ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

FORMULATION AND EVALUATION OF TOLTERODINE EXTENDED RELEASE TABLETS

[1]KAMESWARA RAO SANKULA , [2]HEMAMBARESWARI TAVVA, [3]RAMAYASREE CHINTALA ,[4]CHADALAVADA BHAVANI DEVI ,[5] BADUGU RAJESWARI , [6]PRIYANKA DEVARAKONDA .

CORRESPONDING AUTHOR:- hematavva275@gmail.com

ABSTRACT:-

The present work was aimed with the objective of "" to reduce the overactive bladder problem in elderly patients. The tablets were prepared by using different polymers like HPMC k4M, HPMC K100M, Xanthan gum etc. Particular attention was given to concentration of different polymers. The concentrations of both polymers HPMC K4M and HPMC K100M shown big obstacle to release the drug for 24hrs with similar to innovator Detrol La tablets. The tablets were evaluated in terms of Tolterodine content, mechanical properties, dissolution test, FT-IR studies revealed that there is no interaction between the drug and the polymers used in the study. The promising tablet F11 having the optimal formula showing the greatest dissolution properties when compared to other formulations.

INTRODUCTION :-

Over past 30 year as the expanse and complication involved in marketing newdrug entities have increased, with concomitant recognition of the therapeuticadvantages of controlled drug delivery, greater attention has been focused ondevelopment of sustained or controlled release drug delivery systems. There areseveral reasons for the attractiveness of these dosage forms. It is generally recognizedthat for many disease states, a substantial number of therapeutically effectivecompounds already exist 1,2.For many decades treatment of acute diseases or chronic illnesses have beenmostly accomplished by delivery of drugs to patients usingvarious pharmaceuticaldosage forms, including tablets, capsules, suppositories, creams, ointments, liquids,aerosols, and injectables. Even today these conventional dosage forms are the primarypharmaceutical vehicles commonly seen in the prescription and over the counter drugmarket. The oral conventional types of drug delivery systems are known to provide aprompt release of drug. Therefore, to achieve as well as to maintain the drugconcentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. Thisresults in a significant fluctuation in drug levels often with sub-therapeutic and / ortoxic levels and wastage of drug. Recently, several technical advancements haveresulted in the development of new systems of drug delivery capable of controllingthe rate of drug delivery, sustaining the duration of therapeutic activity, and / ortargeting the delivery of drug to a tissue 1,3 .

Oral drug delivery has been known for decades as the most widely utilised route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. Nowadays most of the pharmaceutical scientists are involved in developing an ideal DDS. This ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific site. Scientists have succeeded to develop a system that can be as near to an ideal system and it encourages the scientists to develop controlled release system.

The design of oral sustain drug delivery system(OSDDS) should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimisation of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose. Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability. For most of the drugs, conventional methods of formulation are quite effective. However some drugs are unstable and toxic and have a narrow therapeutic range, exhibit extreme solubility problems, require localisation to a particular site in the body or require strict compliance or long-term use. In such cases a method of continuous administration of drug is desirable to maintain fixed plasma drug levels[3,4].

The need in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localisation at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood follows, in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective. In controlled drug delivery systems designed for long-term administration, the drug level in the blood remains constant, between the desired maximum and minimum, for an extended period of time[5].

Drug level verses time profile showing differences between zero order, controlled release, slow first order sustained release and release from conventional tablet[1].

The term "controlled release," implies a system that provides continuous delivery of the drug or a predetermined period with predictable and reproducible kinetics and known mechanism of release. This means reproducible kinetics and known mechanism of release. This means that the release of drug ingredient(s) from a controlled-release drug delivery system proceeds at a rate that is not only predictable kinetically, but alsoreproducible from one unit to another. On the other hand, the term "sustained release" is usually used to describe a pharmaceutical dosage form formulated such that the liberation of the drug in the systemic circulation is prolonged over time resulting in a plasma profile which is sustained in duration[6].

During the last two decades there has been remarkable increase in interest in controlled release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems.

Modified release dosage forms: According to the United States Pharmacopoeia (USP) the term 'modified release dosage forms' is used to denote the dosage forms for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic objectives not offered by the conventional dosage forms.

Two types of modified release dosage forms are recognised

1) **Extended release dosage forms:** It is defined as the one that allows at least a twofold reduction in dosing frequency as compared to that of conventional dosage forms.
2) **Delayed release dosage forms:** It is defined as the one that release the drug at a time other than immediately after administration, e.g. enteric coated tablets, pulsatile-release capsules.

It is interesting to note that the USP considers that the terms controlled release; prolonged release and sustained release are interchangeable with extended release.

A variety of terms were used to describe these systems:

Delayed release indicates that the drug is not being released immediately following administration but at a later time, e.g. enteric coated tablets, pulsatile-release capsules.

Repeat action indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

Prolonged release indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

Sustained release indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period.

Extended release (ER) dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 24 hours).

Controlled release (CR) dosage forms release drug at a constant rate and provide plasma concentrations that remain invariant with time[7-8].

2.1 ORAL CONTROLLED RELEASE DOSAGE FORMS:

The development of controlled-release formulations continues to be a big success for the pharmaceutical industry. The success of any technology relies on the ease of its manufacturing process and its reproducibility of desirable biopharmaceutical properties. The basic goal of drug therapy is to achieve a steady-state blood concentration level within the therapeutic effective and non-toxic range for an extended period of time. The market for oral controlled drug delivery alone is expected to grow at 9% or more every year through 2007.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Oral route has been the commercially adopted and most convenient route for the drug delivery. Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes[9-10].

Controlled-release technology evolved with matrix technology. Several articles in the 1950s and1960s reported simple matrix tablets or monolithic granules. In1952, Smith Kline & French introduced the Spaniel, a timed-release formulation that launched a wide spread search for other applications in the design of dosage forms. The goal behind the development of oral controlled-release formulations at that time was the achievement of a constant release rate of the entrapped drug. On the basis of that concept, the zero-order osmotic delivery system used in Procardia XL became one of thetop 10 bestselling medicines in the past century[11-12].

Extended release oral drug formulations have been used since the 1960s to enhance performance and increase patient compliance. By incorporating the dose for 24hrs into one tablet from which the drug is slowly released, peaks of high plasma concentration and troughs of low plasma concentrations can be prevented.

This helps to avoid the side effects associated with high concentration and lack of activity associated with low plasma concentrations-giving better overall therapy. In addition, in the treatment of diseases that is asymptomatic-such as hypertension-patients generally remember morning and evening medication, but tend to forgot doses in between. Once or twice daily dosing thus improves therapy through the constant presence of the drug[13].

The oral drug delivery design depends on various factors such as type of delivery system, the disease being treated, the patient, the length of the therapy and the properties of the drug. Most of the oral controlled drug delivery systems rely on diffusion, dissolution or combination of both mechanisms, to release the drug in a controlled manner to the gastrointestinal tract. By considering the conventional dosage form of a drug and the drug profile data, such as dose, absorption and elimination rate constants, metabolic properties, drug properties and the quantity of drug needed, one can determine the desired release rate of the drug from controlled release dosage form[9-10].

