3. Research Envisaged

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage form. The development of oral controlled-release dosage forms has attracted much attention in past years. Matrix systems are one of the commonly used methods for developing controlled release drug delivery system employing hydrophilic or hydrophobic polymers, in which the mechanism of drug release is based on a combination of diffusion and erosion processes (Gren and Nyström 1999; Kiil and Dam-Johansen, 2003). Development of sustained release oral dosage forms is beneficial for optimal therapy regarding efficacy, safety and patient compliance (Chien 1990). The hydrophilic gel-forming 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 (Gao and Meury, 1996; Gohel and Amin, 1998). Hydrophobic wax matrix systems are being widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. Sustained release products are designed to bring the blood level of a drug immediately to therapeutic concentrations by means of an initial dose portion and then sustain this level for a certain predetermined time with the maintenance portion (Welling and Dobrinska, 1987). The principal goal of sustained release dosage forms is the improvement of drug therapy. Development of oral controlled release tablets for highly water-soluble drugs with extended release has always been a challenge to the pharmaceutical scientist.

Overactive bladder is a condition defined by its symptoms, those of urgency, with or without urge of urinary incontinence and often with frequency and nocturia or the involuntary loss of urine (Abrams, 2003). Thus, conditions limit and disrupt their sufferer’s everyday life and cause intense feeling of anxiety and depression. OAB is objectively demonstrable as a common medical and social disability. It affects people of all ages and occurs in both men and women; it occurs in up to 30% of individuals over 60 years of age with about two-thirds of sufferers being women. It is a chronic condition that often requires long-term treatment to maintain control of symptoms. Tolterodine tartrate is the most widely used drug for the treatment of OAB (Rovner et al., 2008). It is the first antimuscarinic agent developed specifically for the treatment of this...
disease. Unlike existing antimuscarinic agents, tolterodine tartrate shows functional selectivity for the bladder (Nilvebrant et al., 2000), so it produces a greater effect on the bladder than on salivation (Stahl et al., 1995). The extended release system having three potential benefits: sustained blood levels, attenuation of adverse effects and improvement of patient compliance are proposed in this study. The extended release, once daily therapy, can improve efficacy for reducing urge incontinence episodes with lower frequency of dry mouth as compared to immediate-release formulations that have to be taken twice daily (Nilvebrant et al., 2003, US. 6630162; Kreilgard et al., 2004, US. 6770295). This makes the patients, especially children, non-compliant. The dosing frequency and poor tolerability of tolterodine tartrate immediate release (IR) formulation has led to developing a new extended release formulations for once daily administration, to reduce dosing frequency, improve tolerability and efficacy of the drug. Such formulations can be expected to maximize convenience and improve compliance of the patient with OAB, which is a chronic disease that requires long term therapy. The sustained release system of this drug will provide a consistent dosage through sustaining an appropriate level of the drug over time that eliminates the need for night dosing. This will improve the quality of life of the patient by avoiding the night dose. No work on the extended release tablets of this drug is reported in the literature. Due to the advantages of multiparticulate system over single unit systems like less dependence on gastric emptying time due to small size, better distribution, less likely to cause local irritation and lower risk of dose dumping, it was also developed as one of systems. Microsphere systems have also gained a lot of attention due to their ability to control the drug release and enhance the therapeutic efficacy of a given drug. In this study, extended release systems of tolterodine tartrate was developed using different formulation approaches and process variables.

3.1 PLAN OF WORK

3.1.1 PREFORMULATION STUDIES

Preformulation studies of drug were carried out for identification of drug, characterization of drug and for compatibility study.

3.1.1.1 Identification of drug

Selected drug candidate (tolterodine tartrate) was identified by the following techniques:

- Ultraviolet spectroscopy (UV)
- Infrared spectroscopy (FTIR)
3.1.1.2 Characterization of the drug

Physicochemical properties of the drug were carried out by the following techniques:

- Melting point determination: Melting point was determined using melting point apparatus.
- Particle size determination (PSD): Particle size was determined using Malvern Mastersizer 2000.
- X-ray diffraction: The drug powder was investigated using XRD.

3.1.1.3 Compatibility study

Compatibility study of the drug and other polymers were performed by differential scanning calorimetry (DSC) technique and FTIR. The pure drug, pure polymers and the physical mixture of drug-polymers (1:1) were subjected to DSC and FTIR analyses.

3.1.1.4 Development of analytical method

Ultraviolet spectrophotometric and HPLC chromatographic techniques were developed for determination of the drug

- UV spectrophotometric method was developed for estimation of the drug in pure powder form and developed formulations.
- HPLC chromatographic analysis method was developed and validated for estimation of drug in plasma.

3.1.2 DEVELOPMENT OF SINGLE UNIT EXTENDED RELEASE SYSTEMS

Matrices tablets of the drug as extended release formulations were prepared using different type of polymers (hydrophilic matrices, hydrophilic natural gums and hydrophobic matrices).

3.1.2.1 Hydrophilic based matrix systems

Hydrophilic matrix systems were developed using different types and concentration of hydrophilic polymers (HPMC K4M, HPMC K100M, Acrypol® 971G and Carbopol® 71G).

3.1.2.2 Natural polysaccharide based matrix systems

New natural polysaccharide gums like Boswellia gum, Odina gum and Xanthan gum were used as a drug release retarding polymers to prepare matrix tablets.
3.1.2.3 Hydrophobic based matrix systems

Hydrophobic matrix tablets of drug were prepared by different techniques (hot melt technique and direct compression technique), using waxes.

3.1.3 EVALUATION OF THE DEVELOPED MATRIX TABLET SYSTEMS

- The developed single unit dosage form was subjected to the testing for both pharmacopoeial (drug content, hardness, friability, thickness and weight variation) and non-pharmacopoeial parameters (shape, colour, etc.).
- *In-vitro* drug release studies were carried out using USP apparatus type II.
- Swelling studies of the developed formulations were used to measure the weight gain by the tablets due to exposure to water.
- Drug release kinetics of prepared matrix tablets was evaluated using different mathematical equations to determine drug release mechanism.

3.1.4 DEVELOPMENT OF MULTIPARTICULATE SYSTEMS

Matrix pellets as extended release formulations were prepared by extrusion-spheronization technique using different waxes (e.g. stearic acid, glyceryl monostearate and carnauba wax). The selected formulations were further coated with a hydrophobic polymer, ethyl cellulose, using air suspension technique (GLATT particle coater).

3.1.5 EVALUATION OF THE DEVELOPED MULTIPARTICULATE SYSTEMS

- The prepared pellets were evaluated and characterized for various parameters, such as particle size, shape, angle of repose, bulk density, tapped density, drug content, elongation, rectang, roundness, granule fracture strength, Carr’s index, flowability, compressibility and Hausner ratio.
- *In-vitro* drug release studies of prepared pellets were carried out using USP apparatus type II.
- Drug release kinetics of prepared matrix pellets was evaluated using different mathematical equations to determine drug release mechanism.

3.1.6 DEVELOPMENT OF MICROENCAPSULATION SYSTEMS

Microencapsulation systems of the drug as extended release formulations were prepared using retarding polymers (e.g. ethyl cellulose, Eudragit® RL100 and Eudragit® RS100) by solvent evaporation technique.
3.1.7 EVALUATION OF THE DEVELOPED MICROSPHERES

- The prepared microsphere formulations were evaluated for various parameters, such as particle size, surface topography, yield, drug loading and entrapment efficiency.
- In-vitro drug release studies of prepared microspheres were carried out using Eppendorf tube shaking method (Berchane et al., 2010; Jordan et al., 2010).
- Drug release kinetics of prepared microspheres was evaluated using different mathematical equations to determine the mechanism of drug release.

3.1.8 IN-VIVO PHARMACOKINETICS STUDIES

- In-vivo pharmacokinetic studies of the placebo tablets, immediate release tablets, and test formulations were carried out in rabbits according to Institutional Animal Ethical Committee (IAEC).

3.1.9 STABILITY STUDY

- The accelerated stability studies of the selected formulations like tablets, pellets, and microspheres were conducted.