablets after friability test.

g. Assay by HPLC

Ten tablets were finely powdered; quantities of the powder equivalent to 0.4 mg of Tamsulosin Hydrochloride were accurately weighed, transferred to a 50 ml volumetric flask containing 20 ml of methanol and allowed to stand for 30min with intermittent sonication to ensure complete solubility of the drug. The mixture was made up to volume with methanol. Filter the solution through 0.45µ nylon membrane filter. The solution was suitably diluted and the absorption was determined by UV-detector in HPLC at λmax 225nm. The drug concentration was calculated from the below formula.

$$\frac{At}{As} \times \frac{Ws}{100} \times \frac{2}{50} \times \frac{2}{50} \times \frac{500}{1} \times \frac{P}{Lable\ claim\ in\ mg}$$

Where,

At=Absorbance of sample

AS=absorbance of standard

Ws= weight of working standard in drug in mg

Wt=weight of sample in mg

P= Potency of Tamsulosin Hydrochloride working standard.

g. Uniformity of dosage units

Uniformity of dosage units is defined as the degree of uniformity in the amount of drug substance in each unit. As per USP uniformity of dose units was performed Table for Application of content uniformity (CU) and weight variation test (WV) for tablet dosage form USP was presented below.

Table 11: Uniformity of dosage units

Dosage form	Type	Subtype Dose and Ratio of drug substance		
TABLETS			≥ 25 mg & ≥25%	< 25mg or < 25%
	Uncoated	----	WV	CU
	Coated	Film coated	WV	CU
		Others	CU	CU

Uniformity of dosage units performed by content uniformity method because percentage of drug is less than 25mg

h.Dissolution

Method of analysis for Tamsulosin Hydrochloride tablets 0.4mg

Methodology:

The Dissolution method adopted for analyzing the tablets was as per the current USP Monograph for Tamsulosin Hydrochloride Capsules.

Invitro dissolution Studies:

Preparation of pH 2.0 solution:

Dissolve 8.7 ml of perchloric acid in 1900 ml of water. Adjust with 2.0N Sodium hydroxide solution to a pH of 2.0, and add sufficient water to make 2000 ml. Filter the solution through 0.45µ membrane filter.

Preparation of Mobile Phase:

Prepare a filtered and degassed mixture of pH 2.0 solution and Acetonitrile in the ratio 1400:600.

Chromatographic Conditions:

Column	: Inertsil ODS 3V, 150 x 4.6 mm, 5 µm.
Flow rate	: 1.5ml/min.
Detector	: UV,225 nm
Column temperature	: 40°C
Injection volume	: 100µl
Run time	: 15 minutes

1. Acid stage:

Dissolution Parameters:

Medium	: 500 ml of Acid stage medium
Apparatus	: USP Type-II (Paddle)
RPM	: 100
Temperature	: 37 ± 0.5°C
Time intervals	: 2^{nd} hr

Preparation of acid stage medium:

Dissolve 2.0 g of sodium chloride in 5.7 ml of hydrochloric acid, and add water to make up to 1000 ml.

Preparation of Polysorbate 80 solution:

Take 3.0g of Polysorbate 80 into a 200 ml of volumetric flask, add 150 ml of water and sonicate to dissolve and dilute to volume with water.

Preparation of diluent:

Prepare a mixture of water and acetonitrile in the ratio 70:30.

Preparation of Standard Solution: (Acid stage standard)

Weight accurately about 50 mg of Tamsulosin Hydrochloride working reference standard transfer 100 ml volumetric flask add 70 ml of diluent, sonicate to dissolve the content and make up to the mark with diluent. Transfer 2 ml of above solution into a 50 ml volumetric flask and make up to the mark with acid stage medium.

Transfer 2 ml of above solution into a 50 ml volumetric flask and make up to the mark with acid stage medium. Filter the solution through 0.45µ membrane filter.

Procedure:

Set the parameters of dissolution apparatus as mentioned above, Transfer the tablets in to an each of the six dissolution jars, run the apparatus and immediately add 1 ml of polysorbate 80 solutions into each dissolution jar. After completion of 2 hours withdrawn 15 ml of the sample solution from each dissolution jars. Filter the solution through 0.45µ membrane filter.

Separately inject 100µL of dissolution media, five replicate injections of standard solution and single injection of Sample solutions into the chromatograph, record the chromatograms and measure the peak responses.

System Suitability:

Chromatograph the standard preparation and sample preparation record the peak responses. The relative standard deviation for five replicate standard solution injections is not more than 2.0%.

The tailing factor of peak should be not more than 2.0 and the theoretical plates of peak should be not less than 2000.

Calculation:

% Labeled amount of Tamsulosin Hydrochloride dissolved at the end of the 2nd hr ($D_{2\ acid\ stage}$) in Acid stage medium**.**

$$\frac{A_{T1}}{A_{S1}} \times \frac{W_{S1}}{100} \times \frac{2}{50} \times \frac{2}{50} \times \frac{500}{1} \times \frac{P}{\text{Label claim in mg}}$$

Where,

A_{T1} = The area of the Tamsulosin Hydrochloride peak in sample solution.