2.2 ORAL CONTROLLED RELEASE DOSAGE FORMS VS. CONVENTIONAL SYSTEMS:

Over the years there has been an enormous amount of work put into designing drug delivery systems that can eliminate or reduce the cyclical plasma concentrations seen after conventional drug delivery systems are administered to a patient according to a specified dosage regimen[14].

One of the first commercially available products to provide controlled release of a drug was Dexedrine Spaniels, made by Smith Kline & French in 1952. After this many more controlled release systems came to the market, some successful, others potentially lethal[15].

The design of oral sustain drug delivery system(DDS) should be primarily aimed to achieve themore predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimisation of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose. Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability. For most of the drugs, conventional methods of formulation are quite effective. However some drugs are unstable and toxic and have a narrow therapeutic range, exhibit extreme solubility problems, require localisation to a particular site in the body or require strict compliance or long-term use. In such cases a method of continuous administration of drug is desirable to maintain fixed plasma drug levels[4]

ADVANTAGES OF ORAL CRDDS:

Oral controlled-release (OCR) formulations have many advantages over traditional, immediate release products[16].

- **Reduced fluctuations**
- **Reduced side effects**
- **Patient comfort and compliance**
- **Reduced health care cost**
- **Reduced total dose**
- **Improved efficiency in treatment**

OTHER ADVANTAGES:

- Avoidance of night time dosing..

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

➢·More uniform effect.

➢·Reduction in GI irritation and dose related (local and systemic) side effects.

LIMITATIONS OF ORAL CRDDS:

On the other hand oral CRDDS suffer from a number of potential disadvantages:

➢·Relatively poor in vitro-in vivo correlation

➢·Possible dose dumping

➢·Less flexibility in accurate dose adjustment

➢·Patient variation

➢·High cost

➢·Need additional patient education.

➢·Poor CR formulation with the drugs having:

➢·Extensive first pass metabolism (except pro-drugs)

➢·Extremely short elimination half life (low therapeutic index)

➢·Extremely long elimination half life (narrow therapeutic range)

➢·Bioavailability problems.

➢·Instability in GI environment[4&]

REASONS FOR ORAL CRDDS:

Criteria to be met by drug proposed to be formulated in sustained release dosage forms.

□□Desirable half-life.

□□High therapeutic index

□□Small dose

□□Desirable absorption and solubility characteristics.

□□Desirable absorption window.

□□First past clearance.

AN IDEAL CANDIDATE FOR CRDDS:

The desired biopharmaceutical characteristics of drugs to be used in the development of per oral CR dosage forms are[17]:

➢·**Molecular weight** **:**< 1000 mg

➢·**Solubility** **:**> 0.1 mcg/ml at pH 1 to 7.8

➢·Pk **:** non ionised moiety > 0.1% to 1% at pH 1 to 7.8

➢·**Apparent partition coefficient:** 0.5 to 2.0

➢·**General absorbability** **:** From all GI segments

➢·**Stability** **:** Stable in GI environment

➢·**Release should not be influenced by pH and enzymes**

➢·**Less protein binding**

To evaluate whether or not a drug is viable candidate for the design of per oral CR formulations, one must consider the following pharmacokinetic parameters of the drug:

➢·**Elimination half life** **:** Preferably between 0.5 and 8 hours

➢·**Total clearance** **:**Should not be dose dependant

➢·**Elimination rate constant:** Required for the design

➢·**Absolute bioavailability** **:** Should be 75% or more

➢·**Absorption rate** **:** Must be much greater than release rate

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

- **Therapeutic concentration:** The lower the C^{ss}_{av} and the smaller the $V_{d,}$ the lesser is the amount of drug required.
- **Minimum toxic concentration**, MTC: MTC and MEC, the further apart these two values are, the "safer" the dosage form and also suitable for drugs with very short t ½.
- **Apparent volume of distribution:** The larger the V_d and MEC, the larger will be the required dose size. The maximum dose to be incorporates into a per oral CR formulations is about 500mg. The smaller the $V_{d,}$ the easier is incorporation of drug into dosage form[9, 10&14].

ORAL CONTROLLED DRUG DELIVERY SYSTEMS:

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

Classification of oral controlled release systems[18, 19]:

- Diffusion sustained system.
  - Reservoir type.
  - Matrix type
- Dissolution sustained system.
  - Reservoir type.
  - Matrix type
- Dissolution and Diffusion Controlled CR systems
- Ion-exchange resin CR systems.
- Osmotic pressure controlled CR systems.
- pH independent formulations.
- Altered density formulations.

FACTORS INFLUENCING THE DESIGN AND PERFORMANCE OF SUSTAINED RELEASE PRODUCTS:

The type of delivery system and route of administration of the drug presented in Sustained drug delivery system may depend upon two properties. They are[18]

- Physicochemical Properties of drugs
- Biological Factors.

Physicochemical Properties of Drugs:

1. **Dose size**
2. **Ionisation, p^{Ka} & Aqueous Solubility**
3. **Partition coefficient**
4. **Drug Stability**
5. **Protein Binding**
6. **Molecular size and diffusivity**

Biological Factors[19]:

1. **Biological half-life**
2. **Absorption**
3. **Distribution**
4. **Metabolism**

MONOLITHIC MATRIX SYSTEM:-

In pharmaceutical CRDDS, matrix based systems are the most commonly used type of release controlling methodology owing to their simple manufacturing process. The preparation of a tablet with the matrix involves the direct compression of the blends of drug, release retardant and other additives, in which the drug is uniformly distribute

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

throughout the matrix core of the release retardant. Alternatively, drug-release retardant blends may be granulated to make the mix suitable for the preparation of tablets by wetgranulation or beads [10,20].To characterise and define the matrix systems the following properties of the matrix are considered:

1. Chemical nature of the support.

2. The physical state of the drug.

3. The matrix and alteration in volume as the function of the time.

4. The routes of administration.

5. The release kinetics model (in accordance with Higuchi's equation, these system considered to release the drug as a function of square root of time).

The classification of the matrix-based systems is based on the following criteria.

□□Matrix structure

□Release kinetics

□□Controlled release properties (diffusion, erosion and swelling).

□□Chemical nature and the properties of the applied release retardant(s).

AIM& OBJECTIVES:-In recent years, considerable attention has been focused on hydrophilic polymermatrix systems that are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance.

The purpose of controlled release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible. .

AIM:

The aim and objective of the work is to develop and evaluatetolter iodine extended release tablets 2 mg.

OBJECTIVES:

1. To construct the calibration curve oftolter iodine .

2. To perform the *in-vitro* dissolution profile of the formulated tablets and compare the release pattern with innovator **(**Detrol LA) tablets 2 mg.

