Chapter 2
Drug Profile & Literature Review

2.1. Drug Profile

2.1.1. Drug profile of cilostazol

2.1.1.1. Nomenclature and physico-chemical properties[1-4]

- **Chemical Name:** 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2 (1*H*)-quinolinone
- **Empirical formula:** $C_{20}H_{27}N_5O_2$
- **Structural formula:**

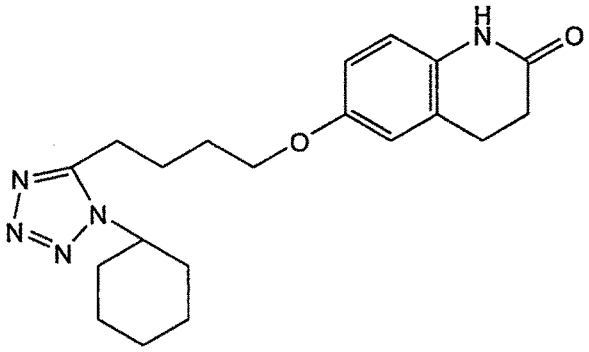


Fig. 2 Structure of cilostazol

- **Molecular Weight:** 369.47
- **Appearance:** Cilostazol is a white to off-white crystals or as a crystalline powder.
- **Solubility:** Slightly soluble in methanol and ethanol, and is practically insoluble in water, 0.1 N HCl, and 0.1 N NaOH.
- **Melting point:** 160° C
- **Storage:** Store in controlled room temperature

2.1.1.2.Pharmacology[5-7]

2.1.1.2.1Pharmacodynamic properties[8]

Cilostazol affects both vascular body and cardiovascular function. It produces non-homogeneous dilation of vascular beds, with greater dilation in femoral body than in vertebral, carotid or superior mesenteric arteries. Renal arteries are not responsive to the effect of cilostazol.

In dogs or cynomolgous monkeys, cilostazol increased heart rate, myocardial contractile force, and coronary blood flow as well as ventricular automaticity, as would be expected for a PDE III inhibitor. Left ventricular contractility was increased at doses required to inhibit

platelet aggregation. A-V conduction was accelerated. In humans, heart rate increased in a dose-proportional manner by a mean of 5.1 and 7.4 beats per minute in patients treated with 50 and 100 mg b.i.d., respectively. In 264 patients evaluated with Holter monitors, numerically more cilostazol-treated patients had increases in ventricular premature beats and non-sustained ventricular tachycardia events than did placebo-treated patients; the increases were not dose-related.

2.1.1.2.2 Mechanism of action

The mechanism of the effects of cilostazol on the symptoms of intermittent claudication is not fully understood. Cilostazol and several of its metabolites are cAMP PDE III inhibitors, inhibiting phosphodiesterase activity and suppressing cAMP degradation with a resultant increase in cAMP in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilation. Cilostazol reversibly inhibits platelet aggregation induced by a variety of stimuli, including thrombin, arachidonic acid, epinephrine, and shear stress. Effects on circulating plasma lipids have been examined in patients taking cilostazol. After 12 weeks, as compared to placebo, cilostazol 100 mg b.i.d. produced a reduction in triglycerides of 29.3 mg/dL (15%) and an increase in HDL-cholesterol of 4.0 mg/dL (≅ 10%).

2.1.1.2.3 Pharmacokinetics[9-11]

Absorbtion

Cilostazol is well absorbed after oral administration. A high fat meal increases absorption, with an approximately 90% increase in C_{max} and a 25% increase in AUC. Absolute bioavailability is not known.

Distribution

Plasma Protein and Erythrocyte Binding: Protein binding capacity of cilostazol is 95-98%, predominantly to albumin. The mean percent binding for 3, 4-dehydro-cilostazol is 97.4% and for 4′-trans-hydroxy-cilostazol is 66%.

Mild hepatic impairment did not affect protein binding. The free fraction of cilostazol was 27% higher in subjects with renal impairment than in normal volunteers. The displacement of

cilostazol from plasma proteins by erythromycin, quinidine, warfarin, and omeprazole was not clinically significant.

Metabolism and Excretion:-Cilostazol is extensively metabolized by hepatic cytochrome P-450 enzymes, mainly 3A4, with metabolites largely excreted in urine. Two metabolites are active, with one metabolite appearing to account for at least 50% of the pharmacologic (PDE III inhibition) activity after administration of cilostazol. Pharmacokinetics is approximately dose proportional. Cilostazol and its active metabolites have apparent elimination half-lives of about 11-13 hours. Cilostazol and its active metabolites accumulate about 2-fold with chronic administration and reach steady state blood levels within a few days. The pharmacokinetics of cilostazol and its two major active metabolites were similar in healthy normal subjects and patients with intermittent claudication due to peripheral arterial disease (PAD).

2.1.1.2.4 Therapeutic indications[12-14]

Cilostazol is indicated for the reduction of symptoms of intermittent claudication, as indicated by an increased walking distance.

2.1.1.2.5 Adverse effects[15-16]

More frequent adverse events: Headache, palpitation and diarrhea, asthenia, hypertension, vomiting, leg cramps, hyperesthesia, paresthesia, dyspnea, rash, hematuria, urinary tract infection, flu syndrome, angina pectoris, arthritis, and bronchitis.

Less frequent adverse events: Chills face edema, fever, generalized edema, malaise, neck rigidity, pelvic pain, retroperitoneal hemorrhage.

Cardiovascular: Atrial fibrillation, atrial flutter, cerebral infarct, cerebral ischemia, congestive heart failure, heart arrest, hemorrhage, hypotension, myocardial infarction, myocardial ischemia, nodal arrhythmia, postural hypotension, supraventricular tachycardia, syncope, varicose vein, vasodilation, ventricular extrasystoles, ventricular tachycardia.

Digestive: Anorexia, cholelithiasis, colitis, duodenal ulcer, duodenitis, esophageal hemorrhage, esophagitis, GOT increased, gastritis, gastroenteritis, gum hemorrhage,

hematemesis, melena, peptic ulcer, periodontal abscess, rectal hemorrhage, stomach ulcer, tongue edema.

Endocrine: Diabetes mellitus.

Haemic and Lymphatic: Anemia, ecchymosis, iron deficiency anemia, polycythemia, purpura.

Metabolic and Nutritional: increase creatinine, gout, hyperlipemia, hyperuricemia.

Musculoskeletal: Arthralgia, bone pain, bursitis.

Nervous: Anxiety, insomnia, neuralgia.

Respiratory: Asthma, epistaxis, hemoptysis, pneumonia, sinusitis.

Skin and Appendages: Furunculosis, skin hypertrophy, urticaria.

Special Senses: Amblyopia, blindness, conjunctivitis, diplopia, ear pain, eye hemorrhage.

2.1.1.2.6 Contraindications

Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III. Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III-IV congestive heart failure. Cilostazol is contraindicated in patients with congestive heart failure of any severity. Cilostazol is contraindicated in patients with haemostatic disorders or active pathologic bleeding, such as bleeding peptic ulcer and intracranial bleeding. Cilostazol inhibits platelet aggregation in a reversible manner. Cilostazol is contraindicated in patients with known or suspected hypersensitivity to any of its components.

2.1.1.2.7 Dose and administration

The recommended dosage of cilostazol is 100 mg b.i.d. taken at least half an hour before or two hours after breakfast and dinner. A dose of 50 mg b.i.d. should be considered during coadministration of such inhibitors of CYP3A4 as ketoconazole, itraconazole, erythromycin and diltiazem, and during coadministration of such inhibitors of CYP2C19 as omeprazole. Patients may respond as early as 2 to 4 weeks after the initiation of therapy, but treatment up to 12 weeks may be needed before a beneficial effect is experienced.

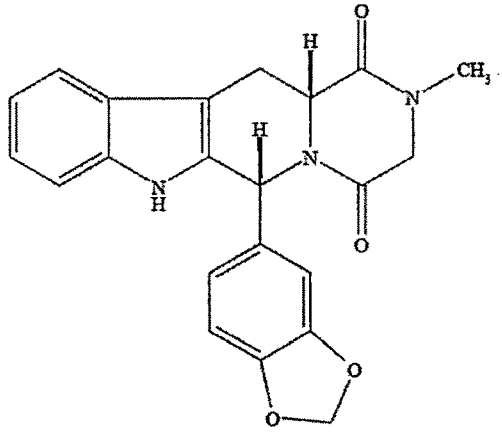
2.1.1.2.8 Overdose

Information on acute overdosage with cilostazol in humans is limited. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: severe headache, diarrhea, hypotension, tachycardia, and possibly cardiac arrhythmias. The patient should be carefully observed and given supportive treatment. Since cilostazol is highly protein-bound, it is unlikely that it can be efficiently removed by hemodialysis or peritoneal dialysis. The oral LD_{50} of cilostazol is >5.0 g/kg in mice and rats and >2.0 g/kg in dogs.

2.1.2.Drug Profile of Tadalafil

2.1.2.1 Nomenclature and physico-chemical properties

- **Chemical Name:** pyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5- yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-
- **Empirical formula:** $C_{22}H_{19}N_3O_4$
- **Structural formula:**



- **Molecular Weight:** 389.41
- **Appearance:** White crystalline solid
- **Solubility:** Practically insoluble in water and very slightly soluble in ethanol.
- **Melting point:** 307° C
- **Storage:** Store in controlled room temperature

  Tadalafil is available as film-coated tablets for oral administration. Each tablet contains 5, 10, or 20 mg of Tadalafil

2.1.2.2. Mechanism of Action

Penile erection during sexual stimulation is caused by increased penile blood flow resulting from there laxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by Tadalafil has no effect in the absence of sexual stimulation.

Studies in vitro have demonstrated that Tadalafil is a selective inhibitor of PDE5. PDE5 is found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas.

In vitro studies have shown that the effect of Tadalafil is more potent on PDE5 than on other phosphodiesterases. These studies have shown that Tadalafil is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle, and other organs. Tadalafil is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. Additionally, Tadalafil is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10 and 14-fold more potent for PDE5 than for PDE11A1, an enzyme found in human skeletal muscle.Tadalafil inhibits human recombinant PDE11A1 activity at concentrations within the therapeutic range[17-20]. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined.

2.1.2.3.. Pharmacokinetics

Absorption — After single oral-dose administration, the maximum observed plasma concentration (Cmax) of Tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours)[19]. Absolute bioavailability of Tadalafil following oral dosing has not been determined. The rate and extent of absorption of Tadalafil are not influenced by food.

Distribution — The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that Tadalafil is distributed into tissues. At therapeutic

concentrations, 94% of Tadalafil in plasma is bound to proteins. Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism — Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite[21]. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatehol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. In vitro data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Elimination — The mean oral clearance for Tadalafil is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects[19]. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

2.1.2.4. Dosage and administration

The recommended starting dose of Tadalafil in most patients is 10 mg, taken prior to anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients. Tadalafil was shown to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of Tadalafil, this should be taken into consideration.

Tadalafil may be taken without regard to food.

Renal Insufficiency — No dose adjustment is required in patients with mild renal insufficiency. For patients with moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency, a starting dose of 5 mg not more than once daily is recommended, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. For patients with severe (creatinine clearance <30 mL/min) renal insufficiency on hemodialysis, the maximum recommended dose is 5 mg [21].

Hepatic Impairment — For patients with mild or moderate degrees of hepatic impairment (Child-Pugh Class A or B), the dose of Tadalafil should not exceed 10 mg once daily. In patients with severe hepatic impairment (Child-Pugh Class C), the use of Tadalafil is not recommended[21].

Concomitant Medications -When Tadalafil is co-administered with an alpha-blocker, patients should be stable on alpha-blocker therapy prior to initiating treatment with Tadalafil, and Tadalafil should be initiated at the lowest recommended dose. For patients taking

concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of Tadalafil is 10 mg, not to exceed once every 72 hours [21].

Concomitant use of nitrates in any form is contraindicated.

Geriatrics — No dose adjustment is required in patients >65 years of age[21].