As_1 = The Average area of the Tamsulosin Hydrochloride peak in standard solution.

Ws_1 = Weight of the Tamsulosin Hydrochloride working standard taken in mg

P = Potency of the Tamsulosin Hydrochloride working standard used (on as is basis).

2. Buffer stage:

Dissolution Parameters:

Medium : 500 ml of pH 7.2 Phosphate Buffer

Apparatus : USP Type-II (Paddle)

RPM : 100

Temperature : 37 ± 0.5°C

Time intervals: 4, 6, 8, 12, 16, 20, 24 and 30 hr

Preparation of 0.5N Hydrochloric Acid Solution:

Mix 41.5 ml of Hydrochloric Acid (35%) in 1000 ml of water.

Preparation of pH:7.2 Phosphate Buffer:

Dissolve 6.8 gms of Potassium hydrogen orthophosphate and 0.8 gms of sodium hydroxide in 1000 ml of water and adjust the pH 7.2±0.05 with 2N Sodium Hydroxide Solution.

Preparation of Standard Solution: (Buffer stage standard)

Weight accurately about 50 mg of Tamsulosin Hydrochloride working reference standard transfer 100 ml volumetric flask add 70 ml of diluent, sonicate to dissolve the content and make up to the mark with diluent. Transfer 2 ml of above solution into a 50 ml volumetric flask and make up to the mark with buffer stage medium.

Transfer 2 ml of above solution into a 50 ml volumetric flask and make up to the mark with buffer stage medium. Filter the solution through 0.45µ membrane filter.

Transfer the 10 ml of above solution into a test tube containing 1.0 ml of 0.5N Hydrochloric acid and mix well. Filter the solution through 0.45 µ nylon filters.

Preparation of Sample solution:

After completion of the dissolution in acid stage medium, drain the solution from each jar. Add about 500 ml of pH 7.2 Phosphate buffer previously maintained at 37 ± 0.5°C into each dissolution jar and run the apparatus. At the end of the specified time interval withdrawn 15ml of the sample solution from each dissolution jar and replace the equal volume of dissolution medium previously maintained at 37 ± 0.5°C.

Transfer the 10 ml of above solution into a test tube containing 1.0 ml of 0.5N Hydrochloric acid and mix well. Filter the solution through 0.45 µ nylon filters.

Procedure:

Separately inject 100µL of dissolution media, Five replicate injections of standard solution and single injection of Sample solutions into the chromatograph, record the chromatograms and measure the peak responses.

System Suitability:

Chromatograph the standard preparation and sample preparation record the peak responses. The relative standard deviation for Five replicate standard solution injections is not more than 2.0%.

The tailing factor of peak should be not more than 2.0 and the theoretical plates of peak should be not less than 2000.

Calculation:

% Labeled amount of Tamsulosin Hydrochloride dissolved at respective time intervals (D_n)

$$\frac{A_{T2}}{A_{S1}} \times \frac{W_{S1}}{100} \times \frac{2}{50} \times \frac{2}{50} \times \frac{500}{W_T} \times P \times 100$$

Label claim in mg

Where,

A_{T2} = The area of the Tamsulosin Hydrochloride peak in sample solution.(Buffer stage sample)

As_1 = The Average area of the Tamsulosin Hydrochloride peak in standard solution.

Ws_1 = Weight of the Tamsulosin Hydrochloride working standard taken in mg

W_T = Weight of the Tamsulosin Hydrochloride pellets taken in mg

P = Potency of the Tamsulosin Hydrochloride working standard used (on as is basis).

