6. SUMMARY AND CONCLUSION

Oral drug administration is the most widely utilized route of administration among all the routes that have been employed for the systemic delivery of drugs. Oral controlled drug delivery systems have gained attention for more than past three decades due to their considerable therapeutic advantage over other systems.

The extended release systems are popular approaches, it enhance the drug action by maintaining the drug plasma concentration constant for 24 h and increased duration of therapeutic effect. Single dosing treatment improved efficiency of treatment with fewer amounts of drug, minimized side effects, less frequent administration, and increased patient convenience and compliance. It helps to avoid the side effect of multiple dosing. In addition, extended release system is more convenient for chronic diseases treatment; in which patient tend to forget night dosing. In extended release formulations, a portion of drug is released immediately, and the remaining parts of drug are released slowly over an extended period of time, normally over 12–18 h.

Overactive bladder is a syndrome of urine storage defined by the International Continence Society as a symptom syndrome suggestive of lower urinary tract dysfunction with or without urge urinary incontinence, usually with frequency and nocturia. Prevalence rates range between 12% and 17% in North America and Europe and are comparable among men and women. The prevalence of overactive bladder in South Asia countries like India (13.6%) is lower, however in South East Asia it is 36.4%. Prevalence of overactive bladder in man is slightly higher in Asian countries as compared with the most of European countries. OAB syndrome is a chronic condition that impairs health related quality of life and it could cause other disorder such as the increased risk of falls, fractures, urinary tract/skin infections, sleep disorders and depression. Overactive or unstable bladder is believed to be caused by uncontrolled detrusor contractions or instability during the filling phase. Antimuscarinics drugs exert their effects on OAB by inhibiting the binding of acetylcholine at muscarinic receptors M2 and M3 on detrusor smooth muscle cells and other structures within the bladder wall. M3 receptors in the human detrusor are thought to be most important for detrusor contraction. The medical treatment of urge
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Urinary incontinence with antimuscarinic (cholinergic) receptor antagonists has played a dominant role for many years, because these drugs block urinary bladder contractions.

Tolterodine tartrate was the selected drug for this study. It is one of the antimuscarinic drug used to treat OAB syndrome. It is the first drug in this class to be specifically developed to treat OAB. Tolterodine is highly effective in the treatment of OAB. It shows a greater selectivity for bladder smooth muscle than salivary glands, and it also shows more selectivity for the bladder over other tissues that contain muscarinic receptors. It significantly reduces the number of incontinence episodes and frequency of micturition.

Aim of the present study was to develop oral extended release systems of tolterodine to be used in the treatment of over active bladder. Tolterodine once daily formulations were developed and evaluated. Developed formulation would control the OAB syndrome and improve patient compliance. Tolterodine extended release formulations were developed using different systems and techniques. Hydrophilic and hydrophobic polymers were used to develop the formulations. Natural gums were used as retardant agents to achieve the proposed goal. Single unit systems (matrix tablet formulations), multi-particulate systems (matrix pellets formulations) and microencapsulation systems of tolterodine extended release formulations were developed. Different techniques to developed tolterodine extended release formulations were used (direct compression, hot melt and solvent evaporations units).

Preformulation studies of the tolterodine were performed using different instruments to identify the drug. Ultra-violet (UV), infrared (IR) spectrum, nuclear magnetic resonance (NMR), melting point, differential scanning calorimetry (DSC), particle size, and X-ray diffraction were carried out. The λ\text{max} absorbance of the drug in different solvent (distilled water, phosphate buffer pH 6.8 and methanol) was determined by scanning the drug in UV spectrum in the range of 200-400 nm. The obtained λ\text{max} of the drug was found to be 283 nm in phosphate buffer pH 6.8, methanol and distilled water. The DSC thermogram of drug showed endothermic peak at 213.63°C, corresponding to melting point (210°C-220°C) of the drug reported in literature. Particle size of drug was analyzed; the mean particle size of tolterodine tartrate obtained was 3.08 μm. The X-Ray diffraction of drug showed halo pattern, which indicated that the drug is disturbed homogeneously/molecularly in the polymer matrix.
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The Infrared spectroscopy of the drug and excipients physical mixture did not show any interactions between the tolterodine tartrate and other polymer excipients. The DSC thermograms of the physical mixture of the drug and all other excipients indicated the absence of any interaction between the drug and the polymer, as the endothermic peak corresponding to the melting point of the drug was retained in the thermograms, very slight change in the values were observed.

