1. **INTRODUCTION**

Development of oral controlled release drug delivery systems (CRDDS) has attracted much attention in recent years due to its ease of administration, patient compliance, lesser side effects and flexible design of dosage forms. Over the past 50 years, a number of controlled release techniques have been developed and employed to sustain the delivery of oral medication to the systemic circulation in order to increase the drug pharmacological action and reduce their side effects. The drug plasma levels can be optimized by controlling the delivery of the drug from the formulation into the gastro-intestinal tract in which the rate of drug absorption can be controlled and adjusted (Bravo-Osuna et al., 2008). Most of the CRDDS developed is aimed to slowing the drug release rate from the dosage form, in which the drug is released by a specific rate over a predetermined period of time based on a desired therapeutic concentration in either systemic circulation or at target site (Ford et al., 1985). The most common types of controlled release formulation are modified drug release, sustained drug release, delayed drug release and targeted drug release (Abdul and Poddar, 2004). In modified release dosage form a portion of the drug is released immediately, and the remaining of the drug is released slowly over an extended period of time, normally over 12–18 h. Figure 1 represents the drug plasma concentration of normal and modified drug release. The drug targeting system releases the drug into or at the specific sites e.g. colon targeting system. However, in delayed drug release dosage form, the drug does not release in the stomach and it releases in the intestine. This type of formulation is developed either to protect the stomach from irritation of drug e.g. aspirin, or to protect sensitive drug from low pH of stomach e.g. erythromycin.

![Figure 1: Comparison of plasma drug concentration in normal and modified release dosage](image-url)
Conventional oral drug administration does not usually provide rate-controlled release or target specificity. Conventional drug delivery provides sharp increase in drug concentration often achieving toxic level and following a relatively short period at the therapeutic level of the drug concentration. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount of the right period of time there by causing little toxicity and minimal side effects. So desired drug release can be provide by rate controlling drug delivery system such as extended drug delivery systems.

Extended release system was introduced in the pharmaceutical market by Smith Kline and French Laboratories in 1952. They made an oral formulation of dextroamphetamine sulphate (Spansule®) by incorporating the drug in pellets coated with wax. The conventional dosage forms are designed to achieve maximum drug bioavailability by administering the dosage form in a particular dose and at particular frequency. This requires frequent daily administration especially when the drug has a short half-life. This may result in wide fluctuation in peak and trough steady-state drug levels, which is undesirable for drugs with marginal therapeutic indices. Moreover, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Extended release dosage forms release drug slowly, so that the plasma concentrations are maintained at a therapeutic level for prolonged period of time (El-Said and Hashem, 1991). The use of extended release dosage form reduces the frequency of dosing by modifying the rate of drug absorption and offers potential advantages to patients (convenience, compliance and therapeutic outcomes) over conventional dosage form (Chien, 1992). In addition, in the treatment of chronic disease such as hypertension, patients can remember the morning and evening dosing but they tend to forget dose in between, so once a day dosing improves treatment through constant drug release.

The role of polymers in development of drug delivery system is vital and has led to the progress of the most of the controlled release technologies. These carriers are capable of producing various types of controlled release systems. The oral systems are usually made of polymers and the mechanisms of release are generally regulated by diffusion, bioerosion or degradation, swelling or generation of osmotic pressure. Thus at present a great opportunity lies in converting solid oral dosage formulation to extended-release forms. Various types of polymers (synthetic and natural) have been used to develop extended release systems.
Matrix systems have gained widespread importance in controlled drug delivery due to simplicity of preparations and lower cost. It is commonly prepared by incorporating the drug into polymer and compressed into tablets. The hydrophilic matrix tablets are extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of systemic toxicity due to dose dumping (Gohel and Amin, 1998). Recently, the use of natural polymers in the design of drug delivery formulation has received much attention due to their excellent biocompatibility and biodegradability. The hot melt technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms. It provides many of advantages over other technique such as minimizing the production steps, solvent free processing, no requirement on compressibility of materials, and it is an elegant and economical way of manufacturing controlled release drug delivery systems. The process involves embedding a drug in a polymer while shaping the composite material to form a pharmaceutical product. The use of hot melt technique to achieve sustained drug release is receiving more attention (Aitken-Nichol et al., 1996).