3. To select the best formula.

4. To study the kinetic applications.

5. To perform the stability studies for the formulated tablets.

MATERIALS & EQUIPMENTS

MATERIALS:-

API USED IN THE CURRENT STUDY

NAME OF THE API	**SOURCE**
TOLTERODINETARTRATE	MAYER ORGANICS ,BANGALORE

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

EXCIPIENTS USED IN CURRENT STUDY

S.No	EXCIPIENTS	PURPOSE	SUPPLIED BY
1.	Lactose anhydrous (DC Grade)	Filler	LOBA CHEMIE PVT.LTD
2.	Dicalcium phosphate (DC Grade)	Diluent	LOBA CHEMIE PVT.LTD
3.	Xanthan gum	Natural polymer	LOBA CHEMIE PVT.LTD
4.	Ethyl cellulose	Rate controlling polymer	LOBA CHEMIE PVT.LTD
5.	HPMC K4M	Rate controlling polymer	OTTO BIOCHEMIKA REAGENTS
6.	HPMC K100M	Rate-controlling polymer	LOBA CHEMIE PVT.LTD
7.	Magnesium stearate	Lubricant	OXFORD LABORATORY REAGENTS
9.	Potassium dihydrogen phosphate	Salt	LOBA CHEMIE PVT.LTD
10.	Sodium hydroxidePellets	Base	LOBA CHEMIE PVT.LTD

EQUIPMENTS USED IN CURRENT STUDY
TABLE
EQUIPMENTS USED IN CURRENT STUDY

S.No	NAME OF THEEQUIPMENT	MANUFACTURER	MODEL NO
1.	Electronic Balance	Shmadzu	ATX224
2.	Sieve sets	Optic technologies	-
3.	DoublebeamUV Spectrophotometer	Thermoscientific	-
4.	FT-IR	Bruker	-
5.	Compression Machine	Gen Pharma	-
6.	Magnetic stirrer	Remi Equipments	-
7.	Coating pan	-	-
8.	Digital pH meter	Elico	LI 120
9.	Dissolution apparatus USP XXII	Lab India	DS-8000
10.	Stability chambers	Thermolab	M-722
11.	Hardness tester	Dolphin	-
12.	Friabilator (USP)	Secor	-
13.	Vernier Callipers	Mitutoyo	-

DRUG AND EXCIPIENTS PROFILE

DRUG PROFILE :-

Tolterodine is used to treat symptoms of overactive bladder, such as frequent or urgent urination, and incontinence (urine leakage).Tolterodine may also be used for other purposes not listed in this medication guide. Tolterodine reduces muscle spasms of the bladder and urinary tract.

DESCRIPTION:

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Nomenclature[42]

Generic Name: Tolterodine

ChemicalName:(2-[(1R)-3-[bis(propan-2-yl)amino]-1-phenylpropyl]-4-methylphenol

Trade Names: Detrol

Formula

Empirical Formula: $C_{22}H_{31}NO$

. PHYSICS-CHEMICAL PROPERTIES:

Description: Tolterodine is a white to almost white crystalline powder.

Molecular weight:325.4

Solubility: Soluble in water, methanol,sparingly in methylene chloride

Partition coefficient (log P) : 5.3

BCS class: Class I

Category: Anti spasmodic

Chemical Stability: Stable under normal temperatures and pressures

Storage: Store in a cool, dry place. Store in a tightly closed Container[43,44].

Half- life : 1.9-3.7 Hrs

. PHARMACOLOGY:

Tolterodine is a competitive muscarinic receptor antagonist. Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of the urinary bladder smooth muscle and stimulation of salivary secretion.

In *vitro* studies using human recombinant muscarinic receptor subtypes show that Tolterodine has greater affinity for the M3 receptor than for the other known muscarinic receptors (9- and 12-fold greater affinity for M3 compared to M1 and M5, respectively, and 59-fold greater affinity for M3 compared to both M2 and M4). M3 receptors are involved in contraction of human bladder and gastrointestinal smooth muscle, saliva production, and iris sphincter function. Adverse drug effects such as dry mouth, constipation and abnormal vision may be mediated through effects on M3 receptors in these organs[45].

PHARMACOKINETICS:

Absorption:

Steady-state plasma levels achieved by day 6 of dosing. Steady-state bioavailability is approximately 15% and 19% for 7.5 and 15 mg doses, respectively. T_{max} is approximately 7 h. Administration with food after a single dose had no effect on AUC, but increased C_{max} by 22% and decreased T_{max} by 3.3 h; no effect was seen on multiple-dose pharmacokinetics. May be administered without regard to meals.

Distribution:

Tolterodine is approximately 98% bound to plasma proteins (primarily to alpha-1-acid-glycoprotein). The steady-state volume of distribution (Vss) is estimated to be 163 L.

Metabolism:

Tolterodine is extensively metabolized by the liver following oral dosing. Metabolism is mediated by cytochrome P450 enzymes CYP2C9 and CYP3A4.

The two main metabolic routes are as follow

(i) N-Dealkylated 5-Hydroxy methyl Tolterodine

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

(ii) N-dealkylation

The initial products of the hydroxylation and N-dealkylation pathways are the major circulating metabolites but they are unlikely to contribute significantly to the overall clinical effect of Tolterodine.

Pharmacodynamics:

Tolterodine is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors. After oral administration, tolterodine is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and the 5-hydroxymethyl metabolite exhibit a high specificity for muscarinic receptors, since both show negligible activity and affinity for other neurotransmitter receptors and other potential cellular targets, such as calcium channels. Tolterodine has a pronounced effect on bladder function. The main effects of tolterodine are an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure, consistent with an antimuscarinic action on the lower urinary tract.

Excretion:

Following administration of an oral dose of 14C-Tolterodine solution to healthy volunteers, approximately 60% of the radioactivity was recovered in the urine and40% in the faeces. Only a small percentage of the excreted dose was unchangedTolterodine (3%). Estimated Tolterodine clearance is 40 litres/hour for EMs and32 litres/hour for PMs. The elimination half-life of Tolterodine following chronic dosing is approximately 12-18 hours[45].

. DRUG INTERACTIONS:-

Drug-Drug Interactions

Effects of other drugs on Tolterodine: Tolterodinemetabolism is primarilymediated by the cytochrome P450 enzymes CYP 2C9 and CYP 3A4. Therefore,inducers of CYP 3A4 or inhibitors of either of these enzymes may alterTolterodine pharmacokinetics.

CYP* 2C9 *inhibitors: No special dosing requirements are necessary in thepresence of CYP 2C9 inhibitors. Tolterodine exposure following 30 mg oncedaily dosing (twice the maximum recommended therapeutic dose) was 33%higher in the presence of the potent CYP 2C9inhibitor paroxetine 20 mg.

CYP 3A4 inhibitors: The daily dose of Tolterodineshould not exceed 7.5 mg when co-administered with potent CYP 3A4 inhibitors (e.g., ketoconazole, itraconazole, miconazole, troleandomycin, clarithromycin, nefazodoneandritonavir. When the 7.5 mg once daily dose of Tolterodine was given to steady-state and co-administered with the potent CYP 3A4 inhibitor ketoconazole, mean Tolterodine exposure wasincreased 5.3-fold. No special dosing requirements are necessary in the presence of moderate CYP 3A4 inhibitors. Tolterodineexposure following 30mg once daily dosing (twice the maximum recommended therapeutic dose) was34%, 84% and 95% higher in the presence of cimetidine, fluconazole and erythromycin, respectively.