RESULTS AND DISCUSSION

6. RESULTS AND DISCUSSION

6.1 Standard Graph of Tamsulosin Hydrochloride

Table 12: Construction of Standard Graph of Tamsulosin Hydrochloride

CONCENTRATION(µg/ml)	PEAK AREA
20	36782
40	73160
80	141534
120	220216
160	293103
200	376210
240	440213

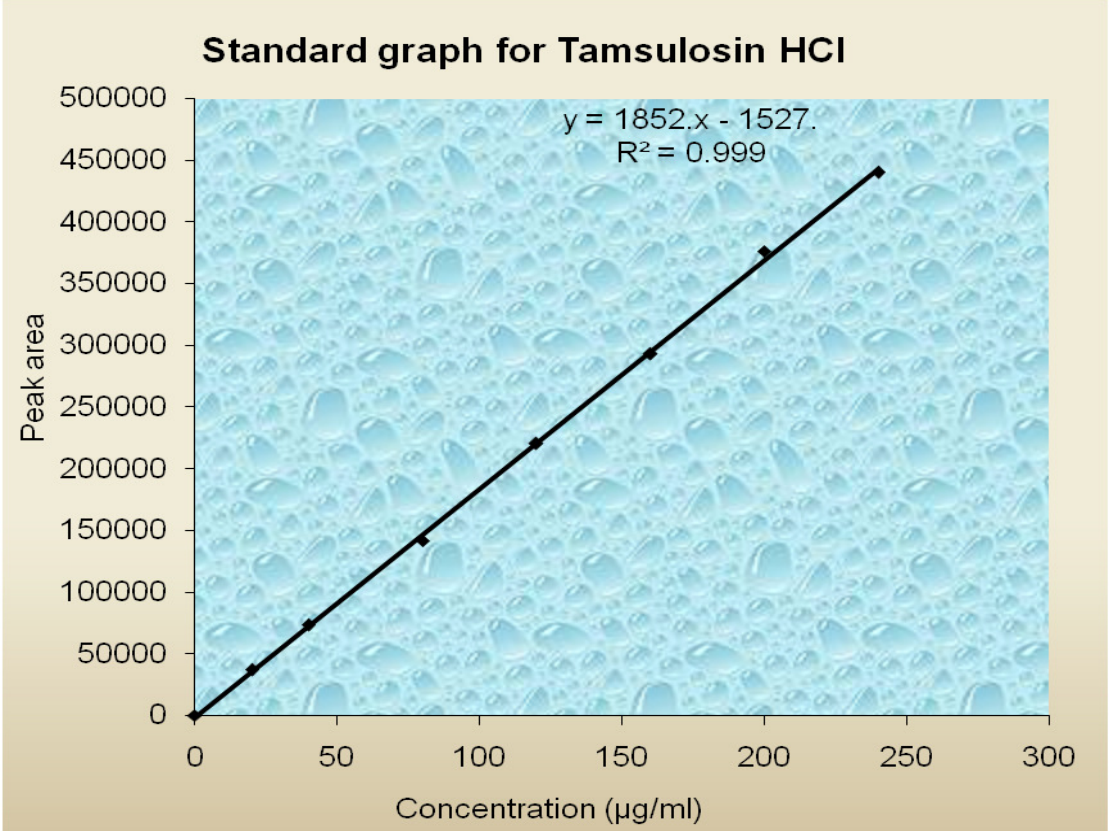


Fig. 4: Standard Graph of Tamsulosin Hydrochloride

6.2 Innovator Product Evaluation

Flomaxtra XL is a successful brand tablet formulation of Tamsulosin Hydrochloride in European market, manufactured by Astellas pharma ltd was selected as the reference product to the present work. The physico-chemical parameters with respect to Flomaxtra XL like thickness, hardness, dissolution rate were evaluated.

Innovator product evaluation

Brand name : FLOMAXTRA XL

Label Claim : Each film coated tablet contains tamsulosin hydrochloride 0.4mg

Mfg. by : Astellas pharma ltd, Europe

Physical Parameters:

Description:

Round, bi-convex, yellow, film-coated tablets debossed with the code '04'

1. Average weight : 250 mg
2. Dimensions : 9.00 mm
3. Thickness : 4.60 - 4.62 mm
4. Hardness : 100 -110N.

Table 13: Dissolution profile for Flomaxtra XL

Time (hrs)	% Tamsulosin Hydrochloride released
2	17.2
4	29.5
6	40.9
8	51.8
12	65.1
16	75.2
20	84
24	90.2
30	91.9

The dissolution profile of innovator product was considered as the standard to compare the dissolution profiles of the present formulations.

6.3 Preformulation studies:

Preformulation Characteristics of final blend of all Formulation were given below**:**

Table 14: Preformulation study of lubricated Blend

Trial	Bulk Density g/cm³	Tapped Density g/cm³	Hausner Ratio	Compressibility Index (%) I=1-V0/V	Angle of Repose (º)
1	0.56	0.65	1.16	13.84	27.5
2	0.54	0.63	1.16	14.28	26.8
3	0.53	0.62	1.15	14.51	26.5
4	0.52	0.60	1.15	13.5	27.8
5	0.53	0.61	1.15	13.1	27.6
6	0.58	0.63	1.14	14.6	26.9
7	0.55	0.66	1.16	14.32	26.6
8	0.51	0.60	1.15	13.55	27.4
9	0.59	0.69	1.14	13.67	27.8
10	0.55	0.62	1.15	14.1	27.6

The above results indicate that all the final lubricated blends have good flow property and compressibility.

6.4. Evaluation of Tamsulosin Hydrochloride Sustained Release tablets

a. Weight variation:

20 intact tablets are selected randomly, individual weights and average weight of the tablets is determined. The result of all the batches were found to be satisfactory and meeting the acceptance criteria.

b. Assay by HPLC

The assay results of Tamsulosin Hydrochloride sustained release tablets are given below. The assay values are between 90% to 110%. All the tablets are within USP specification limit.

Table 15.Percentage Drug Content

S No	Formulation	%Drug Content
1	Trial 1	96.5 ± 0.2
2	Trial 2	97.7 ± 0.3
3	Trial 3	98.1 ± 0.2
4	Trial 4	95.5 ± 0.4
5	Trial 5	97.3 ± 0.3
6	Trial 6	95.7 ± 0.4
7	Trial 7	98.2 ± 0.2
8	Trial 8	100.1± 0.3
9	Trial 9	99.8± 0.2
10	Trial 10	100.2± 0.3

C. Uniformity of dosage units

10 intact tablets are selected randomly, weighed and analyzed for drug individual tablets drug content. The result of all the batches were found to be satisfactory and meeting the acceptance criteria as per USP. All the batches L1 values were less than 15.