Multiparticulate systems are offering many advantages over single unit system such as enhanced absorption, uniform distribution, less gastric irritation and prevention from dose dumping. They also provide many technical advantages such as good flowability due to uniform size and spherical shape, high physical integrity of spherical agglomerates, high strength, low friability, narrow particle size distribution, superior quality for coating application and uniform packing characteristics (Gu et al., 2004a). Drug encapsulating systems are developed to control the drug release at controlled rates for long periods of time, ranging from days to months. Such systems offer numerous advantages over traditional methods of drug delivery, including tailoring of drug release rates, protection of fragile drugs, masking the unpleasant taste or odour of the drug, enhancement of the solubility and therapeutic efficacy of the drug and minimization of its the side effects.

Microparticulate drug delivery systems are ideal delivery systems for many controlled delivery applications with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The drug release from microparticulate system depends on a variety of factors such as the method of preparation, polymers type and their ratio. Microspheres can be prepared by various techniques such as
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Solvent extraction/evaporation, phase separation (coacervation) and spray drying. Microspheres can be developed to control or delay the drug release e.g. indomethacin microspheres were developed as an extended release formulation, to control the drug release (Karasulu et al., 2003).

1.1 Treatment of Urinary Incontinence

Overactive bladder syndrome (OAB) is characterized by symptoms of urgency and urinary frequency with or without urge incontinence. The symptoms and prevalence of OAB increase with age. The OAB reduces quality of life and is associated with the increased risk of falls, fractures, urinary tract and skin infections, sleep disorders and depression.

Muscarinic receptor antagonists are the first line pharmacotherapy for OAB. Acetylcholine activates muscarinic receptors on detrusor myocytes and is the main contractile transmitter. Muscarinic receptors comprise five subtypes encoded by five distinct genes (Caulfield and Birdsall, 1998). The mRNAs for all muscarinic receptor subtypes have been detected in the human bladder (Sigala et al., 2002). The mRNA and protein levels of the M₂ subtype outnumber the M₁ receptor subtype (Yamaguchi et al., 1996). These receptors have been detected in the urothelium, interstitial cells, nerve fibres, and detrusor layers (Mukerji et al., 2006). Detrusor smooth muscle contains muscarinic receptors mainly of the M₂ and M₃ subtypes (Eglen, 2006). Both subtypes are coupled to G proteins, but the signal transduction pathways differ.

Oxybutynin and tolterodine tartrate are the most widely prescribed forms of treatment for the syndrome of overactive bladder and urge urinary incontinence. Oral oxybutynin is currently the most frequently prescribed antimuscarinic drug for the treatment of bladder overactivity in children. It is effective but has systemic adverse effects, most notably hyperpyrexia (accentuated during hot summers), dry mouth, constipation, blurred vision, drowsiness, which limit its use. Due to these adverse effects a significant number of patients discontinue the therapy (Andersson, 1988). Dry mouth can occur in up to 80% of patients receiving oxybutynin immediate release formulation (Yarker et al., 1995).

In India during the hot summers and due to adverse effect of using oxybutynin, almost all the patients discontinue dose during the day time, and hence there is a need to look at drugs with lesser side effects for the summer months in India. Tolterodine tartrate is a new antimuscarinic agent specifically developed for the treatment of overactive bladder and is being used in...
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children. Tolterodine tartrate shows more specificity for the M₂ receptor and also has less M₃ receptor activity with a direct correlation to lesser dry mouth. Tolterodine tartrate has selective action over the bladder and is a therapeutic alternative in patients with neurogenic bladder, enabling them to continue treatment with minimum adverse effects (Hjalmas et al., 2001).