Effects of Tolterodine on other drugs: The potential for clinical doses of Tolterodine to act as inhibitors of CYP 2C9 or CYP 3A4 substrates was investigated in specific clinical interaction studies.

CYP* 2C9 *substrates: Caution should be taken when Tolterodine is used concomitantly with medications that are predominantly metabolized by CYP2D6 and which have a narrow therapeutic window (i.e., flecainide, thioridazine and tricyclic antidepressants). The mean exposure of imipramine, a CYP 2D6substrate, was increased 70% in the presence of steady-state Tolterodine30 mg once daily (twice the maximum recommended therapeutic dose). This was accompanied by a 3.6-fold increase in the exposure of desipramine, the active metabolite of imipramine.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

CYP 3A4 substrates*:* Tolterodine had no clinically relevant effect on the exposure of the CYP 3A4 substrate midazolam. Tolterodine (30 mg once daily) had no effect on the pharmacokinetics of the oral contraceptiveslevonorgestrel or ethinylestradiol.

INDICATIONS AND CLINICAL USE:
(Tolterodine) is indicated for the treatment of overactive bladder, a collection of urinary symptoms composed of urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of proven infection or other obvious pathology.

Contraindications:

- Urinary retention, gastric retention, or uncontrolled angle-closure glaucoma or risk of these conditions.
- Known hypersensitivity to Tolterodine or any ingredient in the formulation.

Adverse effects (1%)
Body as a Whole: Flu-like symptoms, urinary tract infection.
CNS: Headache, asthenia, dizziness.
GI: Constipation, dry mouth, dyspepsia, nausea, abdominal pain, Diarrhea[46].

OVERDOSAGE:
Over dosage with antimuscarinic agents, including (Tolterodine) extended-release tablets can result in severe antimuscarinic effects. Treatment should be symptomatic and supportive. In the event of over dosage, ECG monitoring is recommended. It has been administered in clinical trials at doses up to 75 mg (five times the maximum therapeutic dose) and signs of overdose were limited to abnormal vision.

WARNINGS/PRECAUTIONS:
Caution is required patients with clinically significant bladder outflow obstruction
- ♦ Risk for urinary retention
- ♦ Severe constipation
- ♦ Gastrointestinal obstructive disorders (e.g. pyloricstenosis)
- ♦ Caution in patients at risk for decreased gastrointestinal motility
- ♦ Caution in patients being treated for narrow-angleglaucoma[47,48].

EXCIPIENTS PROFILES:-

The following are the different polymers and excipients used in this work

LACTOSE ANHYDROUS

Lactose s as a natural disaccharide, obtained from milk, which consists of one galactose and one glucose moiety.

Synonyms **:** BP: Anhydrous lactose
JP: Anhydrous lactose
PhEur: Lactosumanhydricum
USPNF: Anhydrous lactose
Lactochem, Pharmatose, NF Lactose, Capsulac,Granulac,

Tablettose, Inhalac, Prismalac, Sachelac.

Description **:** White to off-white crystalline particles or powder, odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose while β-Lactose is 40% as sweet.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Functional Category : Binding agent; diluent for dry-powder inhalers; tablet Binder; tablet and capsule diluent.

Grades : Lactochem powder, coarse powder, fine powder; Pharmatose 50M, 80M, 90M, 100M, Inhalac 70, 120,230; Lactose monohydrate NF 80M.

Solubility : Soluble in water (1 in 5.24), practically insoluble in chloroform, ethanol and ether.

Angle of repose : 33° for Pharmatose DCL 15; 32° for Tablettose 70 and Tablettose 80.

Melting point : 223.08^0C for anhydrous a-lactose;
252.28^0C for anhydrous b-lactose;
232.08^0C (typical) for commercial anhydrous lactose

.**Density (true):**0.88 g/cm^3

Safety : Adverse reactions to lactose are largely attributed to lactose intolerance, whichoccurs in individuals with a deficiency of the intestinal enzymelactase.This results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence.

Incompatibilities : A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, aminophylline, amfetamines, and lisinopril.

Stability : Mold growth may occur under humid conditions (80% RH and above) Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions.

Storage : It should be stored in a well-closed container in a cool, dry place.

Uses : Widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. It is also used as a diluent in dry-powder inhalation[49].

DI CALCIUM PHOSPHATE:-

Synonyms : BP: Anhydrous Calcium Hydrogen Phosphate
JP: Anhydrous Dibasic Calcium Phosphate
PhEur: Calcium Hydrogen Phosphate, Anhydrous
USP: Anhydrous Dibasic Calcium Phosphate

Description : Anhydrous dibasic calcium phosphate is a white, odorless,

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

tasteless powder or crystalline solid. It occurs as triclinic crystals.

Functional category : Tablet and capsule diluent.

Grades : A-TAB and Fujicalin

Solubility : Practically insoluble in ether, ethanol, and water; soluble in dilute acids

Angle of repose : 32° (for Fujicalin)

Melting point : Does not melt; decomposes at 425^0C to form calcium pyrophosphate

Density (true) :0.82 g/cm3 for A-TAB; 0.46 g/cm^3 for Fujicalin

Safety : Dibasic calcium phosphate anhydrous is widely used in Oral pharmaceutical products, food products, and Toothpastes, and is generally regarded as a relatively Nontoxic and nonirritant material.

Incompatibilities: Dibasic calcium phosphate should not be used to Formulatetetracyline antibiotics.

Stability : Dibasic calcium phosphate anhydrous is a no hygroscopic, relatively stable material. Under conditions of high Humidity it does not hydrate toform the dihydrate.

Storage : The bulk material should be stored in a well-closed container in a dry place.

Uses : Anhydrous dibasic calcium phosphate is used both as an excipient and as a source of calcium in nutritional supplements. It is used particularly in the nutritional/health food sectors. It issued inpharmaceuticalproducts because of its compaction Properties, and the good flow properties of the coarse-grade Material.Anhydrousdibasiccalciumphosphate is abrasive and a lubricant is required for tableting[50].

HYPROMELLOSE:-

Hypromellose is a partly *O*-methylated and *O*-(2- hydroxypropylated) cellulose.

Synonyms: Benecel MHPC; Hydroxypropylmethylcellulose (HPMC); Methocel; Metolose; Tylopur.

Description: Odorless and tasteless, white or creamy-white fibrous or granular powder.

Grades: Methocel K100 Premium LVEP, Methocel K4M, K15M, K100M, Metolose 60SH, 65SH, 90SH.

Stability: Stable material, although it is hygroscopic after drying.

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution

Density (true):1.326 g/cm^3.

Melting point: Browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.

Viscosity: Ranges from 3-100000 mPa s.

Methocel K100M (100000 mPa s),

Methocel K15M (15000 mPa s),

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Methocel K4M (4000 mPa s).

Safety: Non-toxic and non-irritant material, although excessiveoral consumption may have a laxative effect.

Uses: As a tablet binder (2% - 5% w/w),

Matrix former (10% - 80% w/w),

Thickening agent (0.45% - 1% w/w),

It is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.

In oral product HPMC is primarily used as tablet binder, in film coating and as an extended release tablet matrix. Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation process. High viscosity grade may be used to retard the release of water-soluble drug from a matrix. Concentration of 0.45-1% w/w may be added as a thickening agent to vehicle for eye drop and artificial tear solution.