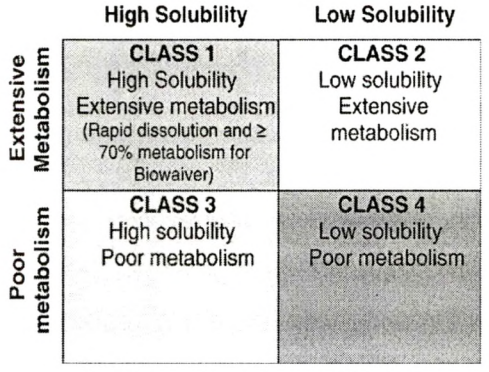
2.1.2.5. Overdosage

Single doses up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses. In cases of overdose, standard supportive measures should be adopted as required. Hemodialysis contributes negligibly to Tadalafil elimination.

2.2. Literature Review

Despite efforts to develop new routes for drug administration, oral route of drug administration is preferred to the non-oral alternatives mainly for the reasons such as lower production cost, better suitability for self-medication, a higher level of patient safety, and better patient compliance. Sufficient intestinal absorption of orally administered drugs from the gastrointestinal tract is one of the prerequisites for successful oral drug therapy. Intestinal drug absorption is controlled by, (i) dissolution rate and solubility, determining how fast a drug reaches a maximum concentration in the luminal intestinal fluid, and (ii), permeability coefficient, which relates to the rate at which dissolved drug will permeate the epithelium of the intestinal mucosa to reach the portal blood circulation.

The Biopharmaceutics Drug Disposition Classification System (BDDCS) where major route of elimination (metabolized vs. unchanged) serves as the permeability criteria[22].



When presented with a new drug candidate certain relatively general criteria may be utilized to classify the drug. The biopharmaceutical classification scheme (BCS) implies that aqueous solubility and membrane permeability are two major factors limiting drug absorption[23]. A drug is considered to be highly soluble when the highest dose strength is soluble in 250 ml or less over a pH range 1–7.5 at 37 °C. In contrast, if the drug solubility is less than 100 μg/ml or the dose to solubility ratio is greater than 250 ml then it is considered poorly soluble. Alternatively, Lipinski's rule of five has been widely proposed as a qualitative predictive model for oral absorption trends. In the discovery setting the 'rule of 5' predicts that poor absorption or poor permeation is more likely when: there are more than 5 H-bond donors, there are more than 10 H-bond acceptors, the molecular weight N500, and the calculated Log PN5[24].

It has been found that approximately 40% of drug candidates have poor water solubility and the oral delivery of such drugs can be frequently associated with implications

of low bioavailability, high intra- and inter subject variability, and lack of dose proportionality[25].To overcome these problems, various formulation strategies are reported in the literature including the use of surfactants, cyclodextrins, nanoparticles, solid dispersions, micronization, lipids, and permeation enhancers[26]. These approaches can be successful in selected cases. Nowadays, the interest of microemulsifying drug delivery systems and self-emulsifying drug delivery systems (SEDDS) to improve the bioavailability of poorly water soluble drugs is well known and documented with various drugs: progesterone[27], halofantrine[28], indomethacin[29] and coenzymeQ10[30], ubiquinone[31], idebenone[32], vitamin E[33]and cyclosporin A[34,35,136,37], ,alendronate[38],antitubercular agents[39],Iron dextran[40]etc.

The use of natural and synthetic lipids has generated much academic and commercial interest as a potential formulation strategy for improving the oral bioavailability of poorly water soluble drugs. When administered in traditional solid formulations, these compounds often exhibit low bioavailability as their absorption can be kinetically-limited by low rates of dissolution and capacity-limited by poor solubility. The well known effect of food for improving the bioavailability of many poorly soluble drugs, where the enhanced absorption is often ascribed to the ingested lipid, is ample evidence of the beneficial role that lipids can have on drug absorption. Although the form, content and volume of such dietary lipids is markedly different to what would be included in a pharmaceutical formulation, food effect bioavailability data can be viewed as offering a prospective approach for the design of superior formulations for such drugs[41].

Table 1: The Lipid Formulation Classification System: characteristic features, advantages and disadvantages of the four essential types of 'lipid' formulations [42]

Formulation type	Materials	Characteristics	Advantages	Disadvantages
Type I	Oils without surfactants (e.g. tri-, di-and monoglycerides)	Non-dispersing, requires digestion	GRAS status; simple; excellent capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	Oils and water-insoluble surfactants	SEDDS formed without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particle size 0.25–2 μm)
Type III	Oils, surfactants,	SEDDS/SMEDDS	Clear or almost	Possible loss of

	cosolvents (both water-insoluble and water-soluble excipients)	and micro emusion formed with water-soluble components	clear dispersion; drug absorption without digestion	solvent capacity on dispersion; less easily digested
Type IV	Water-soluble surfactants and co-solvents (no oils)	Formulation disperses typically to form a micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity on dispersion; may not be digestable

Some encouraging reports on microemulsifying drug delivery systems to improve the oral solubility, bioavailability and absorption rate with simultaneous reduction in the dose dependent toxicity are,

- **P.P.Costantinides**[43] reviewed the pharmaceutical microemulsions with emphasis on self-emulsifying systems, from both a physical and biopharmaceutical perspective, Although the systems have several pharmaceutical applications , the review is mainly focused on their potency for oral drug delivery and intestinal absorption improvement. Case studies in which lipid microemulsion have been successfully been used to improve solubilization/dissolution and /or instestinal absorption of poorly absorbed drug. Drug development issues such as commercial viability, mechanisms involved, range of applicability, safety, scale-up and manufacture are outlined,and future research and development efforts to address these issues are discussed.
- **Christopher J. H. Porter et al.**[44] investigated the impact of lipidic formulation on *in vitro* dispersion and digestion properties and the relationship to oral bioavailability, using danazol as a model lipophilic poorly water soluble drug.Three lipid-based danazol formulations [a long-chain triglyceride solution (LCT-solution) and self-microemulsifying drug delivery systems (SMEDDS) based on long-chain (C18) lipids (LC-SMEDDS) and medium-chain (C8–C10) lipids (MC-SMEDDS)] were administered to fasted beagle dogs and compared with a micronized danazol formulation administered postprandially and in the fasted state. Digestion of microemulsion preconcentrate formulations based on medium-chain lipids may limit it's *in vivo* utility when compared to similar formulations based on long chain lipids.
- **Osmond J. D'Cruz et al.**[45]prepared microemulsion of WHI-07, a microbicide with adequate chemical and physical stability to be used in vaginal drug delivery systems.

It was formulated in an o/w microemulsion-based system composed of water-insoluble lipids (Captex 300, Phospholipon 90G), water-solubleorganic solvents (PEG-200, propylene glycol), and nonionic surfactants (Cremophor EL). This study showed that WHI-07 is stable in natural polymer-based microemulsion for its potentialutility as an anti-HIV spermicide for sexually active women.

- **Prapaporn Boonme et al.**[46] aimed to characterize microemulsion systems of isopropyl palmitate (IPP), water, and 2:1 Brij 97and 1-butanol by different experimental techniques. A pseudoternary phase diagram was constructed using watertitration method. At 45% wt/wt surfactant system, microemulsionscontaining various ratios of water and IPP were prepared and identified by electrical conductivity, viscosity,differential scanning calorimetry (DSC), cryo-field emission scanning electron microscopy (cryo-FESEM) and nuclear magnetic resonance (NMR). The results from all techniques agree well and indicate that the systems containing less than 15% w/w water are likely to consist of reversed micelles. The systems containing 15%-30% wt/wt water were expected to be of the water/oil microemulsion type, while those containing more than 35%w/w water were expected to be of oil/water microemulsion type. The water/oil and oil/water transition point was in the range of 30% to 35% wt/wt water.
- **N. Subramanian et al.**[47] investigated the development of microemulsion system (isopropyl myristate/medium-chain glyceride/polysorbate80/water) for topical delivery of celecoxib. The pseudo ternary phase diagram was constructed with constant surfactant concentration, and several compositions were identified and characterized by using dynamic light scattering. The in vitro permeation rate of celecoxib through rat skin was determined for microemulsions, microemulsion gel, and cream by using the modified Franz-type diffusion cell. In all formulations tested, celecoxib permeated more quickly, and the microemulsions increased the permeation rate of celecoxib up to 5 and 11 times compared with those of microemulsion gel and cream, respectively. In vivo anti-inflammatory study suggested that the developed microemulsion formulations might serve as potential drug vehicle for the prevention of UVB-induced skin cancer.
- **Pradip Kumar Ghosh et al.**[48]studied that the microemulsion formulationcan be employed to improve the bioavailability of a poorly absorbed drug, Acyclovir. The ratio of Labrasol:Plurol Oleique:Labrafac played a major role in formulating the

microemulsion. The optimum microemulsion formulation contained Labrafac10%), Labrasol (32%), Plurol Oleique (8%), and water(50%), which was a transparent and less viscous system. After oral administration in rats, the microemulsion showed an absolute bioavailability of 27.83%, which is 12.78 times higher than that of commercially available tablets (Aquivir).

- **Reza Aboofazeli et al.**[49] evaluated The solvated droplet size of concentrated water-in-oil (w/o) microemulsions prepared from egg and soy lecithin/water/isopropyl myristate and containing short-chain alcohol co-surfactants has been determined using photon correlation spectroscopy (PCS). The effect of increasing the water volume fraction (from 0.04 to 0.26) on the solvated size of the w/o droplets at 298 K has been investigated at 4different surfactant/co-surfactant weight ratios (*K*m of 1:1, 1.5:1, 1.77:1, and 1.94:1); keeping the total surfactant/co-surfactant concentration was kept constant at 25% w/w. For both egg and soy lecithin systems, no microemulsion droplets were detected at water concentrations less than 9 w% regardless of the alcohol and *K*m used, suggesting that at low concentrations of added water, co solvent systems were formed. At higher water concentrations microemulsion droplets were observed. The changes in droplet size followed the expected trend in that for a fixed *K*m the size of the microemulsion droplets increased with increasing volume fraction of water. At constant water concentration, droplet size decreased slightly upon increasing *K*m.
- **Hanan M. El-Laithy et al.**[50] developed the self-emulsifying water continuous microemulsion with high dilution efficiency of dioctyl sodium sulfosuccinate (aerosol OT) which was assessed using pseudoternary microemulsion system aerosol OT/medium-chain triglycerides with oleic acid/glycerol monooleate and water. It was characterized with regard to its electroconductive behavior, eosin sodium absorption, interfacial tension, and droplet size measurements after dilution with water. The per-colation transition law was used to determine the percolation threshold and to identify bicontinuous structures.The investigated particle size and polydispersity using photon correlation spectroscopy after dilution with excess of the continuous phase proved the efficiency of the microemulsion system as a drug carrier that ensures an infinitely dilutable, homogene-ous, and thermodynamically stable system.
- **Cheng-Hsuan Hsu et al.**[51] prepared and characterized nanoparticles into which Coenzyme Q_{10} (CoQ_{10}) had been incorporated (CoQ_{10}-NPs) in microemulsion

precursors composed of emulsifying wax, CoQ_{10}, Brij 78, and/or Tween 20. The nanoparticles were lyophilized, and the stability of CoQ_{10}-NPs in both lyophilized form and aqueous suspension was monitored over 7 days. An in vitro study of the uptake of CoQ_{10}-NPs by mouse macrophage, J774A.1, was completed. The incorporation efficiency of CoQ_{10} was approximately 74% ± 5%.Storage in lyophilized form demonstrated the highest stability. The uptake of CoQ_{10}-NPs by the J774A.1 cells was over 4-fold higher than that of the CoQ_{10}-free nanoparticles ($P < .05$). So CoQ_{10}-NPs with potential application for oral CoQ_{10} delivery were engineered readily from microemulsion precursors.