6.5 COMPATABILITY STUDIES:

Table. No 16: Compatibility study of drug and excipients:

S. No.	Drug and Excipients	Initial Physical Description	25°C / 60% RH & 40°C / 75% RH (Closed)		
			1st Week	2nd Week	4th Week
1	Tamsulosin Hydrochloride	White crystalline powder	*	*	*
2	Tamsulosin Hydrochloride + DITAB	Off-white powder	*	*	*
3	Tamsulosin Hydrochloride+ Eudragit RSPO	white powder	*	*	*
4	Tamsulosin Hydrochloride+Eudragit L100	White powder	*	*	*
5	Tamsulosin Hydrochloride+ Eudragit RLPO	White powder	*	*	*
6	Tamsulosin Hydrochloride + Lubritab	white powder contain crystalline material	*	*	*
7	Tamsulosin Hydrochloride+ Povidone	Off-white powder	*	*	*
8	Tamsulosin Hydrochloride + Isopropyl alcohol	Off-white thick mass	*	*	*
9	Tamsulosin Hydrochloride + Purified Water	Off-white thick mass.	*	*	*

Note: Star mark (*) indicates that there is no interaction between drug and excipients at 25°C/60% RH, 40°C/75% RH.

OBSERVATION: The drug excipient compatibility study was performed based on ICH guidelines in various stress conditions like 25°C/60%RH and 40°/75%RH, for a period of 1 month, there was no interaction found during the study period.

Fourier Transform Infrared Spectroscopy (FTIR):

The FTIR was carried out between drug and the polymers physical mixtures. The FTIR was carried out on the Tamsulosin Hydrochloride and Lubritab, Eudragit L100, Eudragit RLPO. The results obtained by the physical mixtures are compared with the standard graph and the results showed that there occurs no incompatibility with the drug and the excipients. The study was carried out for final confirmed formulation and the results are being compared with the standard drug.

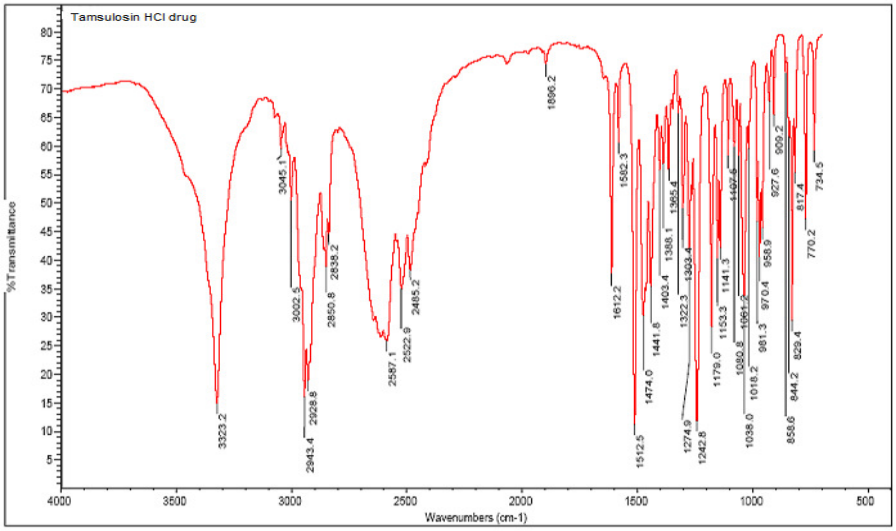


Fig. 5: IR Report of Pure Tamsulosin Hydrochloride drug

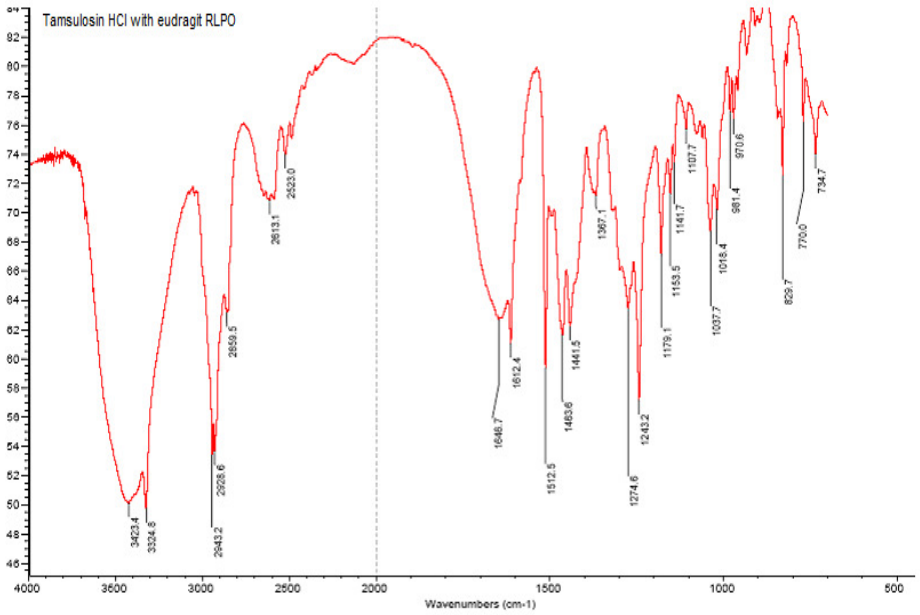


Fig.6: IR Report of Physical Mixture of Tamsulosin Hydrochloride with Eudragit RLPO

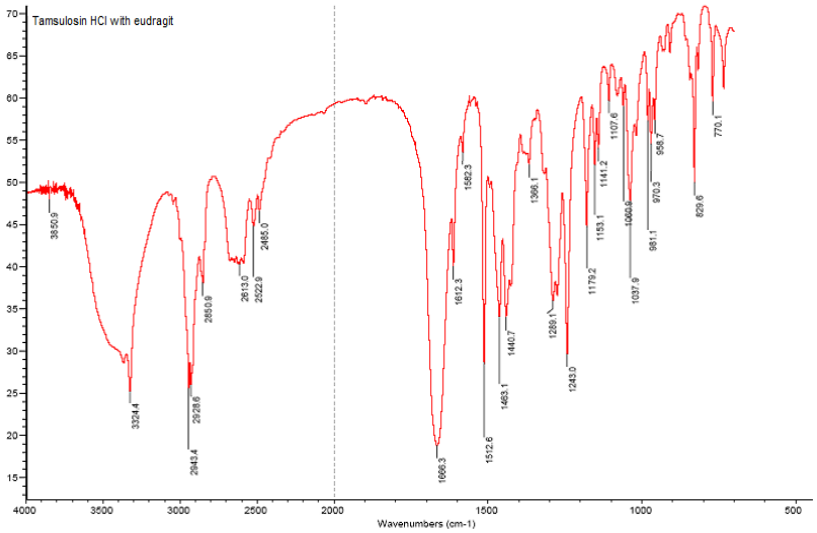


Fig.7: IR Report Of Physical Mixture Of Tamsulosin Hydrochloride with EudragitRSPO

6.6 Formulation development

The originator product "Flomaxtra XL" formula was protected by the patents and use of different polymeric matrices in connection with working formula.

As "Flomaxtra XL" was selected as the reference product and the efforts were continued towards development with different polymers as a Primary choice that need to evaluate. Polymer controls drug release followed by dissolution, initiates the solubility process and its selection reflects the behavior of the drug in vitro and in vivo.

The most widely used polymers like Eudragit RSPO, Eudragit RLPO, Eudragit L100, Lubritab were subjected to the present formulation development of Tamsulosin Hydrochloride and the best opted polymer was identified on trial and error basis and with the scope of Non-infringement.

Different trials were attempted by incorporating various polymers like Eudragit RSPO, Eudragit RLPO, Eudragit L100 and Lubritab. Dissolution tests were carried for the prepared test formulations (trail 1 to trail 10) with the parameters as per the current version of USP Monograph for Tamsulosin Hydrochloride Capsules.

The results of dissolution studies of the formulation were compared to the innovator product dissolution profile.

- From trial 1 to 4 Eudragit RSPO was tried at different concentration with the combination of Lubritab intra granularly with extra granular RLPO. The results of all the 4 trails suggested that in case of control in drug release at the initial hour resulted in incomplete dissolution and whenever the drug was completely released the drug release was faster at the initial stage and the results of the trials were not matching to the reference Originator.
- In trial 5 to 7, RLPO was also used along with above matrix as intra granular at different ratios without any extra granular addition and the drug release was incomplete in these trials and drug release was not comparable to the Originator.
- In trial 8 & 9, in place of RLPO, PEG 20000 was used along with RSPO and Lubritab matrix as intra granular at different ratios without any extra granular addition of any

material and the drug release in case of control in at the initial hour resulted in incomplete dissolution and where the drug was completely released the drug release was faster at the initial stage and the results of the trials were not matching to the reference originator.

- In trial 10, in place of RLPO/ PEG 20000, L 100 was used and in place of RSPO, RLPO used along with Lubritab intra granular without any extra granular addition of any material. The result of this batch was comparable to the originator profile matching In-Vitro similarity factor.
- Hence from the all the above experiment trial 10 was selected as an ideal formulation.

Table no 17: Dissolution data for 10 trials:

Time in hrs	T1	T 2	T 3	T 4	T 5	T 6	T 7	T 8	T 9	T 10
2	27.7 ±0. 06	31.2 ±0.02	40.9 ±0.04	32.6 ±0.11	24.6 ±0.08	32.2 ±0.09	27.9 ±0.09	28.9 ±0.09	40.6 ±0.11	21.2 ±0.06
4	45.2 ±0.09	46.2 ±0.13	51.3 ±0.08	50 ±0.09	36.9 ±0.03	46.1 ±0.12	41 ±0.04	41.5 ±0.07	57.9 ±0.14	35.4 ±0.09
6	51.9 ±0.03	53.1 ±0.12	58.1 ±0.01	58.6 ±0.07	42.8 ±0.05	51.8 ±0.03	45.5 ±0.05	47.1± 0.09	65.2 ±0.09	49.2 ±0.06
8	57.9 ±0.11	58.7 ±0.14	64.6 ±0.09	63.2 ±0.05	46.8 ±0.04	58.2 ±0.08	50.4 ±0.02	51.6± 0.13	69.9 ±0.07	55.4 ±0.04
12	64.6 ±0.09	64.6 ±0.02	74.6 ±0.14	73.1 ±0.1	51.3 ±0.14	64 ±0.09	57.1 ±0.01	56.7 ±0.14	78.9 ±0.06	65.1 ±0.08
16	69.7 ±0.04	71.6 ±0.1	82.3 ±0.13	78.5 ±0.03	56.4 ±0.12	69.3 ±0.14	63.7 ±0.08	63.6 ±0.12	83.8 ±0.14	73.5 ±0.06
20	74 ±0.06	73.9 ±0.12	90.6 ±0.06	81.3 ±0.08	61.0 ±0.1	74.1 ±0.5	68.4 ±0.03	66.1 ±0.08	87.0 ±0.05	82.7 ±0.04
24	77.7 ±0.11	79.9 ±0.04	101.2 ±0.13	86.3 ±0.11	65.5± 0.3	78.4 ±0.1	74.8 ±0.02	71.2 ±0.2	88.1 ±0.06	90.2 ±0.08
30	82.6 ±0.07	84.5 ±0.03	**---**	88.3 ±0.11	65.8 ±0.2	81.4 ±0.4	79.1 ±0.01	76.7 0.14	89.9 ±0.05	100.1 ±0.09

(Time in hrs on X-axis Vs Percent drug release on Y-axis)

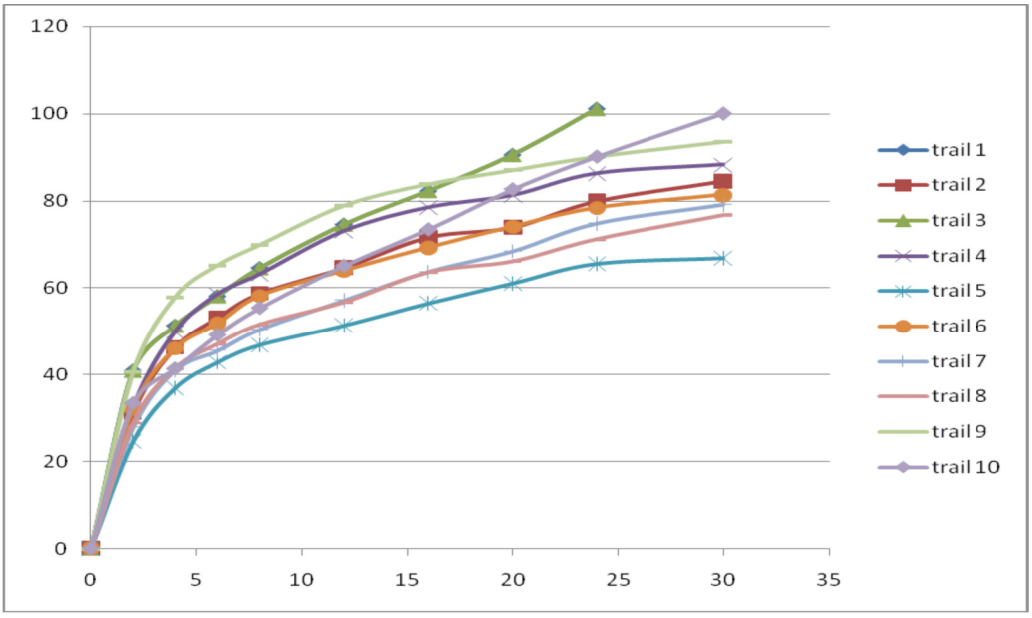

120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
trail 1
trail 2
trail 3
trail 4
trail 5
trail 6
trail 7
trail 8
trail 9
trail 10

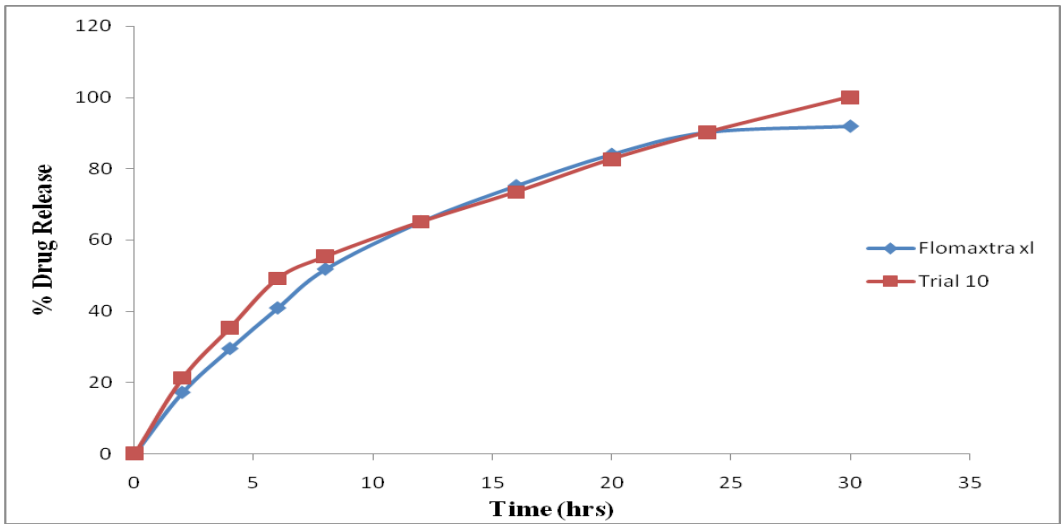
Table.No:18 Dissolution Result of Trial 10

pH	FLOMAXTRA XL	TRIAL 10
pH 1.2 buffer, 500ml basket,100rpm		
2hrs	17.2	21.2
pH 7.2 buffer, 500ml basket,100rpm		
4	29.5	35.4
6	40.9	49.2
8	51.8	55.4
12	65.1	65.1
16	75.2	73.5
20	84	82.7
24	90.2	90.2
30	91.9	100.1
f1		6.05
f2		65.62

f1: Dissimilarity factor

f2: Similarity factor

Fig 9: comparison of Flomaxtra XL with trial 10



6.7 Stability study:

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH CS L6AS and IS6B.

Storage conditions

Stability samples are stored at

Accelerated : 40±2°C/75±5% RH

Intermediate: 30±2°C/65±5% RH

Long term : 25±2°C/60±5% RH

Testing Intervals for

Accelerated: Initial, 1, 2, 3 & 6 months

Long term: Initial, 3, 6, 9, 12, 18, 24 & 36 months.

Intermediate: Initial, 3, 6, 9 & 12 months.

The formula of F10 was optimized and selected for evaluation studies. Further stability study was done for F10

Table No 19: Dissolution profile for trial 10 after stability studies(40±2°C/75±5% RH) *(Time in hrs on X-axis Vs Percent drug release on Y-axis)*

Time	Flomaxtra	Trail 10
pH 1.2 buffer, 500ml basket,100rpm		
2	17.2	23.4
pH 7.2 buffer, 500ml basket,100rpm		
4	29.5	36.5
6	40.9	48.9
8	51.8	55.0
12	65.1	64.9
16	75.2	73.2
20	84	84.2
24	90.2	91.3
30	91.9	99.2

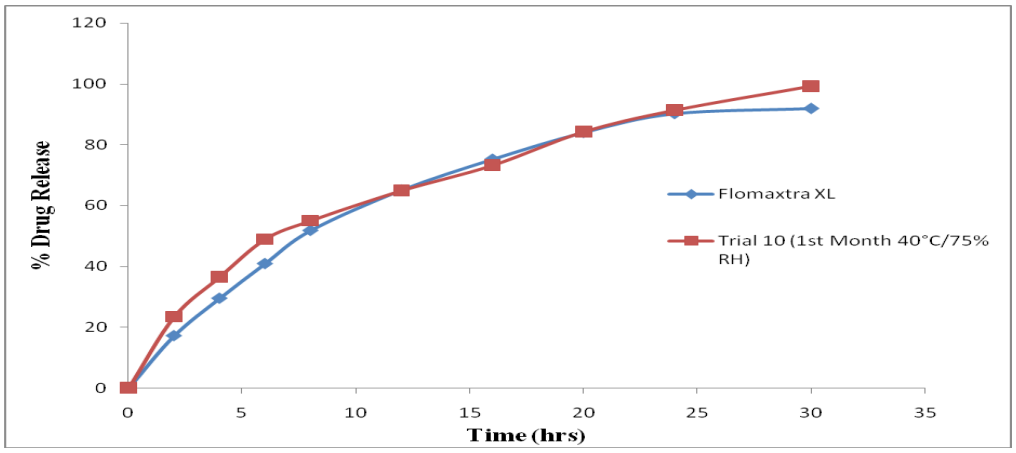


Fig. 10: Dissolution profile for trial 10 after stability studies(40±2°C/75±5% RH)

Table No.20 Dissolution profile for trial 10 after stability studies (30±2°C/65±5% RH) *(Time in hrs on X-axis Vs Percent drug release on Y-axis)*

Time	Flomaxtra XL	Trail 10
pH 1.2 buffer, 500ml basket,100rpm		
2	17.2	22.2
pH 7.2 buffer, 500ml basket,100rpm		
4	29.5	35.9
6	40.9	49.5
8	51.8	54.9
12	65.1	64.8
16	75.2	73.5
20	84	83.6
24	90.2	91.8
30	91.9	98.7