The collected odina gum was used as retardant gum. The mean particle size of the odina gum was found to be 200.82 μm. The viscosity and rheological properties of the gum was studied. The aqueous dispersion of the gum displayed non-Newtonian behaviour. The flow was pseudoplastic without thixotropy.

A simple, sensitive, rapid, precise, cost effective and reproducible UV spectrophotometric method was used to analyse tolterodine in bulk and in developed formulations. Standard plot curves of drug in different solvents (distilled water, phosphate buffer pH 6.8 and methanol) were obtained. The value of $E_{10}$ were found to 60, 50 and 70 in phosphate buffer pH 8.6, distilled water and methanol, respectively.

The HPLC method was developed and validated to determine the tolterodine in plasma samples collected for pharmacokinetics studies. The method was validated for linearity, accuracy and precision. The data confirmed linear relationships over the selected concentration range. The data obtained showed high correlation ($r^2 = 0.997$) and slope of 25.10. The intra-day and inter-day precision and accuracy of the method was studied. The precision determined at each concentration level, which does not exceed 10% of the relative standard deviation (R.S.D). The results revealed good precision and accuracy.

Matrix tablets exploiting the properties of various polymers were prepared for extended release of tolterodine tartrate. Hydrophilic matrix tablets are the most frequently manufactured and used for oral administration. Hydrophilic matrices do not disintegrate and the drug from matrix systems gets released over a defined period of time following exposure to water or after oral administration. This release depends on the polymer selection, formulation and process variable. Direct compression is the simplest and most frequently used technique in preparation of matrix tablets, which may involve of a blend drug with release retardant polymers and other additives.

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HPMC matrix systems allow greater control and reproducible drug release profiles by manipulation of its chemical and physical properties. HPMC K100 and HPMC K4M were used as retardants for the developed ER matrix tablets and evaluated. Different proportion of HPMC was blended with the drug and other additives, and then tablets were compressed by direct compression technique. All prepared HPMC formulations were subjected to the compendial and non-compendial test. Different proportion of HPMC K4M was used to prepare tablets of batches (TH1, TH3, TH5 and TH7) containing 31.5, 40, 50 and 60% w/w of HPMC K4M, respectively. The in-vitro drug release profile of HPMC K4M showed higher drug release in initial hours at the lower concentration of HPMC K4M. Batch TH5 showed drug retardation for over 24 hours. However batch TH7 showed extensive drug retardation as only 67.99±0.41% of drug was released after 12 hours. HPMC K100M was used to prepare tablets of batches (TH2, TH4, TH6 and TH8) containing 31.5, 40, 50 and 60% w/w of HPMC K100M, respectively. The drug release profile of HPMC K100M formulations showed more retardation then the HPMC K4M formulation. Batch TH6 was able to control drug release for over 24 hours and only 76.23±1.84% of drug was released after 12 hours; but the tablet of batch TH8 released 62.35±1.47% of drug after 12 hours. Swelling index results indicated that an increase in the amount of HPMC causes increase in swelling index. As time increases, the swelling index also increased. HPMC matrix tablets absorb water and swell and the drug release takes place by diffusion through the gel layer.