- **A. Akkar et al.**[52] formulated itraconazole and ketoconazole as oil/water emulsions for parenteral delivery by using a solvent-free homogenization process, namely SolEmuls (solubilization by emulsification) technology. The drugs were incorporated in the commercial emulsion Lipo-fundin MCT 20%, composed of a medium-chain triglyceride/long-chain triglyceride (MCT/LCT) oil phase (1:1) and stabilized with 1.2% lecithin and evaluated for various parameters.It can be concluded, after formulating amphotericin B and carbamazepine with SolEmuls technology, that SolEmuls was also applicable to the antimycotic agents itraconazole and ketoconazole, yielding IV-applicable emulsions with cost-effective production technologies.
- **S. Agatonovic-Kustrin et al.**[53] developed a colloidal dosage form for the oral delivery of rifampicin and isoniazid in combination with the aid of artificial neural network (ANN) data modeling. Data from the 20 pseudoternary phase triangles containing miglyol 812 as the oil component and a mixture of surfactants or a surfactant/cosurfactant blend were used to train, test, and validate the ANN model. The weight ratios of individual components were correlated with the observed phase behavior using radial basis function (RBF) network architecture. A novel microemulsion formulation capable of delivering rifampicin and isoniazid in combination was created to allow for their differences in solubility and potential for chemical reaction. The developed model allowed better understanding of the process of microemulsion formation and stability within pseudoternary colloidal systems.
- **K. Tokui et al.**[54] determined the population pharmacokinetic parameters of cyclosporine (CsA) after multiple oral administration of the microemulsion formulation, Neoral, in kidney transplant patients and to propose a limited sampling strategy to predict AUC(0-4h) using them and the Bayesian method. The AUC (0-4h)

is a parameter that has recently been recommended as an index for the dose adjustment in therapeutic drug monitoring of CsA. Blood samples were obtained at the trough level and at hourly intervals up to 5 hours from 125 patients (78 male and 47 female) who were receiving Neoral twice daily, and whole-blood concentrations of CsA were measured. The population pharmacokinetic parameters were estimated using the NONMEM computer program and a linear two-compartment model with first-order absorption. The present findings suggest that a simplified strategy based on population pharmacokinetics can accurately predict AUC (0-4h) from concentrations at 2 or 3 sampling time points, providing an excellent method for the daily dose adjustment of Neoral in routine clinical use for kidney transplant patients.

- **F. Karamustafa et al.**[55] prepared a water-in-oil microemulsion formulation of alendronate. Pseudo-ternary phase diagrams were constructed by using different oils and co-surfactants. The final formulation was decided to be prepared with Captex 200®, lecithin, propylene glycol and bidistilled water. Rheological behaviour, phase stability and type of the microemulsion formulation were investigated by Brookfield viscosimeter, centrifugation test and dye method, consequently. The physical characterization of the formulation (physical appearance, viscosity, refractive index, conductivity, density and turbidity) was investigated at 4°C and 25°C during 6 months while droplet size was investigated for 3 months. Droplet size of the formulation was between 224-280 nm while viscosity was between 89.9-99.5 mPa.S. The release of alendronate from the microemulsion formulation was examined by dialysis method and found to be 97.2% at the end of 7 h.
- **G. C. Actis et al.**[56] used cyclosporin to treat patients with acute steroid-resistant ulcerative colitis since the beginning of 1991. Of the 55 patients so far elected for treatment, 40 received the drug intravenously at 2 mg/kg/day for 14 days, with the responders being maintained on traditional soft-gelatin-capsule cyclosporin at a dose of 6-8 mg/kg/day for 6 months; the remaining 15 received oral microemulsion cyclosporin, 5 mg/kg/day, for 3 months. The microemulsion formulation was therefore more effective than intravenous cyclosporin in achieving the short-term remission of steroid-unresponsive ulcerative colitis. As the maintenance drug, it led to the same frequency of disease relapse as traditional oral cyclosporin. However, because it did not involve invasive in-hospital procedures or cause major toxicity, it was more efficient than the combination of the intravenous and traditional oral drug.

- **B. D. Glass et al.**[57] designed a stable microemulsion formulation to deliver a combination of rifampicin, isoniazid and pyrazinamide in quantities suitable for administration to a paediatric population. The chemical stability of rifampicin, isoniazid and pyrazinamide alone and in various combinations was investigated in different solvents, solubilizing agents and surfactants. An artificial neural network was used to model data from the stability studies and a sensitivity analysis was applied to optimize the selection of the formulation components. Imwitor 308 and Crillet 3, exhibiting the highest overall positive sensitivity were selected to formulate the stable microemulsion. Due to drug dose specifications and solubility limitations, the final formulation contained only rifampicin and isoniazid, since the solubility of pyrazinamide in the lipid and aqueous components of the microemulsion did not achieve the required dose. The stability and solubility of rifampicin were improved in the formulation.
- **P. D. Saussure et al.**[58] prepared a standard oral microemulsion cyclosporin and evaluated it in terms of efficacy and tolerability, of treatment protocol targeting relatively low blood ciclosporin concentrations, in patients with severe, steroid-resistant ulcerative colitis. Sixteen patients were enrolled Even when dosed for a target C0 of 100-200 ng/mL, oral microemulsion cyclosporin for severe, steroid-refractory ulcerative colitis achieves an efficacy similar to that attained with higher, potentially more toxic levels. The oral route should replace intravenous treatment in this clinical setting.
- **P. Keown et al.**[59] compared the safety and tolerability of Neoral-microemusion of cyclosporine with conventional cyclosporine formulation, SIM in a prospective, randomized,d ouble-blind multicenter trial, together with the incidence of acute rejection and graft survival with 167 patients. It was concluded from the results that the superior pharmacokinetic characteristics of the microemulsion formulation of cyclosporine lead to more efficient immunosuppression, without a deleterious impact on clinical safety.
- **M. B. Cheng et al.**[60] investigated the protein (EFE-d, Mr 24177),earthworm fibrinolytic enzyme drug is having a very low oral bioavailability because of its low oil/water partitioning, low membrane permeability and unstable nature in harsh gastric juice. This study explored the possibility of absorption and efficacy enhancement for EFE-d through the delivery of the water-in-oil (w/o)

microemulsions. The w/o microemulsion consisting of Labrafac CC, Labrasol, Plurol Oleique CC 497 and saline (54/18/18/10, % w/w) was developed and characterized, including conductivity, viscosity, particle size and in vitro membrane permeability. The w/o microemulsion and the control solution of EFE-d were administered intraduodenally (or orally) to rats. The w/o microemulsion possessed a higher intestinal membrane permeability in vitro as well as a higher absorption and efficacy in vivo, when compared to control solution. The intraduodenal bioavailability of EFE-d for microemulsions was 208-fold higher than that of control solution and the absolute bioavailability was 17.55%.

- **K. R. Schultz et al.**[61] investigated the Cyclosporine A (CsA) absorption which is highly variable in BMT patients, by giving Neoral, a new microemulsion formulation of CsA that permits increased absorption with less variable pharmacokinetic parameters in non-BMT patients. They evaluated the pharmacokinetics of CsA after BMT in patients received microemulsion CsA. Two oral doses of 3 mg/kg were given 48 h apart between 14 and 28 days after allogeneic BMT in 20 adults, and one dose in seven children, while subjects were receiving a continuous i.v. infusion of CsA. Whole blood samples were taken throughout the dosing interval to calculate the incremental CsA exposure using maximum concentration (Cmax), time to Cmax (*t*max), concentration at 12 h after the dose (C12), the area under the concentration-time curve (AUC), and to establish inter- and intra-patient pharmacokinetic variability. The results suggested that the dose of microemulsion CsA should be adjusted based on recipient age, and the presence of GI inflammation secondary to mucositis or GVHD.
- **A. Pifieyro-Lopez et al.**[62] compared the bioequivalence and tolerability of a generic (test) and abranded (reference) soft-gelatin capsule formulation of cyclosporin A microemulsion 100 mg available in Mexico. This randomized, open-label, 2-period crossover study was perfomed on gealthy males followed by a 2-week washout period and administration of the alternate formulation. In this small study in healthy adult male Mexican volunteers, a single 100-mg dose of the test formulation was bioequivalent to a single 100-mg dose of the reference formulation based on the regulatory definition (rate and extent of absorption). Both formulations were well tolerated.

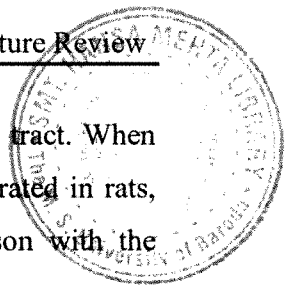
- **J. Y. Zheng et al.**[63] conducted the studies to develop oral leuprolide microemulsions using oleic acid as an absorption enhancer and to evaluate its absorption and pharmacological responses in rats. Oral administration of leuprolide microemulsion at a dose of 3 mg/kg showed a greater in vivo exposure level (*C*max and AUC) than its saline solution. When male rats were orally given a microemulsion formulation of leuprolide acetate at 0.25, 0.5, and 1 mg/day for 14 consecutive days, a significant decrease in testis, prostate and seminal vesicle weights was observed. In a 35-day study, the reduction of the male genital organ weights by once a day treatment (2 mg/rat, qd) was similar to that by twice a day treatment (1 mg/rat, bid) at the same dose level. The activities from oral leuprolide microemulsion were similar to a single subcutaneous injection of Lupron® depot (3.75 mg/rat), a commercial leuprolide product. The results indicated that leuprolide absorbed into systemic blood circulation from the oral microemulsion containing oleic acid reached the plasma level which can exert its pharmacological effects. Increasing oral absorption of leuprolide observed in this study could be mediated by improved membrane permeation from oleic acid and reduced enzymatic degradation from microemulsions.
- **H. Araya et al.**[64] prepared a novel O/W microemulsion formulation, using medium chain fatty acid triglyceride (MCT), diglyceryl monooleate(DGMO-C), polyoxyethylene hydrogenated castor oil 40 (HCO-40), ethanol and PBS (pH 6.8) as an oil phase, a lipophilic surfactant, a hydrophilic surfactant, a solubilizer and an aqueous phase, at the mixture ratio of 5%/1%/9%/5%/80% (w/w), respectively, the O/W microemulsion with an average particle diameter of 20 nm or less was prepared. Moreover, for nine kinds of poorly water soluble compounds, such as Ibuprofen, Ketoprofen, Tamoxifen, Testosterone, Tolbutamide and other new compounds, the solubility to water was increased from 60 to 20,000 times by this O/W microemulsion formulation. The AUCs in plasma concentration of Ibuprofen and a new compound, ER-1039, following single oral administration of these compounds as the O/W microemulsion to fasted rats were equivalent to that of solution administration or increased by nine and two times that of suspension administration, respectively.
- **A. Cilek et al.**[65] developed a microemulsion formulation providing an improved efficacy of orally administered insulin. The microemulsions were prepared using Labrafil M 1944 CS, Phospholipon 90 G (lecithin), absolute alcohol and bi-distilled water. Aprotinin (2500 KIU/g) was added as the enzyme inhibitor tothe formulation.

Upon the administration of intragastric rh-insulin solution (IS) to non-diabetic rats, the plasma glucose and insulin levels were not changed significantly. Therefore, the hypoglycemic effect caused by subcutaneous rh-insulin solution (SC), microemulsion containing rh-insulin (IME) and microemulsion containing rh-insulin and aprotinin (IMEA) were analyzed in diabetic rats. No significant difference could be found between the pharmacokinetic parameters of the IME and IMEA administered groups. Addition of aprotinin to the microemulsion containing rh-insulin increased bioavailability when compared to those not containing it, although the difference is not significant.

- **S. K. Kima et al.**[66]prepared the microemulsion for oral delivery of low molecular weight heparin (LMWH), LMWH–DOCAwas synthesized by chemical conjugation of LMWH and deoxycholic acid (DOCA) and this conjugate. The coupling ratios of DOCA to LMWH for LD1 and LD2 were 1.33 and 2.37, respectively. The microemulsion was composed of tricaprylin, surfactant mixture (TweenR 80 and SpanR 20) and LMWH–DOCA in water, and their volume ratio was 5:3:1: 1. Pharmacokinetic parameters of LMWH were not significantly changed by conjugation with DOCA; however, when LMWH–DOCA in tricaprylin microemulsion was orally administered in mice, its bioavailability was increased up to 1.5%. Furthermore, the enhancing effect of the conjugated DOCA in the tricaprylin microemulsion on the absorption of LMWH in the intestine was more significantly increased in monkey than in mice. Since the tricaprylin microemulsion could dissolve LMWH–DOCA, this formulation could maximize the enhancing effect of the conjugated DOCA on the absorption of LMWH in the intestine.
- **K. C. Lyons et al.**[67] investigated the bioavailability (BA) of radio-labelled *N*-acetylglucosaminyl-*N*-acetylmuramyl dipeptide (GMDP) was low when administered by oral gavage as an aqueous solution to conscious male Sprague–Dawley rats (8.39±4.4% (mean±S.D., n=3). To assess the likely factors contributing to the poor BA of GMDP, the stability of GMDP in the lumen of the gastrointestinal (GI) tract was examined in vitro, using ex vivo GI contents. First pass metabolism was considered to be unlikely to be the primary limitation to the oral bioavailability of GMDP and therefore, that the oral bioavailability of GMDP was likely limited by instability in the lumen of the gastrointestinal tract and low intestinal permeability. A water-in-oil (w:o) microemulsion formulation subsequently developed to address

these problems was trialed in a preliminary bioavailability study in rats and enhanced the bioavailability of GMDP ten-fold when administered intraduodenally, indicating that w:o microemulsions may represent a viable mechanism for enhancing the bioavailability of poorly GI-stable and poorly permeable peptide-based molecules.

- **J. M. Sarciaux et al.**[68] investigated the peptide drugs which are increasingly becoming a very important class of therapeutic agents with the rapid advances in the field of biotechnology engineering. However, these drugs are generally not suitable for oral administration. In this review, the main physico-chemical and biopharmaceutical characteristics of peptides are summarized. The obstacles to peptide drug absorption and the different possibilities for solving these difficulties are listed. Results using this formulation approach for oral drug delivery of peptides are apparently promising with some specific peptides such as cyclosporin. Various mechanisms are only beginning to be understood and further investigations need to be performed in this area to explain the results obtained with some peptides.
- **C. Yong et al.**[69] prepared Rutaecarpine-loaded microemulsion composed of 10.8% polyethylene glycol 400, 7.2% Tween 80, 20% caster oil, and 62% water were previouslyreported to be physically and chemically stable for at least 6 months. For the development of a Rutaecarpine-loaded microemulsion, here we studied the pharmacokinetic profiles of rutaecarpine after oral and intravenous administration of rutaecarpine-loaded microemulsion compared to suspension. The AUC of rutaecarpine from microemulsion after oral and intravenous administration increased about three-fold compared with that from suspension. our results indicated that the microemulsion system composed of castor oil, polyethylene glycol 400, Tween 80, and water could be a more effective oral and parenteral dosage form for rutaecarpine.
- **K. Itoh et al.**[70] prepared and optimized formulation of N-4472, N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N-[4-(Nbenzylpiperidyl)]urea, which was a poorly water-soluble drug, was developed by utilizing the complexation between N-4472 and L-ascorbic acid (VC). It was found that the formulation with Gelucire 44/14, HCO-60 and sodium dodecyl sulfate provided a self-microemulsifying system consisting of fine droplets in approximately 18 nm size with a narrow distribution. 1H-NMR spectroscopic study indicated that the N-4472/VC complex was molecularly incorporated into surfactant molecular assembly in the microemulsion droplets. It was found that the N-4472 microemulsion was stable at the



pH range from 2.0 to 7.0, suggesting the stability in the gastrointestinal tract. When the microemulsion containing N-4472/VC complex was orally administrated in rats, high AUC value of N-4472 (2 to 4-fold) was observed in comparison with the aqueous solution containing N-4472/VC complex..

- **Z. Gao et al.**[71] prepared microemulsionsof cyclosporine A with varying weight ratios of surfactant to cosurfactant were prepared using caprylic:capric triglyceride (Captex 355) as an oil, polyoxyethylated castor oil (Cremophor EL) as a surfactant, Transcutol as a cosurfactant and saline. The area of o:w microemulsion region in pseudo-ternary phase diagram was increased with increasing ratio of Cremophor EL to Trancutol. The solubility of cyclosporin A in microemulsion systems reached the maximum with 2:1 mixture of Cremophor EL and Trancutol. The dispersion rate of oil–surfactant–cosurfactant mixture with varying ratios of Cremophor EL to Trancutol in aqueous media assuming the condition of gastric fluid decreased with the increase of Cremophor EL to Trancutol weight ratio. The absolute bioavailability of cyclosporin A loaded in this microemulsion system was increased about 3.3 and 1.25 fold compared with Sandimmun and Sandimmun Neoral. The enhanced bioavailability of cyclosporin A loaded in this microemulsion system might be due to the reduced droplet size of microemulsion systems.
- **A. Acharya et al.**[72] Studied the phase behaviours of quaternary isopropyl myristate, poly oxyethelene (4) lauryl ether(Brij – 30), isopropyl alcohol (i-PrOH)and water systems have been studied at three different composition of Brij-30-i-PrOH as 2:1, 1:1 and 1:2 (w/w) at 303K.It can form sizable, non-birefrengent and isotropic micro emulsions which shows shear thinning and temperature dependent viscosity decrease. All prepared micro emulsions are fairly poly disperse and have dimensions falling in the range of 2-34 nm.
- **Neubert Reinhard H. H. et al.**[73] investigated the dermal administration of highly hydrophilic drug diphenhydramine, in colloidal system with an aqueous colloidal phase in the presence of glycolipid as a penetration modifier. It has been demonstrated that the drug is sufficiently liberated form micro emulsion and hydro gel containing glycol lipid as a penetration modifier when diphenhydramine was incorporated in micro emulsion systems a high penetration of diphenhydramine into dipper skin layer and acceptor fluid could be observed (without glycolipid).

Work done on Cyclodextrin Inclusion complexes.

- **S. Shimpi et al.**[74] reviewed the use of cyclodextrin in the different routes of drug administration. The article gives the chemistry of cyclodextrins and addresses the issue of the mechanism of drug release from cyclodextrin complexes. Dilution, competitive displacement, protein binding, change in ionic strength and temperature and drug uptake by tissues are the different release mechanisms of the drug from the drug-cyclodextrin complex discussed here. Use and its limitations in the different drug delivery systems like nasal, ophthalmic, transdermal and rectal drug delivery are explained. The application of the cyclodextrins in the oral drug delivery is detailed in this review. Many studies have shown that cyclodextrins are useful additives in the different routes of drug administration because of increased aqueous solubility, stability, bioavailability and reduced drug irritation.
- **K. Uekama et al.**[75] designed and evaluated a number of CyD derivatives, CyD polymers and CyD conjugates have been for pharmaceutical uses. The modification of CyD molecules has proceeded and become more routine. In addition, the preferable combination of CyDs and other pharmaceutical excipients or carriers such as hydrophilic polymers, nanoparticles and liposomes should foster the progress of the advanced dosage forms. Fortunately some hydrophilic β-CyDs have opened the door in practical use in the pharmaceutical formulations. Owing to the increasingly globalized nature of the CyD-related science and technology, development of theCyD-based drug formulation is also rapidly progressing.
- **B. Bendeby et al.**[76] studied the inclusion complexes between a-cyclodextrin (a-CD) and adamantane, 1-adamantanol, 1-(hydroxymethyl)-adamantane, 2-adamantanol, and 1,3-adamantanediol in aqueous solution by 1H-NMRspectroscopy using both non-exchangeable and exchangeable protons. The complexation-induced 1H-NMR shifts (CIS) and NOEs of non-exchangeable protons, as well as the CIS, NOEs, temperature coefficients, and linewidth of signals from exchangeable hydroxy protons have been determined. The stoichiometry of the a-CD/2-adamantanol complex could not be determined with certainty, but the NMR data suggested equilibrium between 2:1 and 1:1 complex.
- **N. Ozdemir et al.**[77] studied enhancement of the bioavailability of furosemide (FR) which is having lower solubility of active material in the gastric medium, first enhancing its solubility by preparing an inclusion complex of it with beta-

cyclodextrin (β-CD) in a 1:1 proportion using the kneading method followed by bilayer floating tablets preparation. After dissolution rate studies were performed using the continuous flow-through cell method, the formulation that provided delivery of active material near the target profile was given to six healthy male volunteer subjects, and in vivo tests were also performed. Further, values of the area under the plasma concentration-time curve (AUC) obtained with the floating dosage form were about 1.8 times those of the conventional FR tablet in blood analyses; maximum and minimum plasma concentrations were also found to be between the desired limits.

- **J. Mielcarek e79t al.**[78] studied the methods of obtaining and physicochemical properties of inclusion complexes of amlodipine (AM) and felodipine (FL) with methyl-b-cyclodextrin (MCD) clathrates have been studied. Solid complexes were obtained by two methods: the kneading one and lyophilization with the drug and MCD at the molar ratio of 1:1. The identity of the obtained clathrates was confirmed by IR, ^{13}C-NMR spectra and DSC measurements.
- **S. Junco et al.**[79] compared the physicochemical characteristics of the solid complexes of naproxen with β-cyclodextrins prepared by traditional methods (kneading, freeze-drying and spray-drying) and using a supercritical fluid technology. The unusual solvent properties of carbon dioxide above their critical temperature and pressure were exploited in order to prepare inclusion compounds. Complexes prepared using supercritical fluid technology showed similar properties to those of freeze-drying and spray-drying complexes as proved by DSC, FT-IR and UV. The new experimental supercritical fluid unit built. The new experimental supercritical fluid unit built to prepare naproxen-β-CD (1:2M) solid complexes avoids the use of dangerous ammonium hydroxide as solvent to prepare naproxen-β-CD (1 : 2 molar ratio) solid complexes avoids the use of dangerous ammonium hydroxide as solvent.
- **J. Peeters et al.**[80] investigated the complex formation of alfaxalone with various cyclodextrins (2-hydroxypropyl-β-cyclodextrine [HPBCD], β-cyclodextrin [BCD] and 2-hydroxypropyl-γ -cyclodextrin [HPGCD]) using phase solubility analysis. The complexation with HPBCD was studied in more detail by looking at the effect of temperature on the stability constants using phase solubility analysis. HPLC-analysis was used to measure the dissolved amount of alfaxalone. The solubility of alfaxalone increases linearly with increasing concentration of cyclodextrin, suggesting the formation of a 1: 1 complex. The effect of temperature on the complexation constant

was also studied at elevated temperature. Increasing the temperature results in an increased S0 (solubility without HPBCD) and a decrease in the value of the complexation constant.

- **P. Schwinte et al.**[81] studied that cyclodextrin amphiphiles heptakis[6-(1_-sulfonato-3_-propyl)-6-thio-2,3-di-O-acetyl]-*β*-cyclodextrin, heptakis[6- (6_ -sulfonato-2_-benzimidazolyl)-6-thio-2,3-di-O-acetyl]-*β*-cyclodextrin, and heptakis[6-(*β*-D-glucosyl)-6-thio-2,3-di-Oacetyl]- *β*-cyclodextrin show to form aggregates in water by fluorescence measurements on the binding of 2-anilinonaphthalene, and by laser light-scattering measurements. Estimates of aggregation number have been obtained. These aggregates successfully incorporate clofazimine, a lipophilic heterocyclic drug, and increase its water solubility by a factor of 30 to 50.
- **M. Ishkawa et al.**[82] studied the effects of modified cyclodextrins HP-β-cyclodextrin and methyl-β-cyclodextrin *in vitro* on cDNA-expressed human cytrochrome P-450 (CYP) activities (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4). The modified CDs inhibited the activities of CYP2C19 and CYP3A4 while enhancing CYP2C9 activity by 140 -176% relative to the control values at lower concentrations.
- **A. Gordano et al.**[83] immobilised O-octyloxycarbonyl β-cyclodextrins in flat sheet PEEK-WC membranes. The membranes were prepared by phase inversion method and characterised. β-cyclodextrin (β-CD) catalytic action in the p-nitrophenylacetate (PNPA) hydrolysis to p-nitrophenol (PNP) was studied. The β-CD acylic carbonate derivative shows an effective catalytic action when incorporated in PEEK-WC membranes, by showing an enzyme-like behaviour. The membranes were tested at different temperatures and substrate concentrations and the value of activation energy for the reaction was estimated. It is well known that β-CD have a catalytic action, but their immobilisation in a polymeric matrix enhances the reaction rate, in fact the entrapment optimises the interaction with the substrate and increases the chemical stability of the catalyst.
- **Y. Tozuka et al.**[84] applied the method of co-grinding with cyclodextrins (CDs) to a poorly water soluble drug, ONO-8713 (solubility; 0.92 lg/ml in H2O at 25 °C) as a method to prepare nanoparticles. ONO-8713 was co-ground with various CDs in a vibration mill. α-Cyclodextrin, β-CD, gamma-CD, CD derivatives and some sugars were used as cogrinding additives. Suitable moisture content in the co-grinding system was required to achieve maximum nanoparticle yield. When ONO-8713 was

co-ground with b-CD (molar ratio of b-CD:drug ¼ 5:1) at 12% moisture, 85% of drug recovered as nanoparticles with a mean particle size of 120 nm. Nanoparticle yield achieved 90% when hydroxypropyl-b-CD was used as a co-grinding additive.

- **K. Rajendrakumar et al.**[85] compared the inclusion behavior of sulfobutyl ether-7 derivative of β-cyclodextrin (SBE7βCD), in solution and solid state with that of natural β-cyclodextrin (βCD) toward a poorly water-soluble anti-inflammatory agent, rofecoxib prepared by grinding in a ball mill. The formation of inclusion complexes with βCD and SBE7βCD in the solid state were confirmed by infrared spectroscopy, differential scanning calorimetry, X-ray diffractometry, scanning electron microscopy and in the liquid state by phase solubility analysis, nuclear magnetic resonance spectroscopy and circular dichroismstudies Solubility enhancementbwas much greater for the rofecoxib-SBE7-β-CDcomplex compared to drug-β-CDcomplex. The stability constant obtained for the SBE7-β-CD inclusion complex of rofecoxib was the highest. Finally, dissolution profiles obtained suggest that SBE7-β-CD is more effective than *β*-cyclodextrin in improving the pharmaceutical properties of rofecoxib.
- **V. Barillaro et al.**[86] determined the pharmacokinetic parameters of miconazole after oral administration of a miconazole/hydroxypropyl-g-cyclodextrin(HPgCD)/ L-tartaric acid inclusion complex produced by supercritical carbon dioxide processing. The pharmacokinetics of the miconazole ternary complex (CPLX), of the corresponding physical mixture (PHYS), and of miconazole alone (MICO) were compared after oral administration. Six mixed-breed pigs received each formulation as a single dose (10 mg miconazole/kg) in a crossover design. Miconazole plasma concentrations were determined by a high performance liquid chromatography method. Preliminary in vitro dissolution data showed that CPLX exhibits a faster and higher dissolution rate than either PHYS or MICO.
- **Y. Michel et al.**[87] studied the methylated cyclodextrins as their properties regarding the solubility and the solubilization power for hydrophobic guests are well documented especially concerning Heptakis (2,6-di-Omethyl)-cyclodextrin (DIMEB) and Heptakis (2,3,6-tri-Omethyl)- cyclodextrin (TRIMEB). In order to avoid the use of human serum albumin (HSA), this property has been applied here to the solubilization of a very sparingly water-soluble fatty acid derivative (16-iodo-3-methylhexadecanoic acid), which is known to localise in viable myocardial cells, allowing the generation of functional images reflecting the viability of the cardiac

tissue through the use of radiolabeled analogue. Nuclear magnetic resonance (NMR) was used throughout this study to evidence that the observed solubilization and stabilisation (under conditions required for sterilisation) induced by cyclodextrins are due to the formation of a true inclusion complex and not to nonspecific interactions; This technique further allows to derive thermodynamic as well as structural informations for this complex.

- **T. Hladon et al.**[88] prepared the inclusion complex of mefenamic acid with β-cyclodextrin by the method of coprecipitation from diethyl ether. The product was identified by the thermogravimetric and X-ray methods. The complex stability constants were determined by the potentiometric method. The effect of β-CD on the solubility and stability of mefenamic acid was analysed.
- **M. E. Pina et al.**[89] investigated the role of b-cyclodextrin (β-CD) on the apparent solubility of theophylline by the solubility method. Binary systems of theophylline and β-CD were prepared using the dry co-grinding method. Their characterization was performed by differential scanning calorimetry (DSC). The dissolution rate of theophylline and theophylline/β-CD and dissolution studies of matrix tablets prepared from mixtures containing theophylline and ground theophylline were carried out. It can be concluded that β-CD is related to an increase in the apparent solubility and dissolution rate of the drug, promoting improvement on the release of theophylline from matrices manufactured with hydroxypropylmethylcellulose (HPMC). This can be attributed to the amorphous state and the increased wettability of the drug.
- **G. Castronuovo et al.**[90] studied he formation of complexes of α-cyclodextrin with 1,2-alkanediols, α,ω-alkanediols and some cycloalkanols calorimetrically at 25 °C in water, in 7 mol kg^{-1} aqueous urea and in 3 mol kg^{-1} aqueous glucose. When a complex is formed, calorimetry enables the calculation of both the enthalpy and the association constant, from which the free energy and the entropy of the process can be obtained. The effect of the variation of the aqueous medium on the hydration of the interacting substances and the consequent changes in the association parameters has been investigated. As respect to water, complexes are less stable in urea and more stable in glucose. The analysis of the data shows that this is the result of a different enthalpy-entropy balance in the two solvent media. Deaquation of the interacting substances plays a major role in determining the stability of the inclusion complexes.

- **I. Bea et al.**[91] studied the complexation of p-tert-butylphenyl p-tertbutylbenzoate and N-(p-tert-butylphenyl)-p-tert-butylbenzamide with a b-cyclodextrin derivative formed by two cyclodextrin units linked by a disulfide bridge on one of the C6atoms has been studied by computational methods. The better amide solubility and the better internal interactions of the ester complex explain the experimentally observed better association constant for the ester. The free-energy perturbation methodology and molecular mechanics/Poisson–Boltzmann surface area analysis have been used to explain the problem and to compare the results.
- **V. J. Stella et al.**[92] studied the i.v. pharmacokinetics of methylprednisolone (20 mg/kg) in six rats after administration in a co-solvent (60:12:28 PEG 400/ethanol/water) mixture, a 0.075 M SBE4-/β-CD solution (a sulfobutyl ether derivative variably substituted on the 2-, 3- and the 6-positions of/β-cyclodextrin) and as its two water-soluble prodrugs, the 21-phosphate ester, disodium salt and the 21-hemisuccinate ester, monosodium salt. The AUC values of methylprednisolone from its 21-phosphate and 21-hemisuccinate esters and that from the co-solvent confirmed that i.v. administered drugs such as methylprednisolone, appear to be rapidly and quantitatively released from SBE4-β-CD inclusion complexes. Modified cyclodextrins such as SBE4-β-CD may provide an alternative to the use of co-colvents, and possibly even prodrugs, for the parenteral delivery of sparingly water-soluble drugs such as methylprednisolone.
- **G. Ceschel et al.**[93] studied *ex-vivo* permeation of newly developed formulations containing dehydroepiandrosterone (DHEA) was carried out to investigate vehicles that increase drug permeation through the skin. To enhance the solubility of DHEA, its complex form with α-cyclodextrin was used. In addition, the two forms (pure drug and complex form) were introduced in hydrophilic (water), lipophilic (paraffin oil), and microemulsion vehicles to evaluate the synergic effect of cyclodextrins and microemulsion vehicles on solubility and permeation. From theresults, DHEA solubility is notably conditioned by the type of the vehicle used: the highest solubilities (both for pure and complex drug forms) were obtained with microemulsion, followed by paraffin oil and water. The major flux was obtained in complex of DHEA with α-cyclodextrins in the microemulsion vehicle. Therefore, this typeof vehicle and drug form would be very useful in the development of a topical formulation containing DHEA.

- **M. M. Ghorab et al.**[94] evaluated β-cyclodextrin (β-CD) as a vehicle, either singly or in blends with lactose (spray-dried or monohydrate), for preparing a meloxicam tablet. The tablets were prepared by direct compression and wet granulation techniques.The effect of β -CD on the bioavailability of meloxicam was also investigated in human volunteers using a balanced 2-way crossover study. Phase-solubility studies indicated an AL-type diagram with inclusion complex of 1:1 molar ratio. The powder blends and granules of all formulations showed satisfactory flow properties, compressibility, and drug content. All tablet formulations prepared by direct compression or wet granulation showed acceptable mechanical properties. The dissolution rate of meloxicam was significantly enhanced by inclusion of β -CD in the formulations up to 30%. The mean pharmacokinetic parameters (Cmax, Ke, and area under the curve [AUC]0-∞) were significantly increased in presence of β-CD. No important difference between tablets prepared by direct compression and those prepared by wet granulation was seen.It was concluded that β -CD is particularly useful for improving the oral bioavailablity of meloxicam.
- **A. Usayapant et al.**[95] studied the effects of 2-hydroxypropyl-β-cyclodextrin (HPCD) on drug solubility and drug release from suppository bases for dexamethasone (DX), dexamethasone acetate (DXA), hydrocortisone (HC), hydrocortisone acetate (HCA), and prednisolone acetate (PNA). It was found that HPCD significantly increased the aqueous solubility of all five steroids, and the increased drug solubility significantly influenced the drug release from the polyethylene glycol (PEG) base but not from the cocoa butter base.
- **T. Ikeda et al.**[96] investigated the inclusion complex formation between cyclodextrin and autoinducer of gram negative bacteria in aqueous solution by 1D 1H-NMR and ROESY spectra. An inhibition effect was observed on autoinducer activities of quorum sensing in *Pseudomonas aeruginosa* by adding cyclodextrins to the bacterial culture medium.
- **Z. H. Qi et al.**[97] studied the solubility of tretinoin, also known as vitamin A acid or *all-trans* retinoic acid (t-RA) has very low water solubility (< 0.2 μg/ml) by using concentrated solutions of *β*- cyclodextrin (BCD) derivatives to increase the aqueous solubility of t-RA. The present study demonstrates that substantial enhancement to the t-RA solubility (e.g., > 2000 fold) can be achieved by using low concentration of BCD (1.5%) plus a small amount of additives (0.1%–1%), such as carboxymethyl

cellulose, sodium acetate and potassium phosphate. This simple yet effective approach can also improve the loading of t-RA up to 10 times over the previously published results using CD derivatives including hydroxypropyl BCD (HPBCD). The findings may lead to development of an oral t-RA formulation in an aqueous medium.