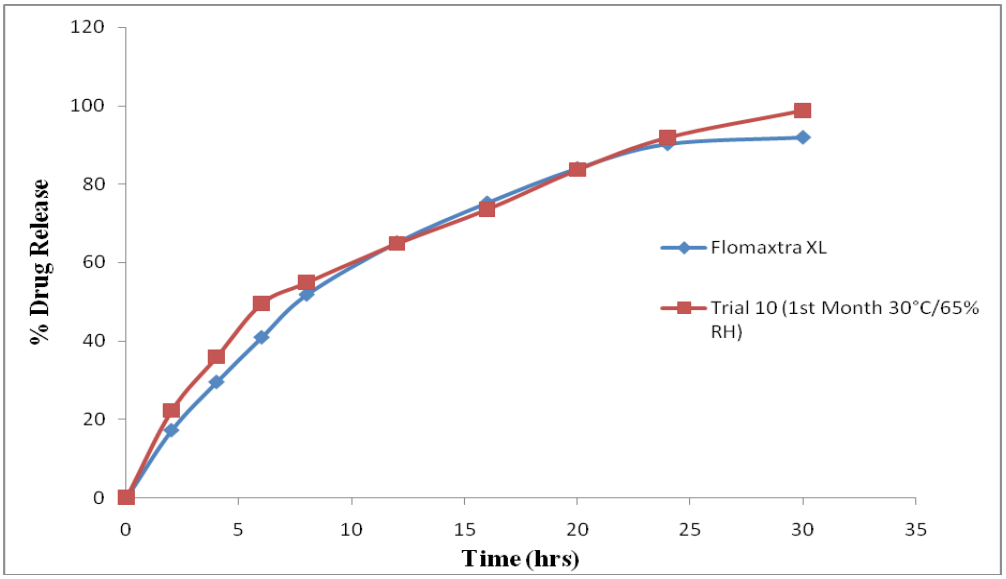


Fig. 11: Dissolution profile for trial 12 after stability studies (30±2°C/65±5% RH)

Table No.21 Dissolution profile for trial 12 after stability studies(25±2°C/60±5% RH) *(Time in hrs on X-axis Vs Percent drug release on Y-axis)*

Time	Flomaxtra	trail 10
pH 1.2 buffer, 500ml basket,100rpm		
2	17.2	21.6
pH 7.2 buffer, 500ml basket,100rpm		
4	29.5	35.5
6	40.9	47.2
8	51.8	53.4
12	65.1	65.1

16	75.2	74.1
20	84	81.9
24	90.2	91.6
30	91.9	99.3

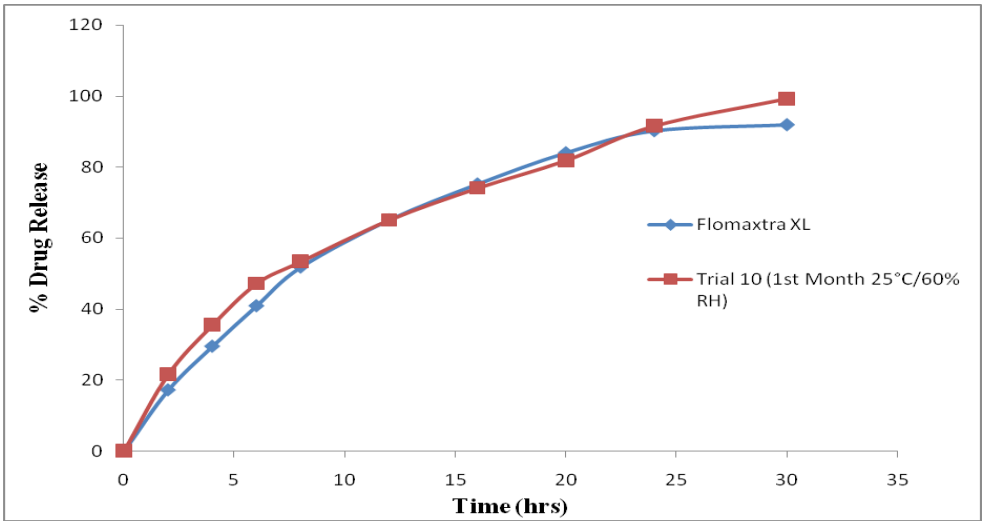


Fig. 12: Dissolution profile for trial 12 after stability studies(25±2°C/60±5% RH)

SUMMARY AND CONCLUSION

7. SUMMARY AND CONCLUSION

The present work, an industrial project, entitled “Formulation and evaluation of sustained release tablets of Tamsulosin Hydrochloride” was taken up in collaboration with Rachem pharma Pvt. Ltd., Hyderabad. The literature review showed that the drug Tamsulosin hydrochloride is an alpha adrenergic blocking agent used in the treatment of benign prostatic hyperplasia.

The present work was aimed towards developing a sustained release oral dosage form having Tamsulosin hydrochloride.

Before going to develop the formulation a detailed product literature review was carried out to know the innovator product and the patent status of the drug.

Preformulation studies were conducted to check the drug polymer and excipients compatibility and the results had confirmed compatibility among them.

As per the proto type evaluation results it was concluded that wet granulation is the best possible method of granulation for the present work.

Granules were evaluated for tests like bulk density, tap density, compressibility index before compression.

Compressed tablets were tested for in-vitro drug release by following the dissolution parameters mentioned in the current version of USP Monograph for Tamsulosin Hydrochloride Capsules. From all the above studies it was concluded that trial 10 which has Eudragit L100 and Eudragit RLPO in the ratio of 1:1.6, had successfully retarded the release of Tamsulosin hydrochloride for 30hrs in a rate controlled manner.

Hence the present work suggests Eudragit L100 and Eudragit RLPO as suitable rate retarding polymer for control release formulation of Tamsulosin hydrochloride and the study recommends in vivo evaluation of the best optimized formula.

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