Carbopol® 71G and Acrypol® 971G is a synthetic high molecular weight cross-linked water-soluble poly (acrylic acid). Different proportion of Acrypol® 971G 40%, 50% and 60% w/w and Carbopol® 71G 40% and 50% w/w were used to prepared extended release matrix tablets of tolterodine by direct compression technique. The drug release results showed that drug retardation increased with increase in Acrypol® 971G or Carbopol® 71G proportions. Carbopol® 71G matrix tablets showed more retardation than Acrypol® 971G matrix tablets containing same level of polymers. Effect of the fillers was also studied e.g. TCA1 and TCA3 batches were prepared with 40 % w/w Carbopol® 71G. Batch TCA1 contained a mixture of Lactopress® and Avicel®, however, TCA3 contained only Lactopress® as filler. The drug release of TCA1 showed more retardation than TCA3 formulation. This may be attributed to higher solubility of the lactose than Avicel®.
Batches TAC3 and TCA3 which contain 60% w/w of Acrypol® 971G and 40% w/w Carbopol® 71G respectively, were selected as the optimum formulations due to their ability to control drug release for 24 hours. The swelling index of Acrypol® 971G and Carbopol® 71G matrix tablets showed a direct relationship with the polymer concentration. The filler also showed the effect on swelling index. Batch TCA3 containing only lactose as filler showed a higher swelling index compared with batch TCA2 which contained a mixture of Avicel® and Lactopress® as filler. Presence of water soluble lactose led to gain of more water, leading to higher swelling of the tablets.

Compritol® 888 ATO was used to prepare extended release matrix tablets by direct compression technique (DC) and by hot melt granulation technique (HM). Different proportion of Compritol® 888 ATO was used (30%, 40% and 50% w/w). The drug release from the formulations showed greater retardation with increase in Compritol® 888 ATO proportion. 50% w/w of Compritol® 888 ATO showed the best and consistent drug release profile extended up to 24 hours. Batches TC6 and TC5 were prepared with 40% w/w of Compritol® 888 ATO, but formulation TC6 contained Lactopress® as filler, however, in formulation TC5 a mixture of Lactopress® and Avicel® were used as fillers. TC6 showed a slightly faster drug release, than drug release from formulation TC5 (71.29%) at the end of 12 hours. This can be attributed to the higher water solubility of lactose than the Avicel®. It was also observed that the tablets prepared by hot melt technique showed more retardation than the tablets prepared by direct compression technique even when they contained same proportion of Compritol® 888 ATO. Batches TC3 and TC6 containing 50% and 40% w/w of Compritol® 888 ATO prepared by direct compression and hot melt granulation technique, respectively showed a drug release of 87.13 ± 0.93% and 74.91 ± 0.70% after 12 hours, respectively. Both the formulations showed the ability to sustain the drug release for 24 hours. Swelling index results indicated that the swelling process does not take place instantaneously and no matrix erosion was observed, hence the drug release was diffusion controlled only. Formulations prepared by direct compression showed more swelling index than formulations prepared by hot melt technique.

The use of naturally occurring hydrophilic biocompatible polymeric materials has been the recent focus in research. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media. An attempt to use odina gum as drug retardant was
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presently carried out. Matrix batches TG1, TG2, TG3 and TG4 containing 40%, 50%, 60% and 70% w/w of odina gum, respectively were prepared by direct compression. The drug release profile indicated that the odina gum can be used as release retarding agents. The drug release was inversely proportional to the concentration of odina gum in the batch. Batch TG4 containing 70% w/w of odina gum was selected as the optimum formulation as it gave the retarded drug release of 82.47 ± 1.56% after 12 hours. The swelling index of odina gum showed a direct relationship with gum concentration in the tablet.

Another natural gum of boswellia was also used for development of matrix tablet. Batches TG5, TG6 and TG7 containing 40%, 45% and 50% w/w of boswellia gum were prepared by direct compression. The drug release showed that the drug retardation increased with the increasing proportion of boswellia gum in the formulation. The batch TG7 containing higher amount of boswellia gum showed incomplete drug release at the end of 24 hours and only 65.67 ± 1.43% of drug was released after 24 hours. The results indicated that batch TG6 prepared with 45% w/w of boswellia gum was able to control the drug release effectively for 24 hours. The swelling study showed that the drug release from boswellia matrix tablets was due to erosion. It has been observed that the cumulative percent drug release decreased by increasing the gum concentration.

Different proportion of natural polysaccharide xanthan gum was also used to prepare extended release formulations of tolterodine. The batch TG8, TG9 and TG10 prepared with 30%, 40% and 50% w/w of xanthan gum respectively were formulated by direct compression technique. The drug release showed that the drug retardation has inverse relation with the amount of xanthan gum in the tablets. Batches TG8 and TG9 showed 90.74 ± 1.42% and 90.50 ± 1.83% of drug released after 10 hours, respectively. These batches were subjected to further modification by adding odina gum. Batch G10 showed good control of drug release over 24 hours; 85.44 ± 1.31% of drug released after 10 hours. Direct relationship was observed between swelling index and gum concentration. It has been observed that the cumulative percent drug release decreased with increasing concentration of gum and swelling index, which may be due to slow erosion of the gelled layer from the tablets containing higher amount of xanthan gum.

A combination of odina gum:xanthan gum was used to prepare matrix tablets, to modify the drug release profile of formulation TG8 and TG9 to the desired level. Batch TG11 containing
30:30% w/w and TG12 containing 30:40% w/w of odina gum:xanthan gum respectively, were prepared. The drug release from batches TG11 and TG12 showed 84.57 ± 4.66% and 80.65 ± 4.69% of drug released in initial 8 hours, respectively. Batch TG12 showed significant retardation in initial hours with increasing amount of odina gum proportion in the formulations. No remarkable improvement in drug retardation was observed. Swelling index results showed that the swelling of tablets was increased till 2-3 h following which there was a decrease in the swelling index due to dissolution/erosion of the gel layer.

To predict the drug release mechanism for developed matrix tablet formulations, the release data was analyzed using zero order, first order, Higuchi, Korsmeyer-Peppa’s and Hixon-Crowell models. The kinetic results showed that the lower concentration of HPMC K4M formulation TH3 and TH5 prepared with 40% and 50% w/w were fitted with first order equation; however batch TH7 containing higher concentration of HPMC K4M (60% w/w) followed Korsmeyer-Peppas equation with non-Fickian transport mechanism. All formulations of HPMC K100M were fitted with Korsmeyer-Peppas equation with non-Fickian transport being the dominant mechanism of drug release. Batch TAC2 containing 50% w/w of Acrypol® 971G followed Korsmeyer-Peppas equation with non-Fickian transport mechanism of drug release. Batch TAC3 (60% w/w) of Acrypol® 971G followed first order equation of drug release. All formulations of Carbopol® 71G followed Korsmeyer-Peppas equation with non-Fickian transport mechanism of drug release. Batches TC1, TC2 and TC3 containing 30%, 40% and 50% w/w of Compritol® 888 ATO prepared by direct compression followed first order equation of drug release. Batch TC4 (30% w/w of Compritol® 888 ATO) prepared by hot melt technique was found to be following first order equation of drug release. Batches TC5 and TC6 followed Korsmeyer-Peppas with non-Fickian transport mechanism of drug release. Batches TG1 and TG2 prepared with lower concentration of odina gum followed Korsmeyer-Peppas equation and drug release mechanism was diffusion. Batch TG3 and TG4 containing higher concentration of odina gum followed first order equation of drug release. All boswellia gum formulations TG5, TG6 and TG7 showed best fit into Korsmeyer-Peppas and diffusion was the predominant mechanism of drug release. Lower concentration of xanthan gum batch TG8 and TG9 showed best fit into first order of drug release. Batch TG10 prepared with higher concentration of boswellia gum followed Korsmeyer-Peppas equation and non-Fickian transport was the
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predominant mechanism of drug release. Formulations formulated with combination of odorina gum:xanthan gum (TG11 and TG12) showed best fit into first order drug release.

Multiparticulate system i.e. pellets of the tolterodine tartrate were also developed using extrusion and spheronization techniques. Different combination of waxes Compritol® 888 ATO, glyceryl monostearate, stearic acid and carnauba wax and MCC were used to prepare tolterodine matrix pellets for controlling the drug release. Prepared pellets were evaluated for various parameters such as angle of repose, bulk density, tap density, compressibility index, shape character, particle size and drug content. The angle of repose obtained for all prepared pellets ranged between 14.40° to 24.19°. The values were well below 30°, indicating good flowability of pellets. The bulk and tapped densities of the pellets containing higher amount of MCC showed higher values in comparison to pellets containing low proportion of MCC. The Carr's index for the prepared pellets ranged from 1% to 7% which was well below 15% indicating good flowability of the pellets for all batches. The particle size and span of the pellets containing MCC showed reduction in the particle size with increase in MCC portion. Shapes of the pellets among all the batches were found to be uniform, which indicated the uniformity in the preparation of the pellet. Results of roundness, elongation and rectang indicated that roundness of the pellets was largely dependent on the proportion of MCC in the pellets. The result of the nominal granule fracture strength increased on increasing the fraction of Compritol® 888 ATO and carnauba wax in formulation. Formulations containing glyceryl monostearate showed decrease in nominal granule fracture strength with increasing glyceryl monostearate proportion. Drug content for all prepared pellets was in the range of 96.03 % ±1.91% to 99.03±1.42%.

