CHAPTER IV
LITERATURE REVIEW OF DRUGS INVESTIGATED

EFAVIRENZ PROFILE

Chemical structure of efavirenz

Molecular Formula : C$_{14}$H$_9$ClF$_3$NO$_2$

Molecular Weight : 315.7

Chemical Name : 2H-3,1-Benzoxazin-2-one,6-chloro-4cyclo propylethnyl)-1,4-dihydro-4-(trifluoromethyl) (4S).

Description: White to slightly pink powder, practically insoluble in water and freely soluble in methanol. Efavirenz should be kept in a well closed container, protected from light.

Melting Point : 139 – 141$^\circ$C

Pharmacology: Efavirenz (Adkins et al., 1998) is a noncompetitive inhibitor of HIV-1 reverse transcriptase (RT). It has no inhibitory effect on HIV-2 RT or human cellular DNA polymerases alpha, beta, gamma, or delta. Efavirenz binds directly to RT and inhibits viral RNA- and DNA-dependent DNA polymerase activities by disrupting the catalytic site. Although the drug RT template complex may continue to bind deoxynucleoside triphosphate and to catalyze its incorporation into the newly forming viral DNA, it does so at a slower rate.
**Pharmacokinetics** (Gazzard, 1999, Arendt et al., 2007, Gallego L et al., 2004, Kuritzkes et al., 2007, Sheran, 2005, Diego Chiappetta et al., 2011)

**Absorption:** Following oral administration of a single 100 mg to 1,600 mg dose of efavirenz in healthy adults, peak plasma drug concentrations ($C_{\text{max}}$) of 0.51 to 2.9 mcg/ml were attained within 5 hours. Increases in $C_{\text{max}}$ and area under the plasma concentration time curve (AUC) were dose proportional for 200, 400, and 600 mg of efavirenz; the increase was less than proportional for a 1,600 mg efavirenz dose, suggesting reduced absorption at higher doses. Times taken for peak plasma concentrations were approximately 3 to 5 hours and steady state plasma concentrations reached in 6 to 10 days. Following oral administration of a single 400 mg efavirenz dose in individuals with chronic liver disease or healthy individuals, $C_{\text{max}}$ averaged 1.2 or 1.8 mcg/ml, respectively, and AUC averaged 94.4 or 96.3 (hr) mcg/ml. Normal meals had no significant effect on the bioavailability of 100 mg of efavirenz administered twice a day for 10 days. The relative bioavailability of a single 1,200 mg dose of efavirenz in uninfected volunteers was increased by 50% following a high fat meal.

**Distribution:** Distribution of efavirenz into body tissues and fluids has not been fully characterized. In animal models, efavirenz volume of distribution following IV administration suggests extensive tissue distribution. In HIV infected patients who received 200 mg to 600 mg of efavirenz once a day for at least 1 month, cerebrospinal fluid concentrations ranged from 0.26% to 1.19% of the corresponding plasma concentration. This proportion is approximately three fold higher than the non-protein bound (free) fraction of efavirenz in plasma. Efavirenz is highly bound (approximately 99.5% to 99.75%) to human plasma proteins, principally albumin.
**Metabolism:** Efavirenz is metabolized primarily by the hepatic cytochrome P450 (CYP) isoenzymes 3A4 and 2B6 into hydroxylated, inactive metabolites. These metabolites undergo subsequent glucuronidation. Ten days of therapy with 200 mg to 400 mg of efavirenz daily resulted in a lower than expected accumulation of medication (22% to 42% lower) and a shorter terminal half-life (40 to 55 hours) compared to the single-dose half-life (52 to 76 hours).

**Excretion:** Efavirenz appears to induce its own metabolism. Terminal elimination half-life is prolonged in patients with chronic liver disease. Following oral administration of a single 400 mg dose of efavirenz, a half-life of 152 and 118 hours was reported, with and without chronic liver disease, respectively. Efavirenz is excreted principally in the faeces, both as metabolites and unchanged drug. Approximately 14% to 34% of a radio labeled dose of efavirenz was recovered in the urine (less than 1% as unchanged drug) and 16% to 61% of a radio labeled dose was recovered (primarily as unchanged drug).

**Uses and Administration:** Efavirenz is a non-nucleoside reverse transcriptase inhibitor with activity against HIV. It is used with other antiretrovirals for combination therapy of HIV infection. Efavirenz is administered by mouth as capsules or tablets in an adult dose of 600 mg once daily, alternatively, it may be given as an oral solution in an adult dose of 720 mg once daily. Dose at bedtime is recommended during the first 2 to 4 weeks of therapy to improve tolerability. Doses (as capsules) for children over the age of 3 years are based on body weight, children weighing 13 to 14 kg are given 200 mg once daily, those weighing 15 to 19 kg, 250 mg once daily, those weighing 20 to 24 kg, 300 mg once daily, those weighing 25 to 32.4 kg, 350 mg once daily, those weighing 32.5 to 39 kg, 400 mg once daily and those weighing 40 kg or more, 600 mg once daily. Bioavailability of efavirenz
from the oral solution is less than that from the capsule and so proportionately higher doses are used, the dose ranges which are again calculated in terms of body weight and depend on the age range.
Recent Past Work on Enhancement of Solubility, Dissolution rate and Bioavailability of Efavirenz

Diego Chiappetta et al., 2011 prepared and evaluated Synergistic encapsulation of the anti-HIV agent efavirenz within mixed poloxamine/poloxamer polymeric micelles. This study investigated the synergistic performance of mixed polymeric micelles made of linear and branched poly (ethylene oxide)-poly(propylene oxide) for the more effective encapsulation of the anti-HIV drug efavirenz. The co-micellization process of 10% binary systems combining different weight ratios of a highly hydrophilic poloxamer (Pluronic F127) and a more hydrophobic poloxamine counterpart (Tetronic T304 and T904) was investigated by means of dynamic light scattering, cloud point and electronic spin resonance experiments. Then, the synergistic solubilization capacity of the micelles was shown. Findings revealed a sharp solubility increase from 4 µg/ml up to more than 33 mg/ml, representing a 8430-fold increase. Moreover, the drug-loaded mixed micelles displayed increased physical stability over time in comparison with pure poloxamine ones. Overall findings confirmed the enormous versatility of the poloxamer/poloxamine systems as Trojan nanocarriers for drug encapsulation and release by the oral route and they entail a relevant enhancement of the previous art towards a more compliant pediatric HIV pharmacotherapy.

Rama Rao et al., (2011) reported on preparation, characterization and evaluation of efavirenz inclusion complexes by employing β-cyclodextrin. The objective of the work was to formulate and evaluate inclusion complexes of efavirenz by using β-cyclodextrin (βCD) for enhancing the solubility. Phase solubility studies were carried out to evaluate the solubilizing power of cyclodextrin (CD) and
determined the apparent stability constant (ks) of the complexes. Inclusion complexes were prepared by four methods namely (i) physical mixing (PM) (ii) coevaporation method (CE) (iii) kneading method (KNE) and (iv) freeze drying method (FD). In each case two different proportions of drug and βCD such as 1:1 and 1:2M ratios were used in the preparation of Inclusion complexes. Characterization of Inclusion complexes was done by means of drug content uniformity, Fourier transmitted infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), powder x-ray diffractometry (X-RD), scanning electron microscopy (SEM) and in vitro dissolution studies. The order of increase in dissolution rate of the drug with different methods were found to be FD > KNE > CE > PM.

Enhancement of dissolution rate and formulation development of efavirenz tablets employing starch phosphate a new modified starch was investigated and reported by Chowdary et al., (2011). The purpose of the study was to prepare, characterize and evaluate starch phosphate, a new modified starch as a carrier in solid dispersions for enhancing the dissolution rate of efavirenz. The feasibility of formulating solid dispersions of efavirenz in starch phosphate into compressed tablets with enhanced dissolution rate was also investigated. Starch phosphate was prepared by reacting starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperatures. It was insoluble in water and has good swelling (400%) property without pasting or gelling when heated in water. Solid dispersions of efavirenz in starch phosphate were prepared by solvent evaporation method employing various weight ratios of drug: starch phosphate such as 2:1(SD-1), 1:1(SD-2), 1:2(SD-3), 1:3(SD-4) and 1:9(SD-5) and were evaluated for dissolution rate and efficiency. All the solid dispersions prepared gave rapid and higher dissolution of efavirenz when
compared to pure drug. Dissolution followed first order kinetics. A 13.98 and 31.37 fold increase in the dissolution rate (K1) of efavirenz was observed with solid dispersions SD-4 and SD-5 respectively. The DE30 was also increased from 10.66% in the case of efavirenz pure drug to 51.13% and 71.51% in the case of these solid dispersions. Efavirenz (50mg) tablets were prepared employing efavirenz alone and its solid dispersions SD-3 and SD-4 by wet granulation method and were evaluated. Efavirenz tablets formulated employing its solid dispersions in starch phosphate gave rapid and higher dissolution rate and DE30 when compared to plain and commercial tablets. A 16.71 and 31.04 fold increase in the dissolution rate (K1) was observed with tablet formulations containing solid dispersions SD-3 and SD-4 respectively when compared to plain tablets.

Vikram et al., (2011) investigated and reported on solubility enhancement of efavirenz hydrochloride by hot melt technique. The investigation was to formulate and characterize the immediate release tablet of efavirenz by using Soluplus as a polymer. The proposed formulation of the immediate release tablet of efavirenz are prepared by using solid dispersion by hot melt technique to improve solubility and dissolution rate of poorly water soluble Efavirenz. The drug to polymer ratio in optimized batch (TABSD13) was 1:3. The obtained batch was characterized for its percent drug content, thermal analysis (DSC), crystallinity (PXRD), FTIR and in vitro drug release. There were no compatibility issues and the crystallinity of drug was found to be reduced in prepared tablet which were confirmed by DSC and PXRD studies. The average dissolution rate of six efavirenz tablet and marketed formulation in 0.5% SLS in distilled water in 45 min were 72.77% and 69.37% respectively while in 120 min they were about 90.08% and 88.24% respectively and the standard
deviations were also within the limits. It shows that the dissolution profiles of hot melt efavirenz tablet and marketed formulation were comparable in 0.5 % SLS in distilled water. This may be because of the SLS which act as good surfactant. Further investigations are required to reduce the amount of polymer in tablet that can provide maximum drug loading and acceptable dosage form.

Oral pharmacokinetics of the anti-HIV efavirenz encapsulated within polymeric micelles was studied and reported by Chiappetta et al., (2011). The aqueous solubility of the drug was increased more than 8400 times (up to 34 mg/mL) and preliminary preclinical data suggested the significantly greater oral bioavailability with respect to an extemporaneous suspension and an oleous solution (similar to the only commercially available pediatric formulation). As the preamble to a bioequivalence trial to evaluate the micellar system in adult healthy volunteers, the present work investigated the effect of parameters such as dose per body weight and drug concentration on the oral pharmacokinetics of the drug. The non-linear pharmacokinetics of the drug was confirmed for all the formulations. Despite the drug concentration and dose, micelles consistently resulted in significantly greater absorption rates, PK parameters increasing up to 3-fold. For example, $C_{\text{max}}$ values increased from 687, 1789 and 2657 ng/mL for the oily system to 1145, 2856 and 7056 ng/mL for the micellar one, for EFV doses between 20 and 80 mg/kg. Data clearly showed that the smaller the micellar size, the higher the bioavailability attained. The effect of micellar size was also assessed. In addition, a comparison between $in\,\text{vitro}$ dissolution rates of EFV for the different micelles and AUC values suggested that micelles releasing faster $in\,\text{vitro}$ lead to a less pronounced absorption $in\,\text{vivo}$. These findings would suggest the involvement of additional absorption mechanisms.
Chowdary et al., (2011) investigated and reported on Enhancement of Dissolution Rate and formulation development of efavirenz tablets employing starch citrate- A new modified starch. The purpose of the study was to prepare, characterize and evaluate starch citrate, a new modified starch as a carrier in solid dispersions for enhancing the dissolution rate of efavirenz. The feasibility of formulating solid dispersions of efavirenz in starch citrate into compressed tablets with enhanced dissolution rate was also investigated. Starch citrate was prepared by reacting starch with citric acid at elevated temperatures. It was insoluble in water and has good swelling (1500%) property without pasting or gelling when heated in water. Solid dispersions of efavirenz in starch citrate were prepared by solvent evaporation method employing various weight ratios of drug: starch citrate such as 2:1(SD-1), 1:1(SD-2), 1:2(SD-3), 1:3(SD-4) and 1:9(SD-5) and were evaluated for dissolution rate and efficiency. All the solid dispersions prepared gave rapid and higher dissolution of efavirenz when compared to pure drug. A 12.94 and 40.41 fold increase in the dissolution rate (K1) of efavirenz was observed with solid dispersions SD-4 and SD-5 respectively. The DE30 was also increased from 10.66% in the case of efavirenz pure drug to 60.93% and 74.23% in the case of these solid dispersions. Efavirenz (50 mg) tablets were prepared employing efavirenz alone and its solid dispersions SD-3 and SD-4 by wet granulation method and were evaluated. Efavirenz tablets formulated employing its solid dispersions in starch citrate gave rapid and higher dissolution rate and DE30 when compared to plain and commercial tablets. A 7.01 and 15.30 fold increase in the dissolution rate (K1) was observed with tablet formulations containing solid dispersions SD-3 and SD-4 respectively when compared to plain tablets.
Indrajit et al., (2010) reported on synthesis of cyclodextrin and sugar-based oligomers for the efavirenz drug delivery. In this study, water-soluble lactose based oligomers of β-cyclodextrin were synthesized by a simple and efficient condensation polymerization process. Proposed water-soluble β-cyclodextrin oligomers were prepared by controlled reaction between β-cyclodextrin and a triazine linker and purification by an ultrafiltration process. Similarly, lactose based β-cyclodextrin oligomers were synthesized for enhanced water solubility. The physical and chemical properties of the synthesized polymers were characterized by FT-IR and 1H NMR spectroscopy, XRD analysis, thermogravimetric analysis (TGA) and aqueous solubility determination. Molecular weights of these β-cyclodextrin based oligomers were measured by ESI technique. These β-cyclodextrin based water-soluble oligomers polymers were used as supramolecular carriers for efavirenz (an anti HIV drug), improving the inclusion property and aqueous solubility properties of this drug. These synthesized oligomers were found to improve stability and aqueous solubility of efavirenz on their (1:1) inclusion complex through phase solubility and dissolution studies. Reduced cytotoxicity than the parent β-CD was observed in hemolysis test.

Enhancement of dissolution rate of efavirenz by solid dispersion technique was studied and reported by Pragati et al., (2010). They studied on improvement in the solubility and oral absorption of the drug in gastric fluid and to enhance its dissolution rate, solid dispersion method was designed and evaluated. Solid dispersions of efavirenz were prepared using PEG 6000. The effect of fusion-solvent methods of preparation of solid dispersion on dissolution behavior was also investigated. Dissolution studies indicated a significant increase in dissolution of Efavirenz when
dispersed in PEG6000. Solid dispersions containing Efavirenz / PEG 6000, 1: 8, showed a 2-fold increase in dissolution after 180 min in the 0.1 N HCL systems.

Yang et al.,(2010) reported on improved kinetics approach to describe the physical stability of amorphous solid dispersions. The recrystallization of amorphous solid dispersions may lead to a loss in the dissolution rate, and consequently reduce bioavailability. The purpose of this work was to understand factors governing the recrystallization of amorphous drug-polymer solid dispersions, and develop a kinetics model capable of accurately predicting their physical stability. Recrystallization kinetics was measured using differential scanning calorimetry for initially amorphous efavirenz-polyvinylpyrrolidone solid dispersions stored at controlled temperature and relative humidity. The experimental measurements were fitted by a new kinetic model to estimate the recrystallization rate constant and microscopic geometry of crystal growth. The new kinetics model was used to illustrate the governing factors of amorphous solid dispersions stability. Temperature was found to affect efavirenz recrystallization in an Arrhenius manner, while recrystallization rate constant was shown to increase linearly with relative humidity. Polymer content tremendously inhibited the recrystallization process by increasing the crystallization activation energy and decreasing the equilibrium crystallinity. The new kinetic model was validated by the good agreement between model fits and experiment measurements. A small increase in polyvinylpyrrolidone resulted in substantial stability enhancements of efavirenz amorphous solid dispersion. The new established kinetics model provided more accurate predictions than the avrami equation.
Effect of hydrophilic polymer on complexing efficiency of cyclodextrins towards efavirenz-characterization and thermodynamic parameters was studied and reported by Renu et al., (2011). This work described the effect of PVP on the complexation efficiency of cyclodextrins towards efavirenz, a poorly soluble antiretroviral agent imparting irritating sensation to buccal cavity. The phase solubility study indicates 1:1 stoichiometry for binary and ternary systems. DSC and XRPD revealed complete inclusion only in the lyophilized systems. The ternary systems were autoclaved before being lyophilized for the best results. Proton NMR suggests that the chlorobenzene part of benzoazinone ring of the drug is involved in inclusion and was confirmed by 2D-COESY. The thermodynamic parameters, indicative of complexation efficiency were calculated calorimetrically by determining the interaction enthalpy of efavirenz with cyclodextrins in the presence and absence of PVP. The value of stability constants increased in the order \( \beta\-CD < HP\-\beta\-CD < M\-\beta\-CD \) and is still higher in the presence of PVP illustrating the facilitation of the inclusion. Molar enthalpy of interaction of autoclaved solid formulation determined calorimetrically indicated stronger interaction for efavirenz:M-\( \beta\-CD \)-PVP system \((-12.20\ \text{kJ/mol})\) which showed highest solubility and dissolution rate. The\textit{ in vitro} measurement of permeability showed a ten fold increase in the flux for the autoclaved formulation containing efavirenz-M-\( \beta\-CD \)-PVP. In conclusion, encapsulation by cyclodextrins increases the solubility and suppresses the oral irritation of efavirenz. PVP further increases the complexation efficiency and decreases the bulk of cyclodextrins.

Sateesh et al., (2009) studied and reported on physicochemical characterization of efavirenz–cyclodextrin inclusion complexes. Efavirenz (EFV) is an oral antihuman
immunodeficiency virus type 1 drug with extremely poor aqueous solubility. Thus, its gastrointestinal absorption is limited by the dissolution rate of the drug. The objective of this study was to characterize the inclusion complexes of EFV with β-cyclodextrin (β-CD), hydroxypropyl β-CD (HPβCD), and randomly methylated β-CD (RMβCD) to improve the solubility and dissolution of EFV. The inclusion complexation of EFV with cyclodextrins in the liquid state was characterized by phase solubility studies. The solid-state characterization of various EFV and CD systems was performed by X-ray diffraction, differential scanning calorimetry, and scanning electron microscopy analyses. Dissolution studies were carried out in distilled water using US Pharmacopeia dissolution rate testing equipment. Phase solubility studies provided an $A_L$-type solubility diagram for β-CD and $A_P$-type solubility diagram for HPβCD and RMβCD. The phase solubility data enabled calculating stability constants ($K_s$) for EFV-βCD, EFV-HPβCD, and EFV-RMβCD systems which were 288, 469, and 1,073 M$^{-1}$, respectively. The physical and kneaded mixtures of EFV with CDs generally provided higher dissolution of EFV as expected. The dissolution of EFV was substantially higher with HPβCD and RMβCD inclusion complexes prepared by the freeze drying method. Thus, complexation with HPβCD and RMβCD could possibly improve the dissolution rate-limited absorption of EFV.

Shown et al., (2008) reported on synthesis and characterization of Linear Water-soluble γ-cyclodextrin based Polymers as drug carrier systems. A series of new linear water-soluble homo and copolymers of γ-cyclodextrin are reported. These water-soluble polymers were synthesized from γ-cyclodextrin (γ-CD) and triazine through a single pot condensation polymerization procedure and the synthetic parameters optimized. Lactose and maltose based γ-cyclodextrin copolymers were
also prepared. The physicochemical properties of these synthesized polymers were characterized by FT-IR spectroscopy, XRD analysis, thermogravimetry analysis (TGA) and aqueous solubility determination. The formation of a 1:1 efavirenz (an anti-HIV drug)/γ-CD polymer inclusion complex was confirmed from FT-IR and UV–VIS spectroscopy and phase solubility studies. The release performance of efavirenz was investigated through phase solubility and dissolution studies. It was found that these copolymers showed improved drug dissolution abilities.
RITONAVIR PROFILE

Chemical structure of Ritonavir

**Molecular Formula:** C$_{37}$H$_{48}$N$_{6}$O$_{5}$S$_{2}$

**Molecular Weight:** 720.9

**Chemical Name:** 5-Thiazolylmethyl {((αS)-α-((1S, 3S)-1-hydroxy-3-((2S)-2-3-((2-isopropyl-4-thiazolyl)methyl)-methylureido)-3-methylbutyramido)-4-Phenylbutyl)phenethyl} carbamate.

**Melting Point:** 120 – 125°C

**Description:**

Ritonavir (Lea and Faulds. 1996) is a white to light tan powder and has a bitter metallic taste. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

**Mechanism of Action:**

Ritonavir is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. Inhibition of HIV protease renders the enzyme incapable of processing the gag-pol polyprotein precursor which leads to production of non-infectious immature HIV particles.
Pharmacokinetics (Hsu Ann et al., 1998, Cooper et al., 2003, Merry et al., 1996, Bertz et al., 1997, Hsu et al., 1997)

Absorption: The absolute bioavailability of ritonavir has not been determined. After a 600mg dose of oral solution, peak concentrations of ritonavir were achieved approximately 2 hours and 4 hours after dosing under fasting and non-fasting (514 KCal; 9% fat, 12% protein, and 79% carbohydrate) conditions, respectively.

When the oral solution was given under non fasting conditions, peak ritonavir concentrations decreased 23% and the extent of absorption decreased 7% relative to fasting conditions. After a single 600 mg dose under non fasting conditions, in two separate studies, the soft gelatin capsule and oral solution formulations yielded mean ±SD areas under the plasma concentration-time curve (AUCs) of 121.7 ± 53.8 and 129.0 ± 39.3igh/mL, respectively. Relative to fasting conditions, the extent of absorption of ritonavir from the soft gelatin capsule formulation was 13% higher when administered with a meal (615 Kcal, 14.5% fat, 9% protein and 76% carbohydrate).

Metabolism: Nearly the entire plasma radioactivity after a single 600 mg oral dose of 

$^{14}$C-ritonavir oral solution was attributed to unchanged ritonavir. Five ritonavir metabolites have been identified in human urine and faeces. The isopropylthiazole oxidation metabolite is the major metabolite and has antiviral activity similar to that of parent drug, however, the concentrations of this metabolite in plasma are low. In vitro studies utilizing human liver microsomes have demonstrated that cytochrome P450 3A (CYP3A) is the major iso-form involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of M-2.

Elimination: In a study of five subjects receiving a 600 mg dose of $^{14}$C-ritonavir oral solution, 11.3 ± 2.8% of the dose was excreted into the urine, with 3.5 ± 1.8% of the dose excreted as unchanged parent drug. In that study, 86.4 ± 2.9% of the dose was
excreted in the faeces with 33.8 ± 10.8% of the dose excreted as unchanged parent drug. Upon multiple dosing, ritonavir accumulation is less than predicted from a single dose possibly due to a time and dose-related increase in clearance.

**Dosage and Administration:**

**Adults:** The recommended dosage of ritonavir is 600 mg twice daily by mouth. Use of a dose titration schedule may help to reduce treatment-emergent adverse events while maintaining appropriate ritonavir plasma levels. Ritonavir should be started at no less than 300 mg twice daily and increased at 2 to 3 day intervals by 100 mg twice daily.

**Pediatric Patients:** Ritonavir should be used in combination with other antiretroviral agents. The recommended dosage of ritonavir is 400 mg/m$^2$ twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m$^2$ and increased at 2 to 3 day intervals by 50 mg/m$^2$ twice daily. If patients do not tolerate 400 mg/m$^2$ twice daily due to adverse events, the highest tolerated dose may be used for maintenance therapy in combination with other antiretroviral agents, however, alternative therapy should be considered. When possible, dose should be administered using a calibrated dosing syringe.
Recent Past Work on Enhancement of Solubility, Dissolution rate and Bioavailability of Ritonavir.

Musle et al., (2012) reported solubility enhancement of poorly water soluble drug (ritonavir) using hot melt extrusion. the enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. complexation, precipitation, adsorption, salt information, particle size reduction, etc. have commonly been used in industry to solubility of the drug, there are practical limitation with these techniques the desired bioavailability enhancement may not always be achieved. therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. one such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate prepare solid dispersion using hot melt extrusion. ritonavir is anti hiv drug (bcs class ii), which is often administered orally. ritonavir exhibits very slightly soluble and as a consequence it exhibits low bioavailability after oral administration. therefore the improvement of ritonavir dissolution from its oral solid dosage forms is an important issue for enhancing its therapeutic efficiency. the present study was enhancement of dissolution rate of poorly water soluble drug. the solid dispersion was using soluplus as carrier where leutrol f 68, leutol 127, tpgs was selected as plasticizer. by hot melt extrusion the resultant complexes were evaluated for drug content, dissolution rate, xrd, ftir, dsc and SEM.

Pranjali et al., 2012 prepared and characterized amorphous nanoparticles for solubility enhancement of ritonavir. Ritonavir is an antiretroviral drug characterized by low solubility and high permeability which corresponds to BCS class II drug. The purpose of the study was to develop amorphous nanoparticles by sonoprecipitation method in order to enhance its solubility.
Ritonavir amorphous nanoparticles were produced by sonprecipitation method. HPMC and SDS are used as a surfactant. The effect of process variables on particle size and physical state of ritonavir was investigated. The physicochemical properties of pure drug and amorphous nanoparticles were characterized by X-ray powder diffraction (XRPD), Fourier transform infrared (FT-IR) spectroscopy, differential scanning calorimetric (DSC), as well as, measuring the particle size. The DSC and XRPD results indicated that the sonoprecipitation process led to the formation of amorphous nanoparticles. Ritonavir nanoparticles completely dissolved in the dissolution medium of 0.1 N HCl within 60 min, while there was only 28.21% of raw Ritonavir dissolved. The process by combining the antisolvent precipitation under sonication was a promising method to produce small, uniform and stable ritonavir nanoparticles with markedly enhanced dissolution rate due to an increased solubility.

Josephine et al.,(2012) formulated and characterized ritonavir loaded ethyl cellulose microspheres for oral delivery. The objective of the present study was to prepare and evaluate microparticles for the controlled release of ritonavir using cellulosepolymer. The micro particles were prepared by the solvent evaporation method (O/O) using ethyl cellulose as wall materials. In order to increase the encapsulation efficiency, a mixed solvent system comprising 1:1 proportions of ethanol and dichloromethane were used as a dispersed phase. The prepared micro particles were characterized for the percent drug content, entrapment efficiency, FTIR, DSC, scanning electron microscopy (SEM) and in vitro dissolution studies. The prepared micro particles were white, free-flowing, and almost spherical in shape. The drug-loaded microparticles showed 86-111% drug entrapment, mean particle size was in the range of 36-40µm. In vitro drug release
studies were carried out up to 10h in two different pH media, i.e., acidic buffer (pH 1.2) and SLS solution (0.7%). FTIR and DSC thermo grams showed the stable character of ritonavir in the micro particles. SEM showed that the micro particles were porous in nature. The release kinetics study revealed that the prepared micro particles were best fitted to the zero order. The release kinetics data and characterization studies indicated that drug release from microcapsules was diffusion–controlled and that the micro particles were stable.

Gauravl et al.,(2012) investigated and reported complexation approach for fixed dose tablet formulation of lopinavir and ritonavir: an anomalous relationship between stability constant, dissolution rate and saturation solubility. In the present investigation, cyclodextrin complexation process was explored for development of tablet formulation of WHO approved fixed dose combination of lopinavir and ritonavir with reduced tablet size, shorter disintegration time and higher bioavailability in comparison to reference product. In preliminary studies, showed that lopinavir solubility and dissolution rate is poor into the dissolution medium recommended by FDA, whereas ritonavir solubilized fairly into dissolution medium with adequate dissolution rate. Solid-state cyclodextrin complexation technology was used for enhancement of dissolution rate of lopinavir into dissolution medium. Various cyclodextrins were screened by comparison on basis of enhancement of dissolution rate of lopinavir (LPV) and the order was found as gamma cyclodextrin (β-CD) (hydroxypropylbeta-cyclodextrin (HP-β-CD) ( methyl beta-cyclodextrin(M-β-CD) ( beta-cyclodextrin (β-CD), with Q120 values(i.e. percentage of dissolved drug at 120 min.) were 10.1 for the pure LPV and 56.3, 51.3, 30.3 and 10.3 for LPV/γ-CD,LPV/HP-β-CD, LPV/M-β-CD and LPV/β-CD, respectively. Anomalous results were found between stability constant, dissolution rate and saturation solubility. It was
found that cyclodextrin having higher stability constant value with LPV, provides higher saturated solubility of LPV in aqueous media but at slow dissolution rate and vice versa. The \( \gamma \)-CD was selected for complexation with lopinavir in the stoichiometric ratio 1:1.5 M of LPV to \( \gamma \)-CD. Various processes such as kneading method, milling technique, sonication, freeze drying and autoclaving were tried, from which kneading method was found to give best dissolution results. The corresponding solid complexes were characterized by differential scanning calorimetric, X-ray powder diffraction and scanning electron microscopy studies. Based on various studies, the complexation phenomenon between LPV and \( \gamma \)-CD was found to follow non-inclusion behavior. Pharmacokinetic studies were carried out in Sprague-Dawley rats using cross over design with a 3 day wash out period. The bioavailability of lopinavir was found to be enhanced significantly using cyclodextrin complex tablet formulation.

Sunilkumar et al. (2012) prepared, characterized and reported PGS-PVP co-processed excipient as directly compressible vehicle in the formulation development of antiretroviral drugs. Direct compression is the preferred method for the preparation of tablets. Co-processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible vehicles. The objective of the present study is to prepare and characterize pre gelatinized starch-poly vinyl pyrrolidone (PGS-PVP) co-processed excipient and to evaluate its application as directly compressible vehicle in the tablet formulations of three anti-retroviral drugs namely efavirenz, ritonavir and stavudine. PGS-PVP co-processed excipient was prepared by gelatinizing potato starch in the presence of PVP and drying the resulting mass. The co-processed excipient prepared was characterized by determining melting point, solubility, swelling index in water,
pH, and micromeritic characters namely particle size, bulk density, tapped density, angle of repose and compressibility index and evaluated for its application in tablet formulations. PGS-PVP co-processed excipient prepared by gelatinizing potato starch (49 parts) in the presence of PVP (1 part) is a crystalline, discrete and free flowing powder. It is insoluble in water and aqueous fluids of pH 1.2, 4.5 and 7.4 and in several organic solvents. It exhibited high swelling (284 %) in water. PGS-PVP co-processed excipient has excellent flow properties alone and as blends with selected drugs it exhibited excellent to good flow properties. Tablets of (i) efavirenz (100 mg) (ii) ritonavir (100 mg) and (iii) stavudine (30 mg) prepared by direct compression method employing PGS-PVP co-processed excipient as DCV were of good quality with regard to drug content, hardness, friability and disintegration time. All the tablets formulated disintegrating rapidly within 3.5 min. With all the three drugs, the tablets prepared gave rapid dissolution of the contained drug, 100 % within 20 min and fulfilled the official (IP/USP) dissolution rate test specification prescribed in each case.

Chowdary et al.,(2011) reported enhancement of dissolution rate and formulation development of ritonavir tablets employing starch phosphate- a new modified starch. The objective of the study is to prepare, characterize and evaluate starch phosphate, a new modified starch as a carrier in solid dispersions for enhancing the dissolution rate of ritonavir. The feasibility of formulating solid dispersions of ritonavir in starch phosphate into compressed tablets with enhanced dissolution rate was also investigated. Starch phosphate was prepared by reacting starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperatures. It was insoluble in water and has good swelling (400%) property without pasting or gelling when heated in water. Solid dispersions of ritonavir in starch phosphate were prepared by solvent
evaporation method employing various weight ratios of drug: starch phosphate such as 2:1(SD-1), 1:1(SD-2), 1:2(SD-3), 1:3(SD-4) and 1:9(SD-5) and were evaluated for dissolution rate and efficiency. All the solid dispersions prepared gave rapid and higher dissolution of ritonavir when compared to pure drug. A 58.34 and 94.41 fold increase in the dissolution rate (K1) of ritonavir was observed with solid dispersions SD-4 and SD-5 respectively. The DE30 was also increased from 6.80% in the case of ritonavir pure drug to 76.25% and 84.05% in the case of these solid dispersions.

Ritonavir (50 mg) tablets were prepared employing ritonavir alone and its solid dispersions SD-3 and SD-4 by wet granulation method and were evaluated. Ritonavir tablets formulated employing its solid dispersions in starch phosphate gave rapid and higher dissolution rate and DE30 when compared to plain and commercial tablets. A 9.95 and 28.14 fold increase in the dissolution rate (K1) was observed with tablet formulations containing solid dispersions SD-3 and SD-4 respectively when compared to plain tablets.

Chowdary et al.,(2011) reported enhancement of dissolution rate and formulation development of ritonavir tablets employing starch citrate .The objective of the study is to prepare, characterize and evaluate starch citrate, a new modified starch as a carrier in solid dispersions for enhancing the dissolution rate of ritonavir. The feasibility of formulating solid dispersions of ritonavir in starch citrate into compressed tablets with enhanced dissolution rate was also investigated. Starch citrate was prepared by reacting potato starch with citric acid at elevated temperatures. It was insoluble in water and has good swelling (1500%) property without pasting or gelling when heated in water. Solid dispersions of ritonavir in starch citrate were prepared by solvent evaporation method employing various weight ratios of drug: starch citrate such as 2:1(SD-1), 1:1(SD-2), 1:2(SD-3), 1:3(SD-4) and 1:9(SD-5) and were
evaluated for dissolution rate and efficiency. All the solid dispersions prepared gave rapid and higher dissolution of ritonavir when compared to pure drug. A 58.34 and 94.41 fold increase in the dissolution rate (K1) of ritonavir was observed with solid dispersions SD-4 and SD-5 respectively. The DE30 was also increased from 6.80% in the case of ritonavir pure drug to 76.25% and 84.05% in the case of these solid dispersions. Ritonavir (50 mg) tablets were prepared employing ritonavir alone and its solid dispersions SD-3 and SD-4 by wet granulation method and were evaluated. Ritonavir tablets formulated employing its solid dispersions in starch citrate gave rapid and higher dissolution rate and DE30 when compared to plain and commercial tablets. A 9.95 and 28.14 fold increase in the dissolution rate (K1) was observed with tablet formulations containing solid dispersions SD-3 and SD-4 respectively when compared to plain tablets.

Shilpi Sinha et al., 2010 prepared and studied Solid dispersion as an approach for bioavailability enhancement of poorly water-soluble drug ritonavir. Ritonavir is an antiretroviral drug characterized by low solubility and high permeability which corresponds to BCS class II drug. The purpose of the study was to develop solid dispersion by different methods and investigate them for in vitro and in vivo performance for enhancing dissolution and bioavailability, respectively. Since the drug possesses food-related absorption, the effect of biorelevant media (FaSSIF and FeSSIF state) on dissolution behavior was also studied. The solid dispersion was prepared using Gelucire as carrier in 1:4 ratio by different methods and were characterized for differential scanning calorimetry (DSC), X-ray diffractometry, scanning electron microscopy, and FT-IR. Oral bioavailability of 10 mg of ritonavir in solid dispersion prepared by solvent evaporation (SE1) and melt method (MM1) was compared with pure drug after oral administration of solid dispersion and pure drug to
Albino Wistar rats of either sex. The results suggested formation of eutectic solid dispersion. *In vitro* dissolution studies was performed in 0.1 N HCl and biorelevant media showed enhanced dissolution rate as compared to pure drug in both FeSSIF media and 0.1 N HCl. The apparent rate of absorption of ritonavir from SE1 (\(C_{\text{max}} 20221.37 \text{ ng/ml, } t_{\text{max}} 0.5 \text{ h}\)) was higher than that of MM1 (\(C_{\text{max}} 2,462.2, t_{\text{max}} 1 \text{ h}\)) and pure drug (\(C_{\text{max}} 1,354.8 \text{ ng/ml, } t_{\text{max}} 0.5 \text{ h}\)). On the basis of the result obtained, it was concluded that solid dispersion is a good approach to enhance solubility and bioavailability of poorly water-soluble ritonavir.

Oostendorp et al. (2009) reported coadministration of ritonavir strongly enhances the apparent oral bioavailability of docetaxel in patients with solid tumors. To enhance the systemic exposure to oral docetaxel by coadministration of ritonavir, an efficacious inhibitor of CYP 3A4 with minor P-glycoprotein inhibiting effects, in patients with cancer. A proof-of-concept study was carried out in 12 patients with solid tumors. The first cohort of patients (\(n = 4\)) received 10 mg and the subsequent cohort (\(n = 8\)) 100 mg of oral docetaxel, coadministered with 100 mg oral ritonavir randomized simultaneously or ritonavir given 60 minutes before docetaxel on days 1 and 8. On day 15 or 22, patients received 100 mg i.v. docetaxel. The area under the plasma concentration-time curve in patients who received 10 mg oral docetaxel in combination with ritonavir was low, and the dose could safely be increased to 100 mg. The area under the plasma concentration-time curve in patients who received 100 mg oral docetaxel combined with ritonavir simultaneously or ritonavir given 60 minutes before docetaxel was 2.4 ± 1.5 and 2.8 ± 1.4 mg/h/L, respectively, compared with 1.9 ± 0.4 mg/h/L after i.v. docetaxel. The apparent oral bioavailability of docetaxel combined with ritonavir simultaneously or ritonavir given 60 minutes before docetaxel was 131% ± 90% and 161% ± 91%, respectively. The oral
combination of docetaxel and ritonavir was well tolerated. Coadministration of ritonavir significantly enhanced the apparent oral bioavailability of docetaxel. These data are promising and form the basis for further development of a clinically applicable oral formulation of docetaxel combined with ritonavir.

Garren et al., (2009) reported bioavailability of generic ritonavir and lopinavir/ritonavir tablet products in a dog model. In this study, they explored the bioavailability in dogs and chemical potency of generic ritonavir and lopinavir/ritonavir tablet products manufactured by various pharmaceutical companies. Chemical potency of the products was examined by HPLC quantitation of ritonavir and lopinavir. Using a dog model, they determined point estimates for Cmax and AUC of ritonavir and lopinavir/ritonavir for eight generic products compared to Abbott’s Norvir 1 capsule and Kaletra 1 tablet. Chemical potencies ranged from 79.0% to 104.6%. Point estimates for AUC in the generic tablet products ranged from 0.01 to 1.11, indicating that the relative bioavailability of these formulations was in the range of 1–111% compared to the branded products. This study showed significant variability in bioavailability in a dog model amongst generic tablet products containing the protease inhibitors ritonavir or lopinavir/ritonavir. The chemical potency of the generic products was not indicative of the plasma levels of ritonavir or lopinavir that were achieved. These results reinforce the need for human bioequivalence testing of generic products containing ritonavir or lopinavir/ritonavir to assure that efficacy inpatients is not compromised prior to these products being made available to patients. Procurement policies of funding agencies should require such quality assurance processes.

Law et al., (2004) reported ritonavir-PEG 8000 amorphous solid dispersions: \textit{in vitro} and \textit{in vivo} evaluations. Ritonavir is a large, lipophilic molecule that is
practically insoluble in aqueous media and exhibits an exceedingly slow intrinsic dissolution rate. Although it has favorable lipophilicity, in vitro permeability studies have shown that ritonavir is a substrate of P-glycoprotein. Because formulations rarely exert direct influence on local intestinal permeability, the effect of enhanced dissolution rate on oral absorption was explored. More specifically, poly ethylene glycol (PEG) -amorphous ritonavir solid dispersions were prepared with different drug loadings and the in vitro and in vivo performances of the dispersions were evaluated. In vitro dissolution was conducted in 0.1N HCl with a USP apparatus I. A crossover design was used to evaluate the oral bioavailability of amorphous dispersions relative to crystalline drug in beagle dogs. Intrinsic dissolution measurements of the two solid phases indicated a 10-fold improvement in intrinsic dissolution rