REVIEW OF LITERATURE

Jacob et al, 2005 studied single dose pharmacokinetics of Bioadhesive Itraconazole tablets in healthy volunteers. A single-dose, randomized, two-way crossover study in sixteen healthy volunteers was conducted at the Shandon Clinic, Ireland. Volunteers were dosed either with 100mg Sporanox® capsules or Spherazole™ Tablets 20 minutes after a standard breakfast. Blood samples were collected at appropriate intervals and plasma Itraconazole and hydroxyItraconazole levels were determined by LC-MS/MS. Spheres’ bioadhesive formulation resulted in greater bioavailability than the Sporanox® capsules, in terms of C_max and AUC, for both Itraconazole (parent compounds) and hydroxyItraconazole (active metabolite). Analysis of the log transformed data demonstrated a 17% reduction in C_max variability and 37% reduction in AUC variability based on coefficient of variation for Spherazole™ compared to Sporanox® capsules.

Mukherjee et al, 2009 studied design and evaluation of Itraconazole loaded solid lipid nanoparticulate system for improving the antifungal therapy. The microemulsion mediated nanoparticle preparation methodology ensured high drug loading (80%), low and narrow size distribution and provided a reproducible and fast production method. They studied feasibility and suitability of lipid based colloidal drug delivery system, employing optimize design to develop a clinically useful nanoparticle system with targeting potential.

Prasad et al, 2010 prepared and characterize Itraconazole solid dispersions for improved oral bioavailability. The formulations have demonstrated the significant improvement of bioavailability (AUC=14384ng/h/ml) compared to plain drug suspension (AUC=4384ng/h/ml). These results demonstrated the efficacy of solid lipid dispersions for the enhancement of oral bioavailability of Itraconazole by increasing its aqueous solubility

Madgulkar et al, 2008 studied Formulation Development of Mucoadhesive Sustained Release Itraconazole Tablet Using Response Surface Methodology. The optimized mucoadhesive formulation was orally administered to albino rabbits, and blood samples collected were used to determine pharmacokinetic parameters. The solid dispersion markedly enhanced the dissolution rate of Itraconazole. The Bioadhesive strength of formulation was found to vary linearly with increasing amount of both
polymers. Formulations exhibited drug release fitting Peppas model with value of $n$ ranging from 0.61 to 1.18. Optimum combination of polymers was arrived at which provided adequate bioadhesive strength and fairly regulated release profile. The experimental and predicted results for optimum formulations were found to be in close agreement. The formulation showed $C_{\text{max}}\ 1898\pm75.23 \ ng/ml$, $t_{\text{max}}$ of the formulation was 2 h and AUC was observed to be 28604.9 ng h/ml.

Shim et al, 2006 performed characterization of semisolid dosage forms prepared by hot melt technique. In addition, the distinctive functional peaks and chemical shifts of Itraconazole were well retained after processing into semisolid preparations. They concluded from the data that Itraconazole was stable during incorporation into semisolid preparations by the hot melt technique. In particular, Itraconazole semisolid preparations composed of polysorbate 80, fatty acids and organic acids showed good solubility and dissolution when dispersed in an aqueous medium. It was anticipated that the semisolid dosage forms would be industrially applicable to improving the bioavailability of poorly water-soluble drugs.

Punitha and Girish, 2010 reviewed polymers in mucoadhesive buccal drug delivery system. The mucoadhesive interaction is explained in relation to the structural characteristics of mucosal tissues and the theories & properties of the polymers. The success and degree of mucoadhesion bonding is influenced by various polymer-based properties. Evolution of such mucoadhesive formulations has transgressed from first-generation charged hydrophilic polymer net-works to more specific second-generation systems based on lectin, Thiol and various other adhesive functional groups. They reviewed the mucoadhesive polymeric platforms, properties & characteristics to provide basics to the young scientists, which will be useful to circumvent the difficulties associated with the formulation design.

Ahmed et al, 2010 Formulate and evaluate gastric mucoadhesive drug delivery systems of Captopril. The alginate-cellulose acetate phthalate beads showed the better sustained release as compared to all other alginate polymer combinations. Regression analysis showed that the release followed zero order kinetics in 0.1 N hydrochloric acid (pH 1.2). The objectives achieved were formulation, evaluation and usefulness of sodium
alginate mucoadhesive beads of captopril with different mucoadhesive polymers, findings of which can be applied for sustained delivery of drugs with mucoadhesion.

Hong et al, 2006 developed a new self-emulsifying formulation of Itraconazole with improved dissolution and oral absorption. The results demonstrates that the SEDDS of Itraconazole composed of Transculot, Pluronic L64 and tocopherol acetate greatly enhanced the bioavailability of Itraconazole after the dose, particularly not influenced by food intake or not. Thus, the system may provide a useful dosage form for oral water-insoluble drug without food effect.

Rabinow et al, 2007 studied Itraconazole IV nanosuspension enhances efficacy through altered pharmacokinetics in the rat. Their goal was to evaluate an intravenous Itraconazole nanosuspension dosage form, relative to a solution formulation, in the rat. Itraconazole was formulated as a nanosuspension by a tandem process of microcrystallization followed by homogenization. Acute toxicity, pharmacokinetics, and distribution were studied in the rat, and compared with a solution formulation of Itraconazole. Efficacy was studied in an immunocompromised rat model, challenged with a lethal dose of either Itraconazole-sensitive or Itraconazole-resistant C. albicans. Itraconazole nanosuspension was tolerated at significantly higher doses compared with a solution formulation. Pharmacokinetics of the nanosuspension were altered relative to the solution formulation. $C_{\text{max}}$ was reduced and $t_{1/2}$ was much prolonged. The higher dosing of the drug, enabled in the case of the nanosuspension, led to higher kidney drug levels and reduced colony counts. Survival was also shown to be superior relative to the solution formulation. Thus, formulation of Itraconazole as a nanosuspension enhances efficacy of this antifungal agent relative to a solution formulation, because of altered pharmacokinetics, leading to increased tolerability, permitting higher dosing and resultant tissue drug levels.

Jung et al, 1999 studied Enhanced solubility and dissolution rate of Itraconazole by a solid dispersion technique. The aim of the study was to improve the solubility and dissolution rate of a poorly water-soluble drug, Itraconazole, by a solid dispersion technique. Solid dispersion particles of Itraconazole were prepared with various pH-independent and dependent hydrophilic polymers and were characterized by differential scanning calorimetry, powder X-ray diffraction and scanning electron microscopy. Of the
polymers tested, pH-dependent hydrophilic polymers, AEA® and Eudragit® E 100, resulted in highest increases in drug solubility (range, 141.4–146.9-fold increases). The shape of the solid dispersion particles was spherical, with their internal diameter ranging from 1–10 mm. The dissolution rate of Itraconazole from the tablets prepared by spray drying (SD-T) was fast, with 90% released within 5 min. SD-T prepared with AEA® or Eudragit® E 100 at a 1:1 drug to hydrophilic polymer ratio (w:w) showed approximately 70-fold increases in the dissolution rate over a marketed product.

Yang et al, 2008 studied High bioavailability from nebulized Itraconazole nanoparticle dispersions with biocompatible stabilizers. A nebulized dispersion of amorphous, high surface area, nanostructured aggregates of Itraconazole (ITZ):mannitol:lecithin (1:0.5:0.2, w/w) yielded improved bioavailability in mice. The ultra-rapid freezing (URF) technique used to produce the nanoparticles was found to molecularly disperse the ITZ with the excipients as a solid solution. Upon addition to water, ITZ formed a colloidal dispersion suitable for nebulization, which demonstrated optimal aerodynamic properties for deep lung delivery and high lung and systemic levels when dosed to mice. The ITZ nanoparticles produced supersaturation levels 27 times the crystalline solubility upon dissolution in simulated lung fluid. A dissolution/permeation model indicated that the absorption of 3µm ITZ particles is limited by the dissolution rate (BCS Class II behavior), while absorption is permeation-limited for more rapidly dissolving 230nm particles. The predicted absorption half-life for 230nm amorphous ITZ particles was only 15 min, as a result of the small particle size and high super-saturation, in general agreement with the in vivo results. Thus, bioavailability may be enhanced, by decreasing the particle size to accelerate dissolution and increasing permeation with (1) an amorphous morphology to raise the drug solubility, and (2) permeability enhancers.

Beule, 1996 studied pharmacology clinical experience and future development of Itraconazole. Itraconazole is an orally active, broad-spectrum, triazole antifungal agent which has a higher affinity for fungal cytochrome P-450 than ketoconazole but a low affinity for mammalian cytochrome P-450. Itraconazole has a broader spectrum of activity than otherazole antifungals and shows interesting pharmacokinetic features in terms of its tissue distribution. These properties have resulted in reduced treatment times for a number of diseases such as vaginal candidiasis, as well as effective oral treatment of several deep mycoses, including aspergillosis and candidiasis.
Hire et al, 2007 studied microparticulate drug delivery system for topical administration of Itraconazole. The microemulsion-based gels were evaluated for rheological behavior, in-vitro permeation studies and in-vitro antifungal activity. The in-vitro permeation studies was carried out on human cadaver skin, mounted on Keshary-Chien diffusion cell using 10% v/v methanolic solution of pH 1.2 phosphate buffer as diffusion medium and Candida albicans as a model fungus to evaluate the antifungal activity of Itraconazole through the optimized formulations using cup plate method. Statistically significant increase in in-vitro permeation rate was found among the laboratory microemulsion based gel formulated when compared with conventional cream formulation. The rheological behavior of the prepared systems showed pseudoplastic (shear thinning) flow pattern. The in-vitro antifungal activity of Itraconazole was found to be significant with microemulsion based gel. The microemulsion based gel is better choice of vehicle for delivery of Itraconazole as topical drug delivery system.

Miyake et al, 1999 studied characterization of Itraconazole/2-hydroxypropyl-β-cyclodextrin inclusion complex in aqueous propylene glycol solution. The interaction of Itraconazole, a triazole antifungal agent, with 2-hydroxypropyl-b-cyclodextrin (HP-β-CyD) in water and 10% v/v propylene glycol:water solution at pH 2.0 was investigated by the solubility method and ultraviolet and 1H-nuclear magnetic resonance (NMR) spectroscopies. The solubility of Itraconazole in water significantly increased as the concentrations of HP-β-CyD was augmented, showing an AP type phase solubility diagram. The upward curvature closely corresponded to the simulation curve which was calculated on the basis of the 1:2 (guest:host) complexation model. The 1:2 complex was formed even in the presence of 10% v:v propylene glycol, although the co-solvent system made the interaction with HP-β-CyD weaker due to the competitive inclusion. The ultraviolet spectroscopic studies also supported the 1:2 complex formation of Itraconazole with HP-β-CyD in 10% v/v propylene glycol:water solution at pH 2.0. The 1H-NMR spectroscopic studies suggested that the triazole and triazolone moieties of Itraconazole are involved in the 1:2 inclusion complexation.

Kapsi et al, 2001 studied Processing factors in development of solid solution formulation of Itraconazole for enhancement of drug dissolution and bioavailability. This study investigated solid solutions of Itraconazole, a water insoluble antifungal, for improved dissolution and improved bioavailability. Influence of processing factors on
drug and carrier properties in solid solution and subsequently on drug dissolution behavior was also studied. An optimized solid solution formulation was compared with marketed product in healthy human subjects under fasted and fed conditions for bioequivalency. Polyethylene glycol (PEG) and drug were made into a solid solution at 120 °C. The cooled, solid solution was then ground into granules of different sizes. Solid solutions of lower drug concentration dissolved at a faster rate, and drug dissolution improved considerably with increasing molecular weight of PEG. Initial treatment of Itraconazole with the wetting agent/cosolvent glycerol prior to making Itraconazole into a solid solution improved drug dissolution, and also reduced the PEG amount required to dissolve drug to form solid solution. Addition of a polymer such as HPMC to the solid solution eliminated precipitation of drug following dissolution. As the granule size of the solid solution was reduced, precipitation of drug during dissolution became prominent.

Shao et al, 2007 studied recent advances and challenges in the treatment of invasive fungal infections. The frequency of invasive fungal infections (IFI) has increased over the last decade with the rise in at-risk populations of patients. The morbidity and mortality of IFI are high and management of these conditions is a great challenge. With the widespread adoption of antifungal prophylaxis, the epidemiology of invasive fungal pathogens has changed. Non-\textit{albicans} Candida, non-\textit{fumigatus} Aspergillus and moulds other than Aspergillus have become increasingly recognised causes of invasive diseases. These emerging fungi are characterised by resistance or lower susceptibility to standard antifungal agents. Invasive infections due to these previously rare fungi are therefore more difficult to treat. Recently developed antifungal agents provide the potential to improve management options and therapeutic outcomes of these infections. The availability of more potent and less toxic antifungal agents, such as second-generation triazoles and echinocandins, has led to considerable improvement in the treatment of IFI. They reviewed the changing spectrum of invasive mycosis, the properties of recently developed antifungal agents and their role in the management of these infections.

Junginger et al, 1999 studied recent advances in buccal drug delivery and absorption \textit{in-vitro} and \textit{in-vivo} studies. Their aim was to characterize transport of fluorescein isothiocyanate (FITC)-labelled dextrans of different molecular weights as model compounds for peptides and proteins through buccal mucosa. The penetration of
these dextrans through porcine buccal mucosa (a nonkeratinized epithelium, comparable to human buccal mucosa) was investigated by measuring transbuccal fluxes and by analyzing the distribution of the fluorescent probe in the epithelium, using confocal laser scanning microscopy for visualizing permeation pathways. The results revealed that passage of hydrophilic compounds such as the FITC–dextran through porcine buccal epithelium is restricted to permeants with a molecular weight lower than 20 kDa. The permeabilities of buccal mucosa for the 4 and 10 kDa FITC–dextran (of the order 28 of 10 cm/ s) were not significantly different from each other or from the much smaller compound FITC. The confocal images of the distribution pattern of FITC–dextran showed that the paracellular route is the major pathway through buccal epithelium. In the in vivo part of this study, buccal delivery of FITC-labelled dextran 4400 (FD4) and the peptide drug buserelin was investigated in vivo, in pigs. The delivery device consisted of an application chamber with a solution of FD4 or buserelin, and was attached to the buccal mucosa for 4 h using an adhesive patch. A randomized cross-over study including intravenous administration and buccal delivery without and with 10 mM sodium glycodeoxycholate (GDC) as an absorption enhancer was performed in pigs. After buccal administration, steady-state plasma levels were rapidly achieved. Co-administration of 10 mM GDC increased the absolute bioavailability from 1.860.5 to 12.762.0% for FD4. They concluded that buccal administration is a suitable route for the delivery for macromolecules and hydrophilic compounds such as peptide drugs.

Perioli et al, 2004 developed mucoadhesive patches for buccal administration of Ibuprofen. A new formulation for topical administration of drugs in the oral cavity has been developed using several film-forming and mucoadhesive polymers. The films have been evaluated in terms of swelling, mucoadhesion and organoleptic characteristics. The best film, containing polyvinylpyrrolidone (PVP) as film-forming polymer and carboxymethylcellulose sodium salt (NaCMC) as mucoadhesive polymer, was loaded with Ibuprofen as a model compound and in-vitro and in-vivo release studies were performed. Statistical investigation of in-vitro release revealed that the diffusion process was the main drug release mechanism and the Higuchi’s model provided the best fit. In-vivo studies showed the presence of Ibuprofen in saliva (range 70–210 µg/ml) for 5 h and no irritation was observed. These mucoadhesive formulations offer many advantages in
comparison to traditional treatments and can be proposed as a new therapeutic tool against dental and buccal diseases and disturb.

Linn et al, 2011 studied Soluplus® as an effective absorption enhancer of poorly soluble drugs in-vitro and in-vivo. A novel solubility enhancing excipient (Soluplus®) was tested for its capability to improve intestinal drug absorption. BCS class II compounds danazol, fenofibrate and Itraconazole were tested both in vivo in beagle dogs and in-vitro in transport experiments across Caco-2 cell monolayers. In-vitro transport studies confirm the strong effect of Soluplus® on the absorption behavior of the three tested drugs. Furthermore, the increase of drug flux across Caco-2 monolayer is correlating to the increase in plasma AUC and C_max in vivo. For these poorly soluble substances Soluplus® has a strong potential to improve oral bioavailability.

Patel and Agrawal, 2011 reviewed nanosuspension as an approach to enhance solubility of drugs. Nanosuspension consists of the pure poorly water-soluble drug without any matrix material suspended in dispersion. Preparation of nanosuspension is simple and applicable to all drugs which are water insoluble. A nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy.

Chudasama et al, 2011 investigated microemulsion system for transdermal delivery of Itraconazole. A new oil-in-water microemulsion-based (ME) gel containing 1% Itraconazole (ITZ) was developed for topical delivery. The solubility of ITZ in oils and surfactants was evaluated to identify potential excipients. The optimized microemulsion was incorporated into polymeric gels of Lutrol F127, Xanthan gum, and Carbopol 934 for convenient application and evaluated for pH, drug content, viscosity, and spreadability. In-vitro drug permeation of ME gels was determined across excised rat skins. These results indicate that the studied ME gel may be a promising vehicle for topical delivery of ITZ.

Hayes et al, 2011 studied fungal infection in heart-lung transplant recipients receiving single-agent prophylaxis with Itraconazole. An observational, retrospective study was performed to evaluate the rate of fungal infections in heart and lung transplant recipients at the University of Kentucky Medical Center over 4.5 years who received Itraconazole as a single therapy prophylaxis. Single-agent use with Itraconazole in heart
or lung transplant recipients did not affect the rate of fungal infection as compared with previous reports. The incidence of fungal infection increased significantly within 3 months after escalation of immunosuppressant for treatment of acute rejection.

Lass Floral, 2011 reviewed triazole antifungal agents in invasive fungal infections. Triazole antifungals have emerged as front-line drugs for the treatment and prophylaxis of many systemic mycoses. Itraconazole also has a role in the treatment of fungal skin and nail infections as well as dematiaceous fungi and endemic mycoses. The therapeutic window for triazoles is narrow, and inattention to their pharmacokinetic properties can lead to drug levels too low for efficacy or too high for good tolerability or safety.

Das et al, 2011 studied Oral Itraconazole for the treatment of severe seborrhoeic dermatitis. Itraconazole was given to 30 patients of SD in a dose of 100 mg twice daily for 1 week followed by 200 mg/day for first 2 days of the following 2 months. The response was noted on day 15, 30, 60, and 90. The clinical response was graded as markedly effective, effective, or ineffective. Clinical improvement (evaluated as markedly effective or effective) was observed in 83.3% cases. The anti-inflammatory activity of oral Itraconazole suggests that it should be the first-line therapy in severe SD.

Wang and Huang, 2011 prepared Itraconazole-loaded liposomes coated by carboxymethyl chitosan and its pharmacokinetics and tissue distribution. This study uses a film dispersion method to prepare Itraconazole-loaded liposomes (ITZ-Lips) prior to coating them with CMC. The concentrations of ITZ in selected organs were determined using reversed-phase high-performance liquid chromatography (HPLC). The biodistribution in mice was also changed after ITZ was encapsulated in CMC coated liposomes. CMC-ITZ-Lips performed significant lung targeting efficiency with AUC, Te and Re of lung all showed obvious elevation. They have successfully encapsulated Itraconazole into carboxymethyl chitosan-modified liposomes for application of injection.

Buckner et al, 2011 measured posaconazole, Itraconazole, and hydroxyl-itraconazole in plasma/serum by high-performance liquid chromatography with fluorescence detection. A simple, sensitive high-performance liquid chromatographic method has been developed for the analysis of Itraconazole, hydroxyl-itraconazole, and
posaconazole in serum/plasma. Few of the samples measured from patients participating in the clinical study attained concentrations of the drug/metabolite in serum that have been recommended for effective antifungal therapy.

Miller et al, 2011 studied flocculated amorphous Itraconazole nanoparticles for enhanced in-vitro supersaturation and in vivo bioavailability. Rapid flocculation of nanoparticle dispersions of a poorly water soluble drug, Itraconazole was utilized to produce amorphous powders with desirable dissolution properties for high bioavailability in rats. Antisolvent precipitation (AP) was utilized to form ITZ nanodispersions with high drug loadings stabilized with hydroxypropylmethylcellulose (HPMC) or the pH-sensitive Eudragit® L100-55 (EL10055). The HPMC dispersions were flocculated by desolvating the polymer through the addition of a divalent salt, and the enteric EL10055 by reducing the pH. The ability to generate and sustain high supersaturation in micellar media at pH 6.8 is beneficial for increasing bioavailability of ITZ by oral delivery.

Park et al, 2010 developed novel Itraconazole loaded solid dispersion without crystalline change with improved bioavailability. To develop a novel Itraconazole loaded solid dispersion without crystalline change with improved bioavailability, various Itraconazole-loaded solid dispersions were prepared with water, polyvinylpyrroline, poloxamer and citric acid. The Itraconazole loaded solid dispersion at the weight ratio of Itraconazole/ polyvinylpyrroline/ poloxamer of 10/2/0.5 gave maximum drug solubility of about 20 microg/mL. It did not change the crystalline form of drug for at least 6 months, indicating that it was physically stable. It gave higher AUC, $C_{\text{max}}$ and $t_{\text{max}}$ compared to Itraconazole powder and similar values to the commercial product, suggesting that it was bioequivalent to commercial product in rats. Thus, it would be useful to deliver a poorly water-soluble Itraconazole without crystalline change with improved bioavailability.

Li et al, 2010 Developed and evaluated an Itraconazole loaded gelatin microcapsule with enhanced oral bioavailability. Various gelatin microcapsules were prepared using a spray-drying technique. Their physicochemical properties, dissolution, characteristics and pharmacokinetics in rats were evaluated and compared with those of a commercial product. The Itraconazole loaded gelatin microcapsule without ethanol developed using a spray drying technique at half the dose of the commercial product can
deliver Itraconazole in a pattern that allows fast absorption in the initial phase, making it bioequivalent to the commercial product.

Engers et al, 2010 used a solid-state approach to enable early development compounds with selection and animal bioavailability studies of an Itraconazole amorphous solid dispersion. A solid-state approach to enable compounds in preclinical development is used by identifying an amorphous solid dispersion in a simple formulation to increase bioavailability. Solid dispersions were prepared with different at varied concentrations using two preparation methods (evaporation and freeze drying). The study demonstrated the utility of using an amorphous solid form with desirable physical properties to significantly improve bioavailability and provides a viable strategy for evaluating early drug candidates.

Chen et al, 2011 studied targeted brain delivery of Itraconazole via RVG29 anchored nanoparticles. 29-amino-acid peptide derived from rabies virus glycoprotein (RVG29) peptide conjugated Itraconazole-loaded albumin nanoparticles (RVG29-ITZ-NPs) was developed. Cellular uptake of RVG29-ITZ-NPs was investigated by flow cytometry. Pharmacokinetics and brain distribution of RVG29-ITZ-NPs were investigated after intravenous administration of NPs. The results suggested that RVG29-ITZ-NPs can be exploited as a potential therapeutic formulation for the intracranial fungal infection.

Tang et al, 2010 studied Pharmacokinetics and biodistribution of Itraconazole in rats and mice following intravenous administration in a novel liposome formulation. Novel Itraconazole (ITZ)-loaded liposomes (ITZ-LPs) were prepared and their pharmacokinetics and biodistribution were assessed in comparison with commercial formulations (ITZ-CD). The pharmacokinetics and biodistribution were studied in the rats and mice, and compared with commercially available formulations (Sporanox®) after administration by the tail vein at a dose of 10 mg/kg. In tissue distribution study, there were no differences of distributions in the lung between two formulations. Nevertheless, in the liver and spleen, Itraconazole levels for the group treated with ITZ-LPs were significantly higher than those for the group treated with ITZ-CD. Meanwhile, the low distribution of ITZ-LPs in heart and kidney was of great advantage to reduce the toxicity.
for heart and kidney. The results indicated that the ITZ-LPs can be a potential intravenous formulation of Itraconazole.

Al-Talla et al, 2011 performed bioequivalence assessment of two formulations of ibuprofen. A prestudy validation of ibuprofen demonstrated long-term stability, freeze-thaw stability, precision, and accuracy. Pharmacokinetic parameters were determined from serum concentrations for both formulations. The 90% confidence intervals of the In-transformed test/reference treatment ratios for peak plasma concentration and area under the concentration-time curve (AUC) parameters were found to be within the predetermined acceptable interval of 80%-125% set by the US Food and Drug Administration.

Ranjan et al, 2011 evaluated controlled release chitosan microspheres of mirtazapine. Chitosan microspheres were prepared to prolong the release of the drug into the systemic circulation. The microspheres were evaluated for encapsulation efficiency, particle size, surface morphology, swelling index, in-vitro release, as well as erosion and in vivo studies in rats. Optimized formulation (F-14) was found to be stable under accelerated storage conditions based on International Conference on Harmonisation guidelines. Pharmacokinetic studies revealed that the optimized formulation showed significant increases in systemic exposure (AUC = 177.70 ± 7.39 μg·h/mL), half-life (4.72 ± 0.46 h) and reduced clearance (0.009 ± 0.0001 L/h) compared to pure drug administration. The study demonstrates that controlled release formulation of MTZ microspheres using chitosan can improve pharmacokinetic profiles of MTZ.

Li et al, 2011 studied formulation optimization of chelerythrine loaded O-carboxymethylchitosan microspheres using response surface methodology. The aims of this investigation were to develop a procedure to prepare chelerythrine (CHE) loaded O-carboxymethylchitosan (O-CMCS) microspheres by emulsion cross-linking method and optimize the process and formulation variables using response surface methodology (RSM) with a three-level, three-factor Box-Behnken design (BBD). Mathematical equations and response surface plots were used to relate the dependent and independent variables. The process and formulation variables were optimized to achieve maximum drug loading content and entrapment efficiency by the desirability function. The combination use of RSM, BBD and desirability function could provide a promising
application for O-CMCS as controlled drug delivery carrier and help to develop procedures for a lab-scale microemulsion process.

Bhovar et al, 2011 studied characterization and release kinetics of naproxen encapsulated in lipid-based matrix microspheres. Naproxen was microencapsulated with lipid-like carnauba wax, hydrogenated castor oil using modified melt dispersion (modified congealable disperse phase encapsulation) technique. The shape of microspheres was found to be spherical by SEM. The drug entrapment efficiency of various batches of microspheres was found to be ranging from 60 to 90 %w/w. In-vitro drug release studies were carried out up to 24 h in pH 7.4 phosphate buffer showing 50-65% drug release. In-vitro drug release from all the batches showed better fitting with the Korsmeyer-Peppas model, indicating the possible mechanism of drug release to be by diffusion and erosion of the lipid matrix.

Jha et al, 2011 studied formulation and pharmacokinetic evaluation of bioadhesive microspheres for bioavailability enhancement of raloxifene hydrochloride. The study describes two simultaneous approaches to improve its bioavailability, complexation of R-HCl with cyclodextrin(s), and formulation of mucoadhesive microspheres of the complex using different proportions of carbopol and HPMC. The results of the study showed that mucoadhesive microspheres could be a viable approach to improve the pharmacokinetic profile of R-HCl.

Mishra et al, 2011 developed and evaluated mucoadhesive buccal patches of flurbiprofen. Solubility enhancement was attempted by making solid dispersion of drug with beta-CD (cyclodextrin). Initially preformulation were carried out using reported methods. Buccal patches were prepared by solvent casting technique using polymers like polyvinyl alcohol (PVA), sodium carboxymethyl cellulose (SCMC), and hydroxypropyl methylcellulose (HPMC). The prepared patches were evaluated for their weight variation, thickness, folding endurance, surface pH, swelling index, in-vitro residence time, in-vitro permeation studies, drug content uniformity and bioadhesion test.

Puratchikody et al, 2011 studied development and characterization of mucoadhesive patches of salbutamol sulfate for unidirectional buccal drug delivery. A $3^2$ full factorial design was used to design the experiments for each polymer combination. Patches prepared with PEG-400 showed a high swelling index. The residence time of the
tested patches ranged between 105 and 130 min. Formulations A10, A32, B10 and B32 fitted the Higuchi model best, whereas formulations A19 and B19 showed super case II transport drug release. Stability studies indicated that there was no change in the chemical and physical characteristics during the test period of 6 months.

Obaidat et al, 2011 prepared mucoadhesive oral patches containing tetracycline hydrochloride and carvacrol for treatment of local mouth bacterial infections and candidiasis. The bilayered patches were prepared using ethyl cellulose as a backing layer and carbopol 934 as a matrix mucoadhesive layer. The antimicrobial activity was assessed for the prepared patches using the disc-diffusion method against the yeast Candida albicans and five bacterial strains, including Pseudomonas aeruginosa, Escherichia coli, Bacillus cereus, Staphylococcus aureus, and Bacillus bronchispti. The best formulation was selected based on microbiological tests, drug release, ex-vivo mucoadhesive performance, and swelling index.

Adhikari et al, 2010 formulated and evaluated buccal patches for delivery of atenolol. Various physicomechanical parameters like weight variation, thickness, folding endurance, drug content, moisture content, moisture absorption, and various ex vivo mucoadhesion parameters like mucoadhesive strength, force of adhesion, and bond strength were evaluated. An in-vitro drug release study was designed, and it was carried out using commercial semipermeable membrane. All these fabricated patches were sustained for 24 h and obeyed first-order release kinetics. Ex-vivo drug permeation study was also performed using porcine buccal mucosa, and various drug permeation parameters like flux and lag time were determined.

Nagda et al, 2011 studied development and characterization of mucoadhesive microspheres for nasal delivery of ketorolac. Drug encapsulation efficiency and particle size of the microspheres ranged from 52-78% w/w and 14-46 micron respectively. Interaction studies revealed that there were no drug-polymer interactions. The in-vitro release profiles showed prolonged-release of the drug. In-vitro release data showed a good fit with the Higuchi model, and indicated Fickian diffusion.

Mathew et al, 2011 conducted bioequivalence studies of two tacrolimus formulations under fasting conditions in healthy male subjects. Two open-label, 2-period, single-dose, crossover studies compared 0.5 mg and 5 mg capsule test formulations of
tacrolimus with reference products in fasting, healthy male volunteers. The 90% CIs for 0.5 mg were 102.99%-120.80% for $C_{\text{max}}$ and 91.51%-105.92% for $\text{AUC}_{0-72}$; those for 5 mg were 110.61%-120.96% for $C_{\text{max}}$ and 96.17%-103.55% for $\text{AUC}_{0-t}$. In these comparative bioavailability studies of fasting, healthy male volunteers, the test and reference formulations of tacrolimus 0.5 mg and 5 mg capsules were well tolerated and met the requirements of the European regulatory bioequivalence guidelines.

Badshah et al, 2011 studied development of controlled-release matrix tablet of risperidone: influence of Methocel®- and Ethocel®-based novel polymeric blend on in-vitro drug release and bioavailability. Controlled-release (CR) matrix tablet of 4 mg risperidone was developed using flow bound dry granulation-slugging method to improve its safety profile and compliance. The CR test tablet, containing 30% Methocel® and 60% Ethocel® ($F_3$) with 12kg hardness, exhibited pH-independent zero-order release kinetics for 24 h. The drug release rate was inversely proportional to the content of Ethocel®, while the gel layer formed of Methocel® helped in maintaining the integrity of the matrix. The CR test tablet exhibited bioequivalence to reference conventional tablet in addition to the significantly ($p < 0.05$) optimized peak concentration, $C_{\text{max}}$, and extended peak time, $t_{\text{max}}$, of the active moiety. There was a good association between drug absorption in vivo and drug release in-vitro ($R^2=0.7293$). The successfully developed CR test tablet may be used for better therapeutic outcomes of risperidone.

Al-Jenoobi, 2010 studied effect of Itraconazole on the pharmacokinetics of diclofenac in beagle dogs. The objective of this study was to investigate the potential effect of Itraconazole on the pharmacokinetics of diclofenac potassium in beagle dogs after oral coadministration. Blood samples obtained for 8.0 hours post dose were analysed for diclofenac concentration using a validated high performance liquid chromatography (HPLC) assay method. The area under plasma concentration-time curve (AUC), maximum plasma concentration ($C_{\text{max}}$), time to reach $C_{\text{max}}$ ($t_{\text{max}}$) and elimination half-life ($t_{1/2}$), were calculated for diclofenac before and after Itraconazole administration. The coadministration of Itraconazole with diclofenac potassium has resulted in a significant reduction in AUC and $C_{\text{max}}$ of diclofenac, which was about 31 and 42%; respectively. No statistically significant differences were observed for $t_{\text{max}}$ and $t_{1/2}$ of diclofenac between the two phases. They concluded that oral coadministration of
Itraconazole may have the potential to affect the absorption of diclofenac as indicated by the significant reduction in its AUC and $C_{\text{max}}$ in beagle dogs.

Al-Sarra et al, 2010 performed a comparative study of Itraconazole-cyclodextrin inclusion complex and its commercial product. Itraconazole (ITZ) solid complex using hydroxypropyl-beta-cyclodextrin (ITZ-HP-beta-CD) with 20% polyvinylpyrrolidone was prepared by a co-evaporation method. The complex improved antifungal activity against C. parapasilosis and C. albicans. Capsules containing ITZ-HP-beta-CD at a molar ratio of 1:3 with 20% polyvinylpyrrolidone have a faster dissolution rate than commercial capsules (Sporanox). The intraday precision showed a coefficient of variation less than 3.96%, and that for interday was less than 4.99%. The HPLC method was more accurate and precise than the antimicrobial and UV-spectrophotometric methods for determination of ITZ concentration present in the release medium.

Janssens et al, 2010 studied influence of preparation methods on solid state supersaturation of amorphous solid dispersions (a case study with Itraconazole and eudragit e100). The amorphous solid dispersions were prepared via spray drying and film casting in order to evaluate the influence of the solvent drying rate. The experimental miscibility level was estimated using XRPD, MDSC, FT-IR, HPLC and TGA. The experimental miscibility level was found to be 27.5% w/w for spray-dried and 15% for film-casted solid dispersions. The solid dispersions are significantly supersaturated with respect to both crystalline solubility and amorphous miscibility demonstrating the influence of manufacturing methodology.

Tao et al, 2009 prepared and evaluated Itraconazole dihydrochloride for the solubility and dissolution rate enhancement. The morphology and mean size distribution study by SEM and DLS confirmed that the salt was dispersable nanoparticle aggregation. Aqueous solubility measurements showed that the solubility of the salt, its 1:1, 1:2 and 1:3 (w/w) physical mixtures with beta-cyclodextrin (beta-CD) was 6, 99, 236 and 388 times greater than Itraconazole. More than 94% of Itraconazole was dissolved out of the salt/beta-CD 1/3 physical mixture after 60min. The stability studies indicated that the physical mixture remained stable for 24 months in assay, the related substances and dissolution. They concluded that hydrochloride formation can significantly increase solubility and dissolution rate of Itraconazole, and the formulation of Itraconazole
dihydrochloride/beta-CD (1/3) would be an environment-friendly, economic and practical alternative to the commercially available Itraconazole capsules (Sporanox).

Chudasama et al, 2011 investigated microemulsion system for transdermal delivery of Itraconazole. A new oil-in-water microemulsion-based (ME) gel containing 1% Itraconazole (ITZ) was developed for topical delivery. In-vitro drug permeation of ME gels was determined across excised rat skins. Furthermore, in-vitro antimycotic inhibitory activity of the gels was conducted using agar-cup method and Candida albicans as a test organism. The results indicated that the studied ME gel may be a promising vehicle for topical delivery of ITZ.