- **K. P. R.Chowdary et al.**[98] studied the complexation of celecoxib with hydroxypropyl β-cyclodextrin (HPβCD) in the presence and absence of 3 hydrophilic polymers—polyvinyl pyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG) with an objective of evaluating the effect of hydrophilic polymers on the complexation and solubilizing efficiencies of HPβCD and on the dissolution rate of celecoxib from the HPβCD complexes. Solid inclusion complexes of celecoxib-HPβCD were prepared in 1:1 and 1:2 ratios by the kneading method, with and without the addition of hydrophilic polymers. The solubility and dissolution rate of celecoxib were significantly improved by complexation with HPβCD. The celecoxib-HPβCD (1:2) inclusion complex yielded a 36.57-fold increase in the dissolution rate of celecoxib. The addition of hydrophilic polymers also markedly enhanced the dissolution rate of celecoxib from HPβCD complexes: 72.60-, 61.25-, and 39.15-fold increase was observed with PVP, HPMC, and PEG, respectively.
- **J. L. H. Johnson et al.**[99] developed and evaluated a solid nonaqueous oral dosage form for a new hepatitis C drug, PG301029, which is insoluble and unstable in water. Hydroxypropyl-β-cyclodextrin (HPβCD) and PG301029 were dissolved in glacial acetic acid. The acetic acid was removed by rotoevaporation such that the drug exists primarily in the complexed form. The stability of formulated PG301029 was determined upon dry storage and after reconstitution in simulated intestinal fluid (SIF), simulated gastric fluid (SGF), and water. Formulated PG301029 was found to be stable upon storage and can be reconstituted with water to a concentration 200 times that of the intrinsic solubility. Once reconstituted, the powder dissolves rapidly and PG301029 remains stable for 21 hours in SGF, SIF, and water. The unique use of acetic acid and HPβCD results in a solid dosage form of PG301029 that is both soluble and stable in water.
- **I. Nandi et al.**[100]. made an attempt to improve the aqueous solubility of a model hydrophobic drug, progesterone by using PEG-400, polysorbate 80, and 2 CDs (Trappsol HPB and Captisol). The aqueous solubility of progesterone improved significantly from 0.007 mg/mL by the addition of PEG-400, CDs, and polysorbate

80. In systems containing various amounts of PEG-400 and 3% Trappsol HPB in water (% wt/wt), the theoretical solubility was calculated by adding the solubilities in the individual systems. The observed solubility values were up to 96% higher than the theoretical values. The effect of synergism was significant in 5% to 50% PEG-400/water systems containing Trappsol HPB. Systems containing Captisol did not show such synergistic effects. In general, the addition of polysorbate 80 to the PEG-400/water systems containing CDs affected synergism negatively.

- **S. Lee et al.**[101] showed complexes of itraconazole (ITR), an antifungal agent with 2-hydroxypropyl- β-Cyclodextrin (HP- β-CD) were formed by using a supercritical antisolvent (SAS) process. Optimum The optimum process condition was investigated in the temperature range 35~65^{0}C and pressures ranging from 83-140 bars. To evaluate the degree of complexation, thermal behaviour of solid micro particulate complexes was investigated by Differential Scanning Calorimetry. The experimental results obtained for the solubility and dissolution rate in a buffer solution at pH 1.2 showed a significant increase of the solubility and dissolution rate of water-insoluble itraconazole suggesting that SAS is a promising method for the preparation of inclusion complex.
- **K.Uekama et al.**[102] studied the complex formation of diltiazem, which is freely soluble in water and having a short half life with β-Cyclodextrin derivatives such as Diethyl- β-Cyclodextrin, Triethyl β-Cyclodextrin. The solid complexes of diltiazem with diethyl-and triethyl- β-Cyclodextrin in (1:1 M) were prepared by kneading method. Pharmacokinetic parameters C_{max}, T_{max}, AUC, MRT, VRT were measured following oral administration of tablets of drug alone and its ethylated β-Cyclodextrin complexes to five rats.It was concluded that diethyl- β-Cyclodextrin complex may be a candidate for the sustained release of diltiazem. A combination of triethyl β-Cyclodextrin and hydrophilic cyclodextrin derivatives may also offer a more suitable preparation for the modified release dosage forms.
- **A. H. Al-marzouqi et al.**[103] studied the complex formation of Itraconazole (ITR), an antifungal agent with β-Cyclodextrin (β-CD) which showed an improvement in the solubility of drug in aqueous solution. Drug formulations of Itraconazole were prepared by complexation of drug into β-cyclodextrin using super critical carbon dioxide ($SCCO_2$). The formation of an inclusion complex in $SCCO_2$ method was

verified by UV spectroscopy, P-XRD and SEM analysis and compared to those obtained by physical mixing and co-precipitation method.

- **V. R. Sinha et al.**[104] prepared inclusion complexes of celecoxib with –cyclodextrin in solution and solid state. Complexes were prepared by spray drying while physical mixtures were obtained by simple blending and characterized by IR, X-ray diffraction and NMR spectroscopy, SEM, DSC and polarimetry. Dissolution study showed that celecoxib entrapped in spray dried complexes dissolved much faster than pure drug and physical mixtures.
- **E. Alvarez-parrilla et al.**[105] studied the effect of electrostatic interactions on the complexation of ionic guests by charged β-cyclodextrin derivative. Special attention is paid to the numerous studies concerning the effect of electrostatic interactions on the complexation of fluorescent and UV probes; the catalytic and chiral recognition properties of β-cyclodextrin derivatives; the complexation of two bile salts (sodium cholate, NaC, and sodium deoxycholate, NaDC). The formation of three in one complexes between NaC and Alkyl diamino β-cyclodextrin derivatives is also presented.
- **F. M. G. Hartell et al.**[106] prepared inclusion complex of artesunic acid with β-cyclodextrin and prepared complexes were characterized by UV, NMR and molecular modeling.NMR results indicate artesunic acid forms 1:1 molor complex with β-cyclodextrin and aqueous solubility of the compound was increased.
- **H. H. Yoshii et al.**[107] prepared inclusion complexes of d-limomene, phenyl ethanol, aceto phenone, or methanol in a slurry form α-, β- and γ-cyclodextrins in organic solvents or alcohol under anhydrous conditions. Ethanol and methanol were found to be good solvents for this method. There existed an optimal amount of ethanol for the maximum inclusion of d-limonene as a guest compound. However, an excess ethanol inhibited the inclusion. An adsorption model of alcohol on cyclodextrin, analogous to the substrate inhibition model of enzyme kinetics to correct the inclusion ratio with the amount of alcohol added to cyclodextrin.
- **S. K. Leticia et al.**[108] compared carbamazepine (CBZ) solid dispersions prepared by spray drying of aqueous dispersions with the corresponding physical mixtures. The influence of the association of β-CD and HPMC on the CBZ dissolution profile of the preparations was investigated. Results demonstrated that CBZ release from solid dispersions is dependent on the ratio of β-CD and HPMC. The spray-drying process

confers better homogeneity to CBZ polymeric dispersions than the physical mixture process.

- **I. Corrigan et al.**[109] prepared successfully hydrocortisone-PVP composites using the supercritical fluid gas anti solvent method (GAS). Analysis by DSC and powder XRD indicated that these systems were more crystalline than corresponding systems prepared by spray drying. These composites prepared by the GAS method were more similar in physicochemical properties to co-precipitates prepared by conventional solvent evaporation. However, they have dissolution rates lower than those of corresponding systems prepared by the other processing methods but equivalent to those of corresponding physical mixtures.
- **M. S. Nagarsenker et al.**[110] described the formulation of solid dispersions of ketorolac using HP β-CD and β-CD as carriers, to improve the aqueous solubility of the drug, thus enhancing its bioavailability. DSC and XRD studies indicated loss of crystalline nature of the drug, in the dispersions prepared with HP β-CD, NMR studies revealed a strong interaction between drug and HP β-CD. Solid dispersions of the drug with β-CD retained the crystalline nature of the drug. HP β-CD proved to be superior to β-CD, as a carrier in the kneaded dispersion prepared using 1:1 alcohol-water mixture.

2.3. References

1. P. Bajaj, S.S. Sharma, K.S. Vijayarraghavan, A.S. Gawde, V. Baliga, A. Desai, Role of cilostazol in clinical practice: an overview, ***Indian Practitioner,*****2005**,58 85-98.
2. Cilostazol drug information, Otsuka pharmaceutical co., Ltd, Japan, U.S. Patent No. 4277479.
3. Cilostazol drug information, www.drugs.com/cons/Cilostazol.html.
4. Cilostazol drug information, www.rxlist.com.
5. K. Schror, The pharmacology of cilostazol, ***Diabetes Obes. Metab.,*****2002**,4,14-19.
6. S. Shintani, Y. Toba, S. Suzuki, S. Ninomiya, M. Umezato, T. Hiyama, General pharmacological properties of cilostazol, a new antithrombotic drug. Part I: Effects on the central nervous system, ***Arz. Forsch.,*****1985**,35,1157-1162.
7. S. Shintani, K. Watanabe, K. Kawamura, T. Mori, T. Tani, Y. Toba, H. Sasabe, N. Nakagiri, O. Hongoh, S. Fujita, General pharmacological properties of cilostazol, a new antithrombotic drug. Part II: Effect on the peripheral organs, ***Arz. Forsch.,*****1985**,35 1163-1172.
8. S.K. Woo, W.K. Kang, K.I. Kwon, Pharmacokinetic and pharmacodynamic modeling of the antiplatelet and cardiovascular effects of cilostazol in healthy humans, ***Clin. Pharmacol. Ther.,*****2002**,71,246-252.
9. H. Akiyama, S. Kudo, T. Shimizu, The absorption, distribution and excretion of a new antithrombotic and vasodilating agent, cilostazol, in rat, rabbit, dog and man, ***Arz. Forsch.,*****1985**,35, 1124-1132.
10. H. Toyobuku, I. Tamai, K. Ueno, A.Tsuji, Limited influence of P-glycoprotein on small-intestinal absorption of cilostazol, a high absorptive permeability drug, ***J. Pharm. Sci.,*****2003**,92,2249-2259.
11. R. Abbas, C.P. Chow, N.J. Browder, D. Thacker, S.L. Bramer, C.J. Fu, W. Forbes, M. Odomi, D.A. Flockhart, *In vitro* metabolism and interaction of cilostazol with human hepatic cytochrome P450 isoforms, ***Hum. Exp. Toxicol.,*****2000**,19, 178-184.
12. Y. Kimura, Selective type III phosphodiesterase inhibitor as an antithrombotic agent, ***Nippon Yakurigaku Zasshi.,*****1995**,106, 205-216.
13. P. Collins P, J. Brittenden, Treatment of intermittent claudication: cilostazol, ***Hosp. Med.,*****2004**,65,466-470.
14. J. Kambayashi, Y. Liu, B. Sun, Y. Shakur, M. Yoshitake, F. Czerwiec, Cilostazol as a unique antithrombotic agent, ***Curr. Pharm. Des.*****, 2003**,9, 2289-2302.

15. S. Mallikaarjun, W.P. Forbes, S.L. Bramer, Interaction potential and tolerability of the coadministration of cilostazol and aspirin, ***Clin. Pharmacokinet.***, **1999**,37, 87-93.
16. S.L. Bramer, J. Brisson, A.E. Corey, S. Mallikaarjun. Effect of multiple cilostazol doses on single dose lovastatin pharmacokinetics in healthy volunteers, ***Clin. Pharmacokinet.***, 1999,37, 69-77.
17. J. Angulo et al. IC351 enhancees NO-mediated relaxation of humen arterial and trabecular penial smooth muscle. ***Eur. Urol.*** **2001**,39(5),106.
18. B. Patterson, A. bedding, H. Jewell, C. Payne and M. Mitchell, Dose normalized pharmacokinetics of single-dose Tadalafil(IC351) in healthy volunteers, ***Int. J. Impo. Res.***,**2001**,13(5),S62.
19. B. Patterson, A. bedding, H. Jewell, C. Payne and M. Mitchell,The effect of interensic and extrinsic factors on the pharmacokinetic properties of Tadalafil(IC351). ***Int. J. Impo. Res.***, **2001**,13(5),S63.
20. Summery and producy characterization. Clialis Europian Publec Assessment Report(EPAR).First published June 12,2002. Available at:http//www.emea.eu.int/ humandocs/ Humans/EPAR/clisis/cialis.htm.Accessed January 31,2004.
21. Eli Lilly and Company Limited. Summery of product characterizations: Clilis. www.emc.vhn.net.Acessed January 31,2004.
22. C.Y. Wu, L.Z. Benet, Predicting drug disposition via application of BCS: Transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system, ***Pharm. Res.***,**2005**,22,11–23.
23. G.L. Amidon, H. Lennernäs, V.P. Shah, J.R. Crison, A theoretical basis for a biopharmaceutic drug classification: the correlation in vitro drug product dissolution and in vivo bioavailability, ***Pharm. Res.***,**1995**,12,4,13–420.
24. C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, ***Adv. Drug Deliv. Rev.***,**1997**,23,3–25.
25. J. R. Robinson, Introduction: Semi-solid formulations for oral drug delivery, ***Bull. Technique Gattefosse***, **1996**,89,11—13.
26. B. J. Aungst, Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeability, ***J. Pharm. Sci.***,**1993**,82,979—987.
27. T. Gershanik, S. Benita, Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs, ***Eur. J. Pharm. Biopharm.***,**2000**,50,179—188.