HPMC is used as an adhesive in plastic bandage and as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products. In addition, HPMC is used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particle from coalescing or agglomerating thus, inhibiting the formation of sediments[51].

XANTHAN GUM:-

Synonyms: Corn sugar gum; E415; Keltrol; polysaccharide B-1459;Rhodigel; Vanzan NF; Xantural.

Typical properties

Acidity/alkalinity: pH = 6.0–8.0 for a 1% w/v aqueoussolution.
Freezing point: 0^0C for a 1% w/v aqueous solution.
Heat of combustion: 14.6 J/g (3.5 cal/g)
Melting point: Chars at 270^0C.
Refractive index: nD20 = 1.333 for a 1% w/v aqueous solution.
Solubility: practically insoluble in ethanol and ether; soluble in Cold or warm water.
Specific gravity: 1.600 at 25^0C
Viscosity (dynamic):1200–1600 mPa s (1200–1600 cP) for a1% w/v aqueous solution at 25^0C.
Functional Category: Stabilizing agent; suspending agent; viscosity-increasing agent.

Applications:

Xanthan gum is widely used in oral and topical pharmaceutical formulations,cosmetics, and foods as a suspending andstabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other Pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range. Xanthan gum gels showpseudoplastic behavior, the shear thinning being directly proportional to the shear rateThe viscosity returns to normal immediately on release of shear stress.

When xanthan gum is mixed with certain inorganicsuspending agents, such as magnesium aluminum silicate, oorganic gums, synergistic rheological effects occur.In general, mixtures of xanthan gum and magnesium aluminum silicate in ratios between 1: 2 and 1: 9 produce the optimum properties. Similarly, optimum synergistic effects are obtained with xanthan gum: guar gum ratios between 3: 7 and 1 : 9.

Although primarily used as a suspending agent, xanthangum has also been used to prepare sustained-release matrixtablets.Controlled-release tablets of diltiazem hydrochloride

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

prepared using xanthan gum have been reported to sustain the drug release in a predictable manner and the drug release profiles of these tablets were not affected by pH and agitation rate.

Xanthan gum has been incorporated in an ophthalmic liquid dosage form, which interacts with mucin, thereby helping in the prolonged retention of the dosage form in the precorneal area.

Recent studies have revealed that xanthan gum can also be used as an excipient for spray-drying and freeze-drying processes for better results.

Xanthan gum can be used to increase the bioadhesivestrength in vaginal formulations and as a binder in colon specific drug delivery systems.

Xanthan gum is also used as a hydrocolloid in the food industry, and in cosmetics it has been used as a thickening agent in shampoo[52].

ETHYL CELLULOSE:-

Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β anhydroglucose units joined together by acetal linkages.

Synonyms : Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Description: It is a tasteless, free-flowing, and white to light tan-colored

powder.

Functional Category : Coating agent; flavoring fixative; tablet binder; tablet filler;

viscosity-increasing agent.

Solubility: Itis practically insoluble in glycerin, propylene glycol, and water.Ethyl cellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%).Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Density (bulk) : 0.4 g/cm^3

Viscosity : 7 to 100 m Pas

Stability and Storage: It is a stable, slightly hygroscopic material. It should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Safety : It is generally regarded as a nontoxic, nonallergenic, and nonirritating material. It is not metabolized following oral consumption and is therefore a noncalorific substance.

Uses : It is used in the microencapsulation (10-20% w/w).

As a sustained-release tablet coating (3-20% w/w).

It can be used for tablet coating and tablet granulation (1- 3% w/w)Ethyl cellulose is widely used in oral and topical pharmaceutical formulations

Use	Concentration (%)
Micro encapsulation	10.0–20.0
Sustained-release tablet coating	3.0–20.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

The main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation. Modified-release tablet formulations may also be produced using ethyl cellulose as a matrix former. Drug release through ethyl cellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized.

EC exhibits good stability in pH 3-11 so used for both acidic and alkaline ingredients[53].

MAGNESIUM STEARATE:-

Synonyms: Magnesium octadecanoate; Octadecanoic acid, magnesium salt;Stearic acid, magnesium salt.

Functional category: Tablet and capsule lubricant.

Description: It is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acidandacharacteristic taste. The powder is greasy to the touch andreadily adheres to the skin.

Flowability: Poorly flowing, cohesive powder.

Melting range: 117–150°C (commercial samples); 126–130°C (high purity magnesium stearate).

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Stability and Storage : It 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. It cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Safety : Nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

Uses : It 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% and 5.0% w/w. It is also used in barrier creams[54]

Table-1 : In-vitro dissolution profile for Tolterodine F11

S.no	Time (Hrs)	Absorbance At 286nm	Dilution Factor	Conc (µg/ml)	Conc (mg/ml)	Amount Dissolved	% Drug dissolved	% Drug Undissolved	log % Drug Undissolved
1	0	0	0	0	0	0	0	100	2
2	1	0.101	1	14.96	0.014	13.46	13.46	86.54	1.93
3	2	0.149	1	24.22	0.024	21.80	21.80	78.20	1.89
4	4	0.227	1	36.91	0.036	33.21	33.21	66.79	1.82
5	8	0.351	1	57.07	0.057	51.36	51.36	48.64	1.68
6	12	0.512	1	83.25	0.083	74.92	74.92	25.08	1.39
7	16	0.605	1	98.37	0.098	88.53	88.53	11.47	1.05
8	24	0.654	1	106.34	0.106	95.70	95.70	4.30	0.63

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Table-2 : *In-vitro* dissolution profile for Tolterodine F12

S.no	Time (Hrs)	Absorbance At 286nm	Dilution Factor	Conc (µg/ml)	Conc (mg/ml)	Amount Dissolved	% Drug dissolved	% Drug Undissolved	log % Drug Undissolved
1	0	0	0	0	0	0	0	100	2
2	1	0.102	1	13.42	0.013	13.46	13.46	86.54	1.93
3	2	0.148	1	21.70	0.021	20.60	20.60	79.40	1.89
4	4	0.227	1	33.21	0.033	32.21	32.21	67.79	1.83
5	8	0.350	1	51.26	0.051	48.36	48.36	51.64	1.71
6	12	0.514	1	75.12	0.075	70.91	70.91	29.09	1.47
7	16	0.604	1	88.63	0.088	86.53	86.53	13.47	1.12
8	24	0.658	1	95.80	0.095	90.70	90.70	9.3	0.96

Table-3: *In-vitro* dissolution profile for Tolterodine F13

S.no	Time (Hrs)	Absorbance At 286nm	Dilution Factor	Conc (µg/ml)	Conc (mg/ml)	Amount Dissolved	% Drug dissolved	% Drug Undissolved	log % Drug Undissolved
1	0	0	0	0	0	0	0	100	2
2	1	0.105	1	13.45	0.013	13.46	13.46	86.54	1.93
3	2	0.143	1	21.67	0.021	20.60	20.60	79.40	1.89
4	4	0.217	1	33.31	0.033	32.21	32.21	67.79	1.83
5	8	0.342	1	51.18	0.050	48.36	48.36	51.64	1.71
6	12	0.504	1	75.02	0.075	70.91	70.91	29.09	1.47
7	16	0.608	1	88.59	0.088	86.53	86.53	13.47	1.12
8	24	0.656	1	95.78	0.095	90.70	90.70	9.3	0.96

***In-vitro* drug release profile of Formulations F 11, F12, F13& Innovator**

In-vitro drug release for the three formulations (F11-F13) was performed as discussed in the experimental procedure. The three formulations F11- F13 prepared by using HPMCK4M and HPMC K100M combination. The formulation F11 with 35% HPMCK4Mand 5% HPMCK100M the drug release was 95.70% with in24hrs, F12 with 40% HPMCK4M and 5% HPMCK100M the drug release was 90% with in 24hrs and F13 formulation with 45% HPMCK4M and 5% HPMCK100M the drug release was 89% with in 24 hrs.