Over the age of 45, OAB affects one in five women (Irwin et al., 2006). According to the American Urological Association (AUA), more than 33 million Americans (men and women) suffer from this syndrome. These conditions limit and disrupt the sufferer’s everyday life which causes intense feeling of anxiety and depression (Liberman et al., 2001). A study by the Asian Survey of Aging Males was carried out to determine the prevalence of lower urinary tract symptoms (LUTS) and sexual disorders in Asian men aged 50–80 years from five Asian countries: Hong Kong, Singapore, Malaysia, the Philippines and Thailand. The study investigated the relationship between lower urinary tract symptoms and sexual dysfunction. The results showed that the prevalence of LUTS varied among the countries, ranging from 14% in Singapore to 59% in the Philippines. Moderate to severe LUTS were reported by 36% of men aged 50-59 years, 50% aged 60-69 years and 60% aged 70-79 years. It concludes that an increase in severity of lower urinary tract symptoms (LUTS) was associated with an increased incidence of sexual dysfunction and the severity of LUTS increased with age (Li et al., 2005). The estimated prevalence of overactive bladder in man is slightly higher in Asian countries as compared to most of the European countries (Milsom et al., 2000). The lower prevalence of overactive bladder is observed in South Asian countries like India (13.6%), however in South East Asia it is 36.4% (Moorthy et al., 2003).

Tolterodine tartrate is an antimuscarinic agent indicated for the treatment of overactive bladder. Urgency is the core symptom of OAB, and thus, urgency-related micturitions can be defined as OAB micturitions. Tolterodine tartrate is a muscarinic receptor antagonist approved for marketing by the FDA in 1998. In a recent clinical trial, patients who received tolterodine tartrate reported fewer episodes of dry mouth than those who received conventional oxybutynin (Appell et al., 2001; Abrams et al., 1998). Patient treatment with α-blocker and continued therapy with tolterodine tartrate for 12 week, showed significantly greater improvements in OAB symptom (frequency and urgency episodes) compared with men receiving placebo plus α-blocker. This indicated synergistic effect of tolterodine tartrate to the action of α-blocker in the treatment of OAB (Chapple et al., 2009).
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The objective of the present study was to develop extended release stable formulations of tolterodine tartrate, which are cost effective and can help to improve the quality of life of the patients suffering from OAB. A simple and accurate UV spectrophotometric method was developed and validated to estimate tolterodine tartrate in bulk and in developed formulation. An accurate and precise HPLC method for estimation of tolterodine tartrate in plasma samples was developed and validated. Drug-excipients compatibility studies were carried out using differential scanning calorimeter, and infrared spectroscopy.

Extended release formulations of tolterodine tartrate were developed using different approaches. Single units system (tablets) of tolterodine tartrate was developed to control the drug release over 24 h. Synthetic and natural polymers (hydrophilic and hydrophobic) were used to prepare tablet matrix system by direct compression and hot melt technique. All prepared matrix formulations of tolterodine tartrate were evaluated for various pharmacopoeial and physical evaluations like appearance, weight variation, thickness, hardness, friability, drug content and in-vitro release studies. Multiparticulate system (pellets) of tolterodine tartrate was prepared by extrusion-spheronization technique using various waxes (Compritol® 888 ATO, glycerol monostearate, stearic acid and camauba wax). Batches were further modified by coating with ethyl cellulose to achieve the desired extended drug release profile. Prepared pellets were evaluated for various parameters such as angle of repose, bulk density, compressibility index, Hausner ratio, particle size, shape characterization, nominal granule fracture strength, drug content, in-vitro drug release, scanning electron microscopy, X-ray diffraction and differential scanning calorimetry. Microencapsulated system of tolterodine tartarate was also developed by solvent evaporation method. Microspheres were prepared using Eudragit® RL100, Eudragit® RL100 and ethyl cellulose. Developed microsphere formulation was subjected for various evaluation parameters such as yield, drug loading, particle size, drug entrapment efficiency, in-vitro drug release, differential scanning calorimetry and scanning electron microscopy. Selected formulation of extended release matrix tablet and pellets were subjected to in-vivo study.

The development of tolterodine tartrate extended release formulations for once daily dosing would be expected to improve patient compliance, quality of life and further relieve the symptoms of OAB. The concentration of the tolterodine tartrate will be above the required quantity in the blood while the patient will be is sleep; therefore, a bed time dosing of tolterodine tartrate extended release formulation will improve nighttime symptoms.