28. S. M.Khoo, A. J Humberstone., W. N. Charman, Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine, ***Int. J. Pharm.*****,1998,**167155—16.

29. J. Y. Kim, Y. S Ku.,Enhanced absorption of indomethacin after oral or rectal administration of a self-emulsifying system containing indomethacin to rats ,***Int. J. Pharm.*****,2000,**194, 81—89.

30. T. R. Kommuru, B. Gurley, M. A. Khan, I. K. Reddy, Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q_{10}: formulation development and bioavailability assessment, ***Int. J. Pharm.*****,2001**,212,233—246.

31. S. Nazzal, I. I Smalyukh, O. D. Lavrentovich, M. A.Khan, Preparation and in vitro characterization of a eutectic based semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation, ***Int. J. Pharm.*****,2002,** 235247—265.

32. H. J. Kim Yoon K. A., Hahn M., Park E. S., Chi S. C., Preparation and In Vitro Evaluation of Self- Microemulsifying Drug Delivery Systems Containing Idebenone, ***Drug Dev. Ind. Pharm.*****,2000,**26523—529.

33. T.Julianto, K. H. Yuen, A. M Noor., Improved bioavailability of vitamin E with a self emulsifying formulation, ***Int. J. Pharm.*****, 2000,**200, 53—57.

34. Z. G. Gao, H. G. Choi, H. J. Shin, Physicochemical characterization and evaluation of a microemulsion system for oral delivery of cyclosporine A, ***Int. J. Pharm.*****,1998,**161, 75—86.

35. L. Navazol,H.Salata,S. Morales,C. Dorta Ma,E. Perez, De-Las Casad and J. Aviles, Oral microemulsion cyclosporine in the treatment of steroid-refractory attacks of ulcerative and indeterminate colitis, Scandinavian, ***J. of Gastroenterology,*** **2001,** 36(6),610-614.

36. G. C. Actis,G. Aimo,G. Prilopo,D. Moscato,M. Rizzetto and R. Pagni, Efficacy and efficiency f oral microemulsion cyclosporine versus intravenous and soft gelatin capsule cyclosporine in the treatment of severe steroid-refractory ulcerative colitis :an open-label retrospective trial, ***Inflamm. Bowel Dis.,*** **1998,**4 (4),276-279.

37. K. Tokui, T. Kimata,K. Uchida, H. Yuasa, Y. Hayaski, T. Itatsu and T. Nabershime, Dose adjustment strategy for oral microemulsion formulation of cyclosporine: population pharmacokinetics-based analysis in kidney transplantation, ***Ther. Drug Monit,*** **2004,**26(3),287-94.

38. F. Karamustafa and N. Celebe, Development of an oral microemulsion formulation of alendronate: Effect of oil and co-surfactant type on phase behavior, ***J. of microencapsulatuon*,2008**,25(5),315-323.

39. Prediction of a stable microemulsion formulation for the oral delivery of a combination of antitubercular drugs using ANN methodology, ***Pharm. Research*,2003**,11,1760-1765.

40. M. Svoboda and J. Drabek, Effect of oral administration of iron microemulsion on the erythrocyte profile of suckling piglets in compression with parenteral application of iron dextran, ***Czech. Anim. Sc.*, 2002**,47(6),213-218.

41. A.J. Humberstone, W. N. Charman, Lipid-based vehicles for the oral delivery of poorly water soluble drugs, **Adv. Drug Del. Rev.,1997**,25103- 128.

42. C.W. Pouton, C.J.H. Porter, Formulation of lipid-based delivery systems for oral administration:Materials, methods and strategies, ***Advanced Drug Delivery Reviews***, 2008,60,625–637S.

43. P.P.Costantinides, Lipid Microemulsions for Improving Drug Dissolution and Oral Absorption: Physical and Biopharmaceutical Aspects, ***Pharm. res.*,1995**, 12,1561-1572.

44. C. J. H. Porter, A. M. Kaukonen, B. J. Boyd, G. A. Edwardsand W. N. Charman Susceptibility to Lipase-Mediated Digestion Reduces the Oral Bioavailability of Danazol After Administration as a Medium-Chain Lipid-Based Microemulsion Formulation, ***Pharm. Res.*, 2004**,21,1405-1412.

45. O. J. D'Cruz, and F. M. Uckun Influence of Long-term Stability Conditions on Microbicidal Nucleoside Prodrug (WHI-07)-loaded Gel-Microemulsion, ***AAPS Pharm. Sci. Tech.* 2006**, 7 (3), Article 73.

46. P. Boonme, K. Krauel, A.Graf, T. Rades and V.B. Junyaprasert Characterization of Microemulsion Structures in the Pseudoternary Phase Diagram of Isopropyl Palmitate/Water/Brij 97:1-Butanol, ***AAPS Pharm. Sci. Tech.* 2006**, 7 (2), Article 45.

47. N. Subramanian, S. K. Ghosal, S. P. Moulik, Enhanced In Vitro Percutaneous Absorption and In Vivo Anti-Inflammatory Effect of a Selective Cyclooxygenase Inhibitor Using Microemulsion, ***Drug Dev. and Ind. Pharm.*, 2005**, 31,405–416.

48. P. K. Ghosh, R.J. Majithiya, M. L. Umrethia and R. S. R. Murthy , Design and Development of Microemulsion Drug Delivery System of Acyclovir for Improvement of Oral Bioavailability, ***AAPS Pharm. Sci. Tech.*, 2006**, 7 (3), Article 77.

49. R. Aboofazeli, D. J. Barlow, and M. J. Lawrence Particle Size Analysis of Concentrated Phospholipid Microemulsions: II Photon Correlation Spectroscopy ,***AAPS Pharm. Sci. Tech.,*** **2000,** 2(2), Article 19.
50. H. M. El-Laithy, Preparation and Physicochemical Characterization of Dioctyl Sodium Sul-fosuccinate (Aerosol OT) Microemulsion for Oral Drug Delivery, ***AAPS Pharm. Sci. Tech.,*** **2003,** 4 (1), Article 11 .
51. C.Hsu, Z. Cui, R.J. Mumper, and M. Jay, Preparation and Characterization of Novel Coenzyme Q_{10} Nanoparticles Engineered from Microemulsion Precursors, ***AAPS Pharm. Sci. Tech.,*** **2003,** 4 (3), Article 32.
52. A. Akkar, P. Namsolleck, M. Blaut, and R. H. Müller, Solubilizing Poorly Soluble Antimycotic Agents by Emulsification via a Solvent-Free Process ***AAPS Pharm. Sci. Tech.,*** **2004,**5 (1) Article 24.
53. S. Agatonovic-Kustrin, B. D. Glass, M. H. Wisch, and R. G. Alany Prediction of a Stable Microemulsion Formulation for the Oral Delivery of a Combination of Antitubercular Drugs Using ANN Methodology ***Pharm. Res.,*** **2003,** 20,1760-1765.
54. K. Tokui, T. Kimata, K. Uchida, H. Yuasa, Y. Hayashi, T. Itatsu and T. Nabeshima, Dose adjustment strategy for oral microemulsion formulation of cyclosporine: population pharmacokinetics-based analysis in kidney transplant patients. ***Ther. Drug Monit.,*** **2004,** 26,287-94.
55. F. Karamustafa, and N. Celebi, Development of an oral microemulsion formulation of alendronate: Effects of oil and co-surfactant type on phase behaviour, ***J. of Microencap.,*** **2008,** 25,315 – 323.
56. G. C.Actis, G. Priolo, D. Moscato , M. Rizzetto and R. Pagni, Efficacy and efficiency of oral microemulsion cyclosporin versus intravenous and soft gelatin capsule cyclosporin in the treatment of severe steroid-refractory ulcerative colitis: an open-label retrospective trial. ***Inflamm. Bowel. Dis.,*** **1998,** 4,276-279.
57. B. D. Glass, S. Agatonovic-Kustrin and M. H. Wisch , Artificial neural networks to optimize formulation components of a fixed-dose combination of rifampicin, isoniazid and pyrazinamide in a microemulsio ,***Curr. Drug Discov. Techno.,*** **2005,** 2, 195-201.
58. P. D. Saussure, C. Soravia, P. Morel and A. Hadengue, Low-dose oral microemulsion cyclosporine for severe, refractory ulcerative colitis, ***Aliment Pharmacol Ther.,*** **2005,** 22, 203–208.

59. P. Keown and D. Niese, on the behalf of the International Sandimmun Neoral Study Group, Cyclosporine microemulsion increases drug exposure and reduces acute rejection without incremental toxicity in de novo renal transplantation, ***Kidney Int.,*** **1998,** 54,938-944.

60. M.B. Cheng , J.C. Wang , Y.H. Li , X.Y. Liu , X. Zhang , D.W. Chen, S.F. Zhou and Q. Zhang Characterization of water-in-oil microemulsion for oral delivery of earthworm fibrinolytic enzyme. ***J. Cont. Rel.,*** **2008,** 129,41-48.

61. K.R. Schultz, T.J. Nevill, R.F. Balshaw, C.L. Toze, T. Corr, C.J. Currie, D.K. Strong and P.A.Keown, Effect of gastrointestinal inflammation and age on the pharmacokinetics of oral microemulsion cyclosporin A in the first month after bone marrow transplantation, ***Bone Marrow Transplantation,*****2000,** 26,545–551.

62. A. Pifieyro-Lopez, E. Pifieyro-Garza, O. Torres-Alanis, R. Reyes-Araiza, M. Gornez-Silva, N. Waksman, M. E. Salazar-Leal, and R. Lujan-Rangel, Evaluation of the Bioequivalence of Single 100-mg Doses of Two Oral Formulations of Cyclosporin A Microemulsion: A Randomized, Open-Label, Two-Period Crossover Study in Healthy Adult Male Mexican Volunteers, ***Cli. Ther.,*** **2007,** 29,2049-2054.

63. J. Y. Zheng, M. Fulu Decrease of genital organ weights and plasma testosterone levels in rats following oral administration of leuprolide microemulsion, ***Int. J. of Pharm.,*** **2006,** 307,209–215.

64. H. Araya, M. Tomita, M. Hayashi, The novel formulation design of O/W microemulsion for improving the gastrointestinal absorption of poorly water soluble compounds, ***Int. J. of Pharm.,*** **2005,** 305,61–74.

65. A. Cilek, N. C, elebi ,F. Tırnaksız , A. Tay, A lecithin-based microemulsion of rh-insulin with aprotinin for oral administration: Investigation of hypoglycemic effects in non-diabetic and STZ-induced diabetic rats ,***Int. J. of Pharmaceu.*** **2005,** 298,176–185.

66. S. K.Kima, E. H. Leea, B. Vaishalia, S. Leea, Y. Leea, C.Kimb, H. T. Moonc, Y. Byuna ,Tricaprylin microemulsion for oral delivery of low molecular weight heparin conjugates, ***J. of Cont. Rel.,*** **2005,** 105,32– 42.

67. K. C. Lyons, W. N. Charman, R. Miller,C. J.H. Porter,Factors limiting the oral bioavailability of *N*-acetylglucosaminyl-*N*-acetylmuramyl dipeptide (GMDP) and enhancement of absorption in rats by delivery in a water-in-oil microemulsion ***Int. J. of Pharmaceu.,*** **2000,** 199,17–28.

68. J.M. Sarciaux, L. Acar, P.A. Sado ,Using microemulsion formulations for oral drug delivery of therapeutic peptides ***Int. J. of Pharmaceu.*** **1995,** 120,127-136.

69. C. Yong, B. Park, D. Kim, B. Yoo, J. Woo, K. Bhamdari, Y. Jahng and H. Choi, M. H. Lee In Vivo Evaluation of Microemulsion System for Oral and Parenteral Delivery of Rutaecarpine to Rats,***Drug Dev. And Ind. Pharm.,,*** **2007,** 33,531–534.

70. K. Itoh , S. Matsui , Y. Tozuka , T. Oguchi , K. Yamamoto, Improvement of physicochemical properties of N-4472 Part II: characterization of N-4472 microemulsion and the enhanced oral absorption ***Int. J. of Pharmaceu.*** **2002,** 246,75-83.

71. Z. Gao , H. Choi , H. Shin , K.Park ,S. Lim , K. Hwang , C. Kim Physicochemical characterization and evaluation of a microemulsion system for oral delivery of cyclosporin A ***Int. J. of Pharmaceu.,*** **1998,** 161,75–86.

72. A. Acharya, S.K. Sanyal and S. P. Moulik, Formation and characterization of a pharmaceutically useful microemulsion derived from isopropyl myristat, polyoxy ethelene(4),lauryl ether(Brij-30),iso propyl alcohol and water, ***Current. Sci.,*** **2001,**81,362-370.

73. R. H. H. Neubert, U. Schmalfub, R. Wlolf and W. A. Wohlrab, Microemulsions as colloidal vehicle systems for dermal drug delivery. PartV: Microemulsion without and with glycolipid as penetration enhancer. ***J. of Pharm. Sci.,*****2005,**94,821-827.

74. S. Shimpi, B. Chauhan, P. Shimpi Cyclodextrins: Application in different routes of drug administration, ***Acta Pharm.*****2005** ,55, 139–156.

75. K. Uekama ,Recent Aspects of Pharmaceutical Application of Cyclodextrins ***J. of Inc. Pheno. and Macro. Che.,*** **2002,** 44: 3–7.

76. B. Bendeby, L. Kenne and C. M. Sandstro, 1H-NMR Studies of the Inclusion Complexes between a-Cyclodextrin and Adamantane Derivatives Using Both Exchangeable Hydroxy Protons and Non-Exchangeable Aliphatic Protons, ***J. of Inc. Pheno. and Macro. Chem.,*** **2004,** 50, 173–181.

77. N. Ozdemir, S. Ordu and Y. Zkan, Studies of Floating Dosage Forms of Furosemide: In Vitro and In Vivo Evaluations of Bilayer Tablet Formulations, ***Drug Dev. and Ind. Pharm.,*** **2000,** 26,857–866.

78. J. Mielcarek, A. Czernielewska and B.czarczynska, Inclusion Complexes of Felodipine and Amlodipine with Methyl-β-cyclodextrin, ***J. of Inc. Pheno. and Macro. Chem.,*** **2006,** 54, 17–21.

79. S. Junco, T. Casimiro, N. Ribeiro, M. N. D. Ponte and h. C. Marques, A Comparative Study of Naproxen – Beta Cyclodextrin Complexes Prepared by Conventional Methods

and Using Supercritical Carbon Dioxide, ***J. of Inc. Pheno. and Macro. Chem.*, 2002,** 44, 117–121.

80. J. Peeters, P. Neeskens, J. Adriaensen and M. Brewster. Alfaxalone: Effect of Temperature on Complexation with 2-Hydroxypropyl-β-cyclodextrin, ***J. of Inc. Pheno. and Macro. Chem.*, 2002,** 44, 75–77.
81. P. Schwinte, M. Ramphul, R. Darcy and J. F. Osullivan, Amphiphilic Cyclodextrin Complexation of Clofazimine ***J. of Inc. Pheno. and Macro. Chem.*, 2003,** 47,109–112.
82. M. Ishikawa, H. Yoshi, T. Furuta, Interaction of Modified Cyclodextrins witrh Cytochrome P-450. ***Biosci.Biotechnol.Biochem*, 2005,** 69,246-248.
83. A. Gordano, F. Trotta , C. Manferti and E. Drioli.,Catalytic Behaviour of Carbonate β-CD Entrapped in PEEK-WC Membranes, ***J. of Inc. Pheno. and Macro. Chem.*, 2002,**44, 433–437.
84. Y. Tozuka, A. Wongmekiat, K. Sakata1, K. Moribe, T. Oguchi and K. Yamamoto, Co-grinding with Cyclodextrin as a Nanoparticle Preparation Method of a Poorly Water Soluble Drug .***J of Inc. Pheno. and Macro. Chem.*, 2004,** 50, 67–71.
85. K. Rajendrakumar, T. Pralhad and S. Madhusudan, Comparative Study on Co-Ground Products of Rofecoxib with β-Cyclodextrin and Its Sulfobutyl Ether-7 Derivative in Solution and in the Solid State ***J. of Inc. Pheno. and Macro. Chem.*,2004,** 49, 259–266.
86. V. Barillaro, B. Evrard,1 L. Delattre, and G. Piel, Oral Bioavailability in Pigs of a Miconazole/Hydroxypropyl-g-cyclodextrin/L-tartaric Acid Inclusion Complex Produced by Supercritical Carbon Dioxide Processing , ***The AAPS Pharm. Sci. Tech.*, 2005**; 7 (1), Article 16.
87. Y. Michel, B. Perly,Djedaini-Pilard, E. Berthommier, C. Baudin, C.Fajolles, B. Hamann, R. Pasqualini and L. Mauclaire. A Use of Modified Cyclodextrins as a Transporter for a Radiolabeled Tracer NMR Investigation, ***J. of Incl.Pheno. and Macro. Chem.*, 2005,** 51, 159–163.
88. T. Hladon, J. Pawlaczyk and B. Szafran, Stability of Mefenamic Acid in the Inclusion Complex with -Cyclodextrin in the Solid Phase, ***J. of Inc. Pheno. and Macro. Chem.*, 1999**, 35, 497–506.
89. M. E. Pina and F. Veiga, The Influence of Diluent on the Release of Theophylline from Hydrophilic Matrix Tablets, ***Drug Dev. and Ind. Pharm.*, 2000,** 26,125–1128.
90. G. Castronuovo, V. Elia, M. Niccoli and F. Velleca The Effects of Cosolvents on the Complexation of α-Cyclodextrin with Alkylated Substances. Calorimetric Studies at 25◦C,***J. of Incl. Pheno. and Macro. Chem.*, 2002,** 44, 229–234.

91. I. Bea, C. Jaime and P. Kollman Molecular recognition by b-cyclodextrin derivatives: molecular dynamics, free-energy perturbation and molecular mechanics/Poisson–Boltzmann surface area goals and problems, ***Theor. Chem. Acc.,* 2002,** 108:286–292.

92. V. J. Stella, H. K. Lee, D. O. Thompson, The effect of SBE4-/3-CD on i.v. methylprednisolone pharmacokinetics in rats: Comparison to a co-solvent solutionand two water-soluble prodrugs, ***IntJ. of Pharmaceutics,* 1995**,120,189-195.

93. G. Ceschel, V. Bergamante, P. Maffei, S. L. Borgia, V. Calabrese, and S. Biserni, Solubility and Transdermal Permeation Properties of a Dehydroepiandrosterone Cyclodextrin Complex from Hydrophilic and Lipophilic Vehicle, ***Drug Delivery,* 2005**,12,275–280.

94. M. M. Ghorab, H. M. Abdel-Salam, M. A. El-Sayad and M. M. Mekhel, Tablet Formulation Containing Meloxicam and βCyclodextrin: Mechanical Characterization and Bioavailability Evaluation. ***AAPS Pharm.Sci.Tech.,* 2004,** 5 (4), Article 59.

95. A. Usayapant and B. R. Iyer, The Effect of 2-Hydroxypropyl-bcyclodextrin on In Vitro Drug Release of Steroids from Suppository Bases, ***Drug Dev. and Ind. Pharm.,* 1999**,25, 387–390.

96. T. Ikeda, Y. Inoue, A. Suehiro, H. Ikeshoji, T. Ishida, N. Takiguchi, A. Kuroda, J. Kato and H. Ohtake, The Effects of Cyclodextrins on Autoinducer Activities of Quorum Sensing in *Pseudomonas aeruginosa*, ***J. of Incl. Pheno. and Macro. Chem.,* 2002,** 44, 381–382.

97. Z. H. Qi and W. J. Shieh, Aqueous Media for Effective Delivery of Tretinoin, ***J. of Incl. Pheno. and Macro. Chem.,2002,*** 44, 133–136.

98. K. P. R.Chowdary and S. V. Srinivas, Influence of Hydrophilic Polymers on Celecoxib Complexation With Hydroxypropyl β-Cyclodextrin, ***AAPS Pharm. Sci. Tech.,* 2006**; 7 (3), Article 79.

99. J. L. H. Johnson, Y.He, A. Jain, and S. H. Yalkowsky, Improving Cyclodextrin Complexation of a New Antihepatitis Drug With Glacial Acetic Acid, ***AAPS Pharm. Sci. Tech.,* 2006**; 7 (1), Article 18.

100. I. Nandi, M. Bateson, M. Bari, and H. N. Joshi, Synergistic Effect of PEG-400 and Cyclodextrin to Enhance Solubility of Progesterone, ***AAPS Pharm. Sci.Tech.,* 2003;** 4 (1), Article 1.

101. S. Lee, J. Kim, W. Kim, J. Ryu and G. Lim Preparation of Cyclodextrin Inclusion Complexes of an Antifungal Drug using a SAS Process ***Asian Pacific Confederation of Chem. Engg. Cong. program and abs.,* 2004,** Vol-2004 , 583-588.

102. K. Uekama, N. Hirashima, Y. Hourriuchi, F. Hirayama, T. Ijitsu and M. Ueno, Ethylated β-cyclodextrins as Hydrophobic Drug Carriers: Sustained Release of Diltiazem in the Rat, ***J. of Pharm.Sci.*, 1987**, 76,660-661.

103. A. H. Al-maarzouqui, I. Shehatta, B. Jobe and A. Dowaidar, Phase Solubility and Inclusion Complex of Itraconazole with β-cycloextrin using Supercritical Carbon Dioxide,***J. of Pharm.Sci.*,2006,** 95,292-304.

104. V. R. Sinha, R. Anitha,S. Ghosh, A. Nanda and R. Kuamria, Complexation of Celecoxib with β-cyclodextrin:Characterization of the Interaction in Solution of the Interaction in Solution and in Solid State, ***J. of Pharm.Sci.*,2005,** 94,676-687.

105. E. Alvarez-parrilla, P. R. Cabrer, L. A. D. Rosa,W. Al-soufi, F. Meijide and J. V. Tato,"Three-in-one" Complexes formed by Anionic Guests & Monosubstituted Cationic Alkyldiamino β-Cyclodextrin Derivatives, ***Supramolecular Chemistry,* 2003**, 15,207-211.

106. M. G. Hartell, R. Hicks, A. K. Bhattacharjee, B. W. Koser, K. Carvalho and J. E. V. Hanmot, Nuclear Magnetic Resonance and Molecular Modeling Analysis of the Interaction of the Antimalarial Drugs Artelinic Acid and Artesunic Acid with β-yclodextrin, ***J. of Pharm.Sci.*,2004,** 93,2076-2089.

107. H. Yoshii, T. Kometani, T. Furuta, Y. Wantanabe, Y. Linko and P. Linko., Formation of Inclusion Complexes of Cyclodextrin with Ethanol under Anhydrous Conditions, ***Biosci. Biotechnol. Biochem.*, 1998,** 62,2166-2170.

108. S. K. Leticia, M. Paulo and L.B. Valquiria, Carbamazepine/β-CD/HPMC Solid dispersions. I. influence of the spray-drying process and β-CD/HPMC on the drug dissolution profile, ***Drug Dev. Ind. Pharm.., 2003,*** 29, 139-144.

109. I. Corrigan and A. M. Crean, Comparative physicochemical properties of hydro-cortisone-PVP composites prepared using supercritical carbon dioxide by the GAS anti-solvent recrystallization process, by co-precipitation and by spray drying, ***Int. J. Pharm.*, 2002,** 245,75-82.

110. M. S. Nagarsenker, R. N. Meshram and G. Ramprakash, Solid dispersion of hydroxy-propyl β-cyclodextrin and ketorolac: enhancement of in-vitro dissolution rates, improvement in anti-inflammatory activity and reduction in ulcerogenicity in rats, ***J. Pharm. And Pharmacol.*, 2000,** 52, 949-956.