Hence F11 was further performed the similarity factor with innovators tablets.

Table-4: *In-vitro* dissolution profile for Tolterodine F10

S.no	Time (Hrs)	Absorbance At 286nm	Dilution Factor	Conc (µg/ml)	Conc (mg/ml)	Amount Dissolved	% Drug dissolved	% Drug Undissolved	log % Drug Undissolved
1	0	0	0	0	0	0	0	100	2
2	1	0.136	1	20.14	0.020	18.13	18.13	81.87	1.91
3	2	0.181	1	29.43	0.029	26.48	26.48	73.52	1.86
4	4	0.274	1	44.55	0.044	40.09	40.09	59.91	1.77
5	8	0.456	1	74.14	0.074	66.73	66.73	33.27	1.52
6	12	0.543	1	88.29	0.088	79.46	79.46	20.54	1.31
7	16	0.596	1	96.91	0.096	87.21	87.21	12.79	1.10
8	24	0.639	1	103.90	0.103	93.51	93.51	6.49	0.81

Table-5:- *In-vitro* dissolution profile for Tolterodine F11

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

S.no	Time (Hrs)	Absorbance At 286nm	Dilution Factor	Conc (µg/ml)	Conc (mg/ml)	Amount Dissolved	% Drug dissolved	% Drug Undissolved	log % Drug Undissolved
1	0	0	0	0	0	0	0	100	2
2	1	0.101	1	14.96	0.014	13.46	13.46	86.54	1.93
3	2	0.149	1	24.22	0.024	21.80	21.80	78.20	1.89
4	4	0.227	1	36.91	0.036	33.21	33.21	66.79	1.82
5	8	0.351	1	57.07	0.057	51.36	51.36	48.64	1.68
6	12	0.512	1	83.25	0.083	74.92	74.92	25.08	1.39
7	16	0.605	1	98.37	0.098	88.53	88.53	11.47	1.05
8	24	0.654	1	106.34	0.106	95.70	95.70	4.30	0.63

***In-vitro* drug release profile of Formulations F 10 & F 11**

In-vitro drug release for the two formulations (F10-F11) was performed as discussed in the experimental procedure. The two formulations F10& F11 prepared by using HPMCK4M and Xanthan gum andHPMCK4M and HPMCK100M respectively.The formulation F10was showing similar drug release with innovators tablets but initially the drug was released faster up to 8hrs then followed slow drug release.The formulation F11 was showing similar drug release with innovators tablets. Hence F11 was selected as optimized formula and the both formulations were performed the similarity factor.

***In-vitro* drug release profile of Formulations F 11& Innovator**

TIME	Rt(INNOVATOR)	Tt(TEST)	∑ Rt-Tt	∑(Rt-Tt)2
0	0	0	0	0
1	11	10.9	-0.1	0.01
2	21	25	4	16
4	32.9	33.89	0.99	0.9801
8	51.1	52.6	1.5	2.25
12	73.8	74.8	1	1
16	88.4	88.4	0	0
24	95.5	96.8	1.3	1.69

Table-6 Similarity factor (*f2*)

FACTOR1(DISSIMILARITY FACTOR)

$$f1= \{[\Sigma_{t=1}^{n} |R_t-T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100$$

=2.27

FACTOR2(SIMILARITY FACTOR)

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

=85.6

R_t and T_t are the individual or mean percent dissolved at each time point, t, for the reference and test dissolution profiles, n is the number of dissolution sample times, respectively.The similarity factor should be between 0 and 100. It is 100 when two comparative groups of reference and test are identical and approaches 0 as the dissimilarity increases.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Hence F11 with Hydroxy Propyl Methyl Cellulose of different grades (K4M & K100M) can be considered as the optimized formula.

Formulation code	Zero order		First order		Higuchi		Korsmeyer-peppas	
	r^2	Slope	r^2	Slope	r^2	Slope	r^2	Diffusion exponent (n)
F-1	0.734	11.60	0.989	-0.236	0.934	36.71	0.681	0.43
F-2	0.734	10.53	0.954	-0.169	0.949	35.83	0.691	0.37
F-3	0.921	9.9	0.994	-0.104	0.995	30.93	0.749	0.36
F-4	0.891	6.874	0.994	-0.087	0.995	27.27	0.783	0.52
F-5	0.936	6.64	0.968	-0.073	0.993	25.69	0.809	0.52
F-6	0.894	9.85	0.956	-0.077	0.998	31.28	0.795	0.29
F-7	0.924	7.06	0.991	-0.088	0.994	27.51	0.810	0.23
F-8	0.922	7.06	0.961	-0.067	0.997	22.97	0.859	0.35
F-9	O.835	3.985	0.996	-0.071	0.973	22.47	0.631	0.29
F10	0.883	03.985	0.951	-0.064	0.984	21.97	0.680	0.29
F11	0.859	4.11	0.982	-0.056	0.966	22.11	0.988	0.694
F-12	0.902	3.974	0.967	-0.045	O.969	21.49	0.781	0.67
F-13	0.906	4.013	0.961	-0.04	0.988	21.57	0.812	0.79
F(I)	0.910	4.11	0.984	-0.062	0.981	22.13	0.733	0.6

IN-VITRO DRUG RELEASE KINETICS

Table 7 : The drug release kinetics of the prepared formulations

***IN-VITRO* DRUG KINETICS OF OPTIMIZED FORMULA**

The Zero order release kinetics of optimized formula F-11

the first order release kinetics of optimized formula F-11

The Higuchi release kinetics of optimized formula F-11

The korsmeyer-peppas model release kinetics of optimizedFormula F-11

The *invitro* drug release kinetic models- zero order, First order, Higuchi.The figures from 28-31 represent the graphical representation of release kinetics of the optimized formula F11.

Korsmeyer-Peppas model were performed for all the formulations and was based on the 'diffusion exponent n' of korsmeyer-peppas model where specifications were mentioned in the table.Based on the regression values mentioned in table-49 the drug product follows the Firstorder kinetic model.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Table No.8Stability Summary data of formulation-11

Test Name	Limits	Initial	40°C/75% RH		50°C/90% RH
			1 month	2 months	1 month
Description	Orange colored, round biconvex film coated tablets with plain surface on both sides	Complies	Complies	Complies	Complies
Dissolution by UV Method (%w/w) In Acid Stage	NLT 25% in 1hr	12%	12.4%	13%	11.8%
Dissolution by UV Method (%w/w) in pH 6.8 Buffer stage	NLT 85% at 24th hr	99.2%	99.4%	99.2%	98.8%
Identification by HPLC	To match with Standard	Complies	Complies	Complies	Complies
Average wt	206mg±2%	206.1	206.3	206.2	206.4
Water by KF (% W/W)	NMT 3.5%	2.2	2.7	2.4	2.7
Assay	NLT 90.0 and NMT 110.0	100.1	99.0	99.6	98.8
Related Substances (%w/w):					
Known impurity I (oxidized impurity)	NMT 0.50	0.03	0.03	0.05	0.10
Known impurity II	NMT 0.30	0.08	0.07	0.11	0.11
Unknown impurity	NMT 0.50	0.06	0.06	0.08	0.11
Total impurities	NMT 1.50	0.18	0.16	0.25	0.32

STABILITY STUDY REPORT:

The stability study was performed for 200 tablets of final formulation F-11 at accelerated conditions (40°C/75% RH) for two months and at stress conditions(50°C/90% RH) for one month in stability chambers.. The parameters like Description, Dissolution, Identification, Average weight, moisture content, Assay and related impurities were performed initially to report that the tablets results were in limits. All these parameters were performed again after one month and two months time period and observed no physical reactions and incompatibilities. All the results were found to be in mentioned limits. The results were shown in the table-50. Hence the formulated optimized batch F-11 was found stable and successful.

SUMMARY & CONCLUSION:-

The project work entitled, "Formulation Development and Evaluation of Tolterodine extended release Matrix Tablets" was carried out in the dissertation work. The objective of this study was to develop and evaluateTolterodine Extended Release matrix tablet by using various grades and ratios of hydroxy propyl methyl cellulose (HPMC),Xanthan gum, Ethyl cellulose as rate controlling hydrophilic polymers and bioequivalent testing with the innovator **Detrol**(prepared by Pfizer).

The drug was compatible with the formulation components. Hence Lactose Anhydrous, Di calcium Phosphate (DC grade), Xanthan gum, Ethyl cellulose, HPMCK4M, HPMCK100M, Opadry orange were selected as excipients for the lab scale development.

Blends were evaluated for various parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and the parameters evaluated for the matrix tablet are

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Drug content, hardness, Friability, weight variationand Thickness and all physicochemical properties are within the limits. Drug release from tablets complies with the prescribed limits. Formulation development from F1 to F13 was executed to optimize the composition. At the final, the dissolution profile of the batches F11 was closer with the reference product.

The developed matrix tablets followed the first order release model and it was non- fickian type of diffusion based on the korsmeyer-peppas model.

Similarity factor value for optimized formulation F11was above 50 indicates that the dissolution profile of the batch matched with innovators Tablet.

The stability studies were performed for the optimized formulation F11 at the accelerated conditions (40^0C/75%RH) for two months and at stress conditions (60^0C/90% RH) for one month. The results were indicated that all results were in limits after two months period. Hence the optimized formulation F11 was stable.

Finally the combinations of high viscous and low viscous hydroxy propyl methyl cellulose polymers were used to develop a optimized formula that was similar with the innovators product **Detrol**.

REFERENCES

1. Berner. B. and DinhS. Fundamental concepts in controlled release In: A. Kydonieus, ed.Treatise on controlled drug delivery. MarcelOekker, 1992; 1 - 36
2. Manish ShivadasWani, Dr. DehghanM.H.Controlled released system- A Review.Pharma. Info.net, 2008.
3. Chien.Y-W. Concepts and systems design for rate-controlled drug delivery. In: Chiened. novel drug delivery systems.Marcel Dekker, 1992; 43**.**
4. SampathkumarK.P. DebjitBhowmik and ShwetaSrivastava.Sustained release drug deliverysystem potential. The Pharma Innovation.2, 2012; 42- 68.
5. http://Pharmacrunch.net/archives,novel-drug-delivery-system,Controlled release drug delivery system.Jun-2011-12.
6. Chien.Y. W. Potential developments and new approaches in oral controlled-release drug delivery systems. Drug Dev. Ind. Pharm 1983,9; 1294 –1330.
7. Mitul Shah. Controlled release drug delivery system (CDDS). 8182,Jun29-2010.
8. Gudsoorkar V. R., RambhauD. Sustained release of drugs. The eastern pharmacist, 1993 Sept; 17-21.
9. Colombo P, Conte U, and Gazzaniger A. Drug release modulation by physical restriction of matrix swelling. Int J Pharm 1990, 63;43-48.
10. Colombo P, Bettini R, and Massimo G.Drug diffusion front movementisimportantin drug release control from swellable matrix tablets. J PharmSci 1995, 84 (8) ; 991-997.
11. Nandita G. Das and Sudip K. Das. Control-release of oral dosage forms, formulation.fill& finish 2003; 10-16.
12. Drug delivery technologies–innovations and market challenges. Scrip Reports: PJBpublications Ltd 2003.
13. Peter fyhr and Ken Downie. Extended release drug delivery technology. Innovations in pharmaceutical technology,2012: 80-86.
14. Chien YW. Controlled and modulated-release drug-delivery systems. In: Swarbrick J, Baylan JC, eds. Encyclopedia of pharmaceutical technology. New York: Dekker,1990;281-313.
15. Janos B, Klara P, Odon P, Geza RJ, Rok D, Stane S and Istvan E. Film coating as a method to enhance the preparation of tablets fromdimenhydrinate crystals. IntPharm.2004; 269:393-401.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

16. Leon Shargel, Susanna Wu-Pong and Andrew BC Yu. Modified-release drug products. In: Applied biopharmaceutics&pharmacokinetics, fifth ed. 2004; 845-856
17. Patrick JS. Martin's Physical pharmacy and pharmaceutical sciences. Third ed, Bombay:varghese publishing house, 1991; 512-519.
18. NarasimhaRao R.,Anusha Reddy M.,Swetha Reddy N, Divyasagar P and Keerthana K.Design and evaluation of metformin hydrochloride extended release tablets by direct compression.International journal of research in pharmaceutical and biomedical sciences, 2 (3) Jul – Sep 2011; 1118-1133.
19. Mulye N.V., Turco S.J., A simple model based on first order kinetics to explain release of highly water soluble drugs from porous dicalcium phosphate dehydrates matrices. Drug Dev. Ind. Pharm. 1995, 21; 943–953.
20. Schwartz B.J., Simonelli, A.P. and Higuchi W.I.Drug release from wax matrices & analysis of data with first-order kinetics and with the diffusion-controlled model. J. Pharm. Sci. 57, 274–277.
21. Suvakanta dash, PadalaNarasimha Murthy and PrasantaChowdhury. Kinetic modeling on drug release from controlled drug delivery systems.ActaPoloniaePharmaceutica n Drug Research, 2010, 67(3); 217-223.
22. Silvina A., Bravo M., Lamas C. and Claudio J. J. Pharm. Sci. 2002, 5;213.
23. Dissolution testing. Immediate release dosage forms; Similarity factorURL: http://www.fda.gov/cder.
24. Novartis Pharmaceuticals Corporation, East Hanover, New Jersey-ENABLEX (Tolterodine) Extended release tablets- Rx and prescribing information. Revised Jan 2010.
25. Christopher Chapple. William Steers, Peggy Norton, Richard Millard and Paul Abrams. A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of Tolterodine, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. BJU International, 2005, 95(7); 993–1001.
26. SrinivasK.,Rajeswar ReddyS., G.M. Reddy andPratap Reddy P.Synthesis and characterization of novel and potential impurities of Tolterodine, a potent muscarinic m3 receptor antagonist.Rasayan J. Chem. 2009, 2(1); 151-155.
27. Zinner N., KobashiK.C, EbingerU., Viegas. A., EgermarkM. and Koochaki.P. TolterodineTreatment for overactive bladder in patients who expressed dissatisfaction with prior extended release anti muscarnic therapy. Int. J. Clin. Pract, 2008 November.
28. Jenelle. F., Karin glavind, GeorgKralidis and Jean-Jacques Wyndaele.Treatment of overactive bladder in the older patient: pooled analysis of three phase III studies of Tolterodine, and M3selective receptor antagonist. European Urology 2005, 48; 471–477.
29. Haab.F, Stewart.L and Dwyer.P. Tolterodine, anM3 selective receptor antagonist, is an effective andwell-tolerated once-daily treatment for overactive bladder. European Urology 2004, 45;420–429.
30. Jennifer .L. and Kirwin. An M3-selective muscarinic antagonist for the treatment of overactive bladder. Formulary, 39, June 2004; 291-299.
31. Thomas Kerbusch, Peter A Milligan and Mats O Karlsson. Assessment of the relative *in vivo* potency of the hydroxylated metabolite of Tolterodine in its ability to decrease salivary flow using pooled population pharmacokinetic–pharmacodynamic data. Br J ClinPharmacol. 2004 February,57(2);170–180.
32. Sum lam and Olga Hilas.Pharmacologic management of overactive bladder. ClinIntervAging. 2007 September,2(3); 337–345.
33. Zinner, Tuttle J. and Marks L. Efficacy and tolerability of Tolterodine, A muscarnic receptor antagonist, versus oxybutinin in the treatment of overactive bladder (OAB). University of californiaschool of medicine-1146.
34. http://www.Consumer reports health.org / Best buy drugs • Drugs to treat overactive bladder-updated in June 2010; 1-16.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

35. Matthew Parsons and Swati Jha.Treatment of overactive bladder in the aging population: focus on Tolterodine.ClinIntervAging. 2006 December, 1(4);309–316.

36. Mahesh Chavanpatil Development of sustainedrelease for gastro-retentive drug delivery system for Ofloxacin : In- vitro and In-vivo evaluation.int.j ofpharmaceutics.2005 November 2005, 304 (2) ; 178-184.
37. Sapna N Makhija. Once daily sustained release tablets of Venlafaxine , a novel anti depressant.Eur.J of pharmaceutics and Biopharmaceutics.2002 July,54(1); 9-15.
38. FatmanuTugcu.Development of long acting bioadhesive vaginal gels of oxybutynin: Formulations, invitro and invivo evaluations.int.J of pharmaceutics.2013 November, 457(1);25-39.
39. Ranjani V Nellore .Development of Metoprolol tartrate extended release matrix tablet formulations for regulatory policy consideration. Int.J of Controlled Release.1998 January,50(3), 247-256.
40. Qijun li . Preparation and investigation of novel gastro-floating tablets with extrusion based 3D printing. int.J.pharm .2018 Jan 15;535(1-2):325-332.
41. Soravoot .Modified release from hydroxyl propyl methyl cellulose compression – coated tablets.int.J.pharm.2010 December 402 (2);72-77.
42. http://www.Drug information.com. Tolterodineextended release tablets.
43. http://www.Drug Bank.com : Tolterodine(DB0096).
44. http://www.PharmPK Discussion.com -BCS Classification of Tolterodine HBr.
45. http://www.Enablex.com - DB00496.pdf. 1-22.
46. http://www.Drugs.com.htm - Complete Tolterodineinformation.
47. http://www.Enablex.comEnablex-prescribing information1-2.
48. Enablex- Product Monograph, Novartis Pharmaceuticals Canada Inc.,January 5, 2009; 564-573.
49. Gothi G.D.,Parikh B.N.,Patel T.Dand Patel C.N. Study on design and development of sustained release tablets ofmetoprolol succinate. Journal of Global Pharma Technology.2010, 2(2); 69-74.
50. Raymond C Rowe, Paul J Sheskey and Marian E Quinn. Hand book of pharmaceutical excipients. Sixth ed, Great Britain: Royal pharmaceutical society 2009; 359-361.
51. Raymond C Rowe, Paul J Sheskey and Marian E Quinn. Hand book of pharmaceutical excipients. Sixth ed, Great Britain:Royal pharmaceutical society 2009; 94-96.
52. Raymond C Rowe, Paul J Sheskey and Marian E Quinn. Hand book of pharmaceutical excipients.Sixth ed, Great Britain Royal pharmaceutical society 2009; 326-329.
53. Raymond C Rowe, Paul J Sheskey and Marian E Quinn. Hand book of pharmaceutical excipients. Sixth ed, Great Britain:Royal pharmaceutical society 2009; 782-785.
54. Raymond C Rowe, Paul J Sheskey and Marian E Quinn. Hand book of pharmaceutical excipients.Sixth ed, Great Britain:Royal pharmaceutical society2009; 262-267.
55. Madhusudhanpogula, Nazeer.S. Extended release formulation. International Journal of Pharmacy and Technology Dec-2010, 2(4); 625-684.
56. Aulton M.E. Flow properties - The Science ofdosage form design second ed, 205-209.
57. Y.R.Sharma. Elementary organic chemistry. 4thed, S. Chand publications 2011; 68-151.
58. SridharanD.,Umarani A.,Thenmozhi, Pavan Kumar and YelikaPhanikishore. Development and validation of UV spectrophotometric method ofTolterodineHBrin Bulk and Tablet Dosage Form.Asian J. Pharm. Ana. 2011,1(3); 43-45.
59. Types of Tablets; Available from URL: http://www.pharmpedia.com/Tablet.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

60. Indian Pharmacopoeia. 6th ed. Ghaziabad: Indian pharmacopoeia commission 2010; 2513-2536.
61. ShahD, Shah Y, and Rampradhan M.Development and evaluation of controlled release diltiazemhydrochloridemicroparticles using cross-linked poly(vinyl alcohol). Drug DevInd Pharm.1997,23(6);567-574.
62. http://www.fda.gov/cder/ogd/index.htm.
63. Costa P, Jose Manuel and Lobo J. Modeling and comparison of dissolution profiles. European Journal of pharmaceutical sciences. 2001, 13; 123-133.
64. BrahmankarD.M., Sunil B. Jaiswal. Biopharmaceuticsand Pharmacokinetics A Treatise. Second Edition, VallabhPrakashan 2009; 330-332.