The results of FTIR studies of the pure drug and of prepared matrix pellets of drug and polymers physical mixture were analyzed. It was observed that there was no significant shift of various peaks. So the drug was compatible with the polymers. DSC thermogram was determined for pure drug and for prepared matrix pellets. The DSC results showed no endothermic melting point of the drug in the prepared pellets formulations; indicating the dispersion of drug in the wax matrix.

In-vitro dissolution studies of the prepared matrix pellet formulations were carried out. The obtained results showed that the pellet formulations of MCC, Compritol® 888 ATO, glyceryl
monostearate, stearic acid and camauba wax could not control drug release, and most of the drug was released within two hours.

To prevent the initial burst release of the drug, TCR2 pellets prepared with 60% of camauba wax and TMC1 pellets prepared with MCC, were selected for barrier coating of the pellets with different ratio of ethyl cellulose to sustain the drug release. The pellets were coated with ethyl cellulose solution to different coating thickness as TCR2 coated till 13% w/w weight gain and TMC1 coated till 6, 12 and 18% w/w weight gain. The camauba wax coated pellet formulation TCR6 was significantly able to retard the release of tolterodine up to 24 hours, with 80.45±1.41% of drug released after 12 hours. However, MCC coated pellets (TMC2, TMC3 and TMC4) could not achieve the desired retardation even at higher coating level (18% w/w of EC), with 98.86±0.39%, 98.14±0.42% and 95.74±2.57% of drug release at the end of 6 hours, respectively. MCC and camauba wax coated pellets were evaluated for different parameters; it was observed that the angle of repose of coated pellets was less than uncoated pellets, which indicate the enhanced flowability of coated pellets. The nominal granule fracture strength of coated pellets got increased significantly when it was coated with ethyl cellulose.

The kinetics of drug release from pellets was studied using zero order, first order, Korsmeyer-Peppas, Higuchi and Hixson-Crowell drug release equations. Formulations TCO2, TCO3, TGM1, TGM, TS1, TCR1, TCR4, TCR5, TMC1 and TMC4 followed Korsmeyer-Peppas and R^2 value ranged between 0.983 and 0.906. The diffusion was the predominant drug release mechanism. Formulations TCR2 and TCR3 followed first order release equation with R^2 values of 0.992 and 0.979, respectively. It indicates that the drug release from the camauba wax pellets was via diffusion of the drug from wax matrix. TCR6 camauba wax pellets coated with ethyl cellulose was best fit with Korsmeyer- Peppas equation. It showed high linearity with R^2 value of 0.974 and n value of 0.76. This indicates that the drug release was due non-Fickian transport mechanisms.

Surface topography of matrix pellets of Compritol® 888 ATO, glycercyl monostearate and stearic acid were studied by SEM. The pellets showed a spherical shape. SEM images of the camauba wax coated pellets (TC6A6) before and after dissolution were studied. Photomicrographs of the camauba wax and MCC prepared pellets showed spherical shapes. The camauba wax present in the core pellets is hydrophobic in nature and does not allow the
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permeation of water inside the pellets keeping the shape of the pellets intact even after 24 hour of dissolution studies. However pores were observed in the outer coat, which indicated that the drug was released through these pores. SEM of MCC coated pellets (TMC4) showed spherical shape initially but pellets burst after 24 hour of dissolution studies. This may be due to the hydrophilic nature of MCC which allowed dissolution medium to permeate into the pellets core thus generating pressure leading to bursting of the pellets. This led to faster drug release from the pellets.

XRD diffractogram of prepared pellets showed loss of most of the peak present in the pure drug indicating the loss of crystallinity of the drug due to dispersion of the tolterodine in the pellets.

Microsphere formulations of tolterodine were prepared with Eudragit® RL100, Eudragit® RS100 and ethyl cellulose, by solvent evaporation method. The prepared formulations were evaluated for different parameters, such as yield percentage, mean particle size, drug loading and drug efficiency. The percentage yield of the Eudragit® RL100 microsphere was found to be in the range of 27.30 – 74.22%. The percentage yield for Eudragit® RS100 microspheres was found to be 74.83–87.85% and for ethyl cellulose microspheres it was between 76.72 and 97.62%. The percentage yield increased with increase in the polymer ratio.

The mean particle size of Eudragit® RL100 microsphere was found to be between 107.02 μm and 312.54 μm. The particle size of Eudragit® RL100 microspheres decreased with increasing agitation speed of mechanical stirrer. Particles of Eudragit® RS100 microspheres was found to be 29.83–130.99 μm. Ethyl cellulose microsphere particle size was found to be 167.32–236.77 μm. The particle size of the Eudragit® RL100, Eudragit® RS100 and ethyl cellulose microspheres showed an increase in particle size with increase in polymer proportion.

The drug entrapment efficiency of the Eudragit® RL100 microsphere was found to be between 33.32±0.96% and 73.63±0.84%. The drug loading decreased with increasing proportion of Eudragit® RL100. However the drug entrapment efficiency increased. The drug entrapment efficiency of Eudragit® RS100 microsphere was between 32.80±0.72% and 82.00±1.31%. The drug entrapment efficiency of ethyl cellulose microsphere was found to be between 37.74±0.92% and 85.43±0.89% which was directly proportional to the polymer proportion in the microsphere.
Drug release studies of Eudragit® RL100 microsphere formulations (TEL1, TEL3, TEL4, TEL5 and TEL6) revealed an initial burst release which may be attributed to surface loaded drug. Batch TEL1 containing the lowest proportion of Eudragit® RL100 showed the highest burst of drug release in first 6 hours. However formulations containing higher proportion of polymer showed incomplete drug release after 24 hours (TEL6 and TEL7). Drug release studies of Eudragit® RS100 microsphere formulations (TES1, TES2, TES3, TES4 and TES5) showed sustained drug release with increasing proportion of Eudragit® RS100. Initial burst release of the drug from Eudragit® RS100 microsphere formulations was observed but this effect was lesser than the microspheres prepared using polymer Eudragit® RL100. This may be due to the lower water permeability of polymer Eudragit® RS100.

The microsphere formulations of Eudragit® RS100 showed more retardation in drug release than the Eudragit® RL100 microspheres. This may be due to the differences in the features and the chemical structures of different Eudragit® grades. Eudragit® RL100 contains higher amount of quaternary ammonium groups, which makes the microsphere surface more permeable and facilitates the diffusion of a part of the drug to the surrounding medium. Drug release of ethyl cellulose microsphere formulations did not show any initial burst release. Ethyl cellulose microspheres showed more retardation than microspheres prepared with Eudragit® RL100 and Eudragit® RS100. Drug release from ethyl cellulose microsphere batches showed an incomplete release even at the end of 24 hours, due to decrease in the penetration of the dissolution medium in the hydrophobic ethyl cellulose. This led to slow diffusion of the drug from microsphere particles. The increase in the microsphere particle size decreased the effective surface area which ultimately decreased the drug release rate from various microsphere batches.

The drug release mechanisms of Eudragit® RL100 microspheres batches (TEL1, TEL3, TEL4, TEL5 and TEL6) showed higher correlation with the first order model with $R^2$ value between 0.895 and 0.959. The drug release from Eudragit® RS100 microsphere batches (TES1, TES4 and TES5) showed first order drug release with $R^2$ value between 0.930 and 0.965. However other Eudragit® RS100 microspheres batches (TES2 and TES3) were fitted with Higuchi model of drug release with $R^2$ value of 0.970 and 0.968 respectively, indicating that the mechanism of the drug release was diffusion controlled. Ethyl cellulose microsphere batches (TEC1 and TEC3), showed higher correlation with the Korsmeyer-Peppas model with $R^2$ 0.980.
and 0.937, respectively and diffusion was the predominant mechanism of drug release. Batches (TEC4 and TEC6) showed higher correlation with the Higuchi model with $R^2$ 0.941 and 0.986 respectively, which indicated that the drug release was by diffusion mechanism. However, batch TEC5 was fitted well with Korsmeyer-Peppas model $R^2$ value of 0.945 and anomalous transport release mechanism.

The DSC thermogram of Eudragit® RL100, Eudragit® RS100 and ethyl cellulose microsphere formulations showed that no endothermic peak corresponding to the peak of tolterodine tartrate was observed. This implied the absence of free drug and the molecular dispersion of the drug in the polymeric microspheres.

Scanning electron microscopy (SEM) of the microsphere formulations was carried out at various magnifications before and after dissolution, to observe the surface of the microspheres. SEM of Eudragit® RL100 microspheres were spherical in shape with rough surface. Some crystalline drug was found adhering to the surface of the microsphere. It explains the initial burst drug release from Eudragit® RL100 of microsphere batches. The microsphere surface after drug release studies showed presence of pores on the surface, which may be due to solvent penetration into the microspheres resulting in a release of drug through these pores. The scanning electron microscopy of the Eudragit® RS100 microsphere formulations showed the spherical shape and rough surface which may be due to the surface-associated drug particles. The morphology of Eudragit® RS100 microsphere formulation after dissolution showed an aggregation of the microsphere particles with increase in the porosity of the surface. The SEM of the ethyl cellulose microsphere formulations showed spherical microsphere with smooth surface, which prevent the penetration of the solvent into the microsphere and a retarded drug release. The surface morphology study of ethyl cellulose formulation after dissolution showed pores on the microsphere surface, which were responsible for the diffusion of the drug from the microspheres.

Comparative pharmacokinetic studies were carried out to estimate the drug plasma concentration of tolterodine tartrate used for treatment of overactive bladder syndrome through different routes of administration in which animals were divided into 6 groups:

- Group I-pharmacokinetics placebo tablets: Placebo tablets were orally administered to the rabbits. No drug peak was observed.
**Group II-Pharmacokinetics of immediate release tablets:** An immediate release tablet formulation was administered to the rabbits. The $C_{\text{max}}$ was found to be 5245.27 (ng/ml) at $T_{\text{max}}$ of 0.5 h. The mean $AUC_{\infty}$ was found to be 9291.93 (ng/ml*h), the MRT and $T/2$ was 4.93 and 3.93 h, respectively.

**Group III-pharmacokinetics of extended release tablets:** The extended release formulation of boswellia gum based matrix tablets (TG6) was administered to the rabbits. The $C_{\text{max}}$ of ER test formulation tablets (TG6) was found to be 2610.76 (ng/ml) at $T_{\text{max}}$ of 6 h. The mean $AUC_{\infty}$ was found to be 17985.73 (ng/ml*h), the MRT and $T/2$ was 12.11 and 7.22 h, respectively. The results showed significantly lower $C_{\text{max}}$, delayed $T_{\text{max}}$ and more $AUC_{\infty}$ of TG6 formulation in comparison to the IR reference formulation. The extended release was obtained for the tablet formulation TG6.

**Group IV-pharmacokinetics of matrix pellets:** In this group the extended release formulation of camauba wax coated pellets (TCR6) was administered to the rabbits. The $C_{\text{max}}$ of ER test formulation pellets (TCR6) was found to be 1946.83 (ng/ml) at $T_{\text{max}}$ of 4 h. The mean $AUC_{\infty}$ was found to be 17795.80 (ng/ml*h), the MRT and $T/2$ was 9.55 and 5.15 h, respectively. The results showed significantly lower $C_{\text{max}}$, delayed $T_{\text{max}}$ and the $AUC_{\infty}$ of ER camauba wax coated pellets (TCR6). These values were more than the values obtained for IR reference formulation. The developed pellets formulation TCR6 also showed an extended drug release in-vivo.

**Group V-pharmacokinetics of intravesical:** The tolterodine tartrate solution was administered directly to the urinary bladder of rabbits through a catheter, held in the bladder for two hours, and then released by urination. The mean of $C_{\text{max}}$ was found to be 62.32 (ng/ml) at $T_{\text{max}}$ of 1 h. The mean $AUC_{\infty}$ was found to be 181.40 (ng/ml*h), the MRT and $T/2$ was 4.26 and 2.77 h, respectively. The results showed that the $C_{\text{max}}$ and $AUC_{\infty}$ of intravesical administration was very less compared to other orally administered formulations TG6 and TCR6, which indicate that the drug was not absorbed properly from the bladder.

**Group VI-pharmacokinetics of rectal suppositories formulation:** The rectal suppositories of tolterodine were administered to the rabbits. The $C_{\text{max}}$ of the
suppository formulation was found to be 12.94 (ng/ml) at Tmax of 0.5 h. The mean AUC∞ was found to be 30.51 (ng/ml*h), the MRT and T ½ was 2.49 and 1.60 h, respectively. The result showed that the Cmax and AUC∞ of suppository formulation was the lowest among other administered formulations. Thus confirming that the developed extended release oral formulations showed a sustained drug release for prolonged period.

Stability testing provides evidence of the quality of drug substance or drug product changes with time under the influence of various environmental conditions such as temperature and relative humidity. The stability study of the developed matrix tablets prepared with Compritol® 888 ATO polymer, (TC6), carnauba wax coated pellets formulation (TCR6) and microsphere formulation (TES3) were subjected to the accelerated stability studies by keeping them at 40°C and 75% RH for 3 months. Samples were collected and analyzed at 0 time, 1, 2, and 3 months.

The results indicated no significant changes in the physical appearance, weight variation, thickness, hardness, friability and drug content of the tested Compritol® 888 ATO matrix tablet. All DSC thermograms indicate overlapping of the endothermic peaks obtained at 0 time. Stability study for matrix tablets (TC6) indicated that the developed extended release Compritol® 888 ATO matrix tablets are stable. The stability study of matrix pellets did not show any significant change in the drug content and the DSC thermogram, even after keeping the test formulation for 0 time, 1, 2, and 3 months at 40°C and 75% RH. This indicated the stability of carnauba wax pellets (TCR6) formulation. The Eudragit® RS100 microsphere batch (TES3) was found to be stable. No significant change in drug content and particle size was observed. XRD of the samples also showed no change in pattern at 0 time. DSC thermogram indicated that all the endotherms of the samples after 1, 2 and 3 months did not show any change.

Following is concluded from these studies:

- An optimized tablets batch TH4 and TH5 containing 40% w/w of HPMC K100MC and 50% w/w of HPMC K4MC respectively, was developed as an extended release formulation of tolterodine.
- Tablets of batches TAC3 and TCA3 containing 60% w/w of Acrypol® 971G and 40% w/w of Carbopol® 71G, respectively, were selected as the optimum formulations.
Summary and Conclusion

- Hot melt technique tablets (TC3) showed more retardation than the tablets prepared by direct compression technique. The approaches of hot melt technique using wax (Compritol® 888 ATO) can be used to develop the extended drug delivery system for hydrophilic drugs.

- Natural gums e.g. odina gum (TG4), boswellia gum (TG6) and xanthan gum (TG10) were successfully optimized to be used as a hydrophilic matrix for the preparation of a once-daily extended release formulation. Boswellia gum showed better retardation properties, which can be used to develop the sustained release drug delivery system for hydrophilic and hydrophobic drug. It is cost effective and safer than synthetic polymers used in marketed products.

- The carnauba wax coated pellets (TCR6) were able to significantly retard the release of tolterodine tartrate during the 24 hours.

- Microsphere formulations of Eudragit® RL100 and Eudragit® RS100 were developed and evaluated as extended release formulation TEL5, TES4.

- The animal studies of the developed matrix tablets TG6 and matrix pellets TCR6 showed extended release of the drug.

- The stability studies of the different formulations indicate the stability of the formulations.

Overall, it may be concluded that extended release formulations of tolterodine tartrate were successfully developed using various techniques (tablets, pellets and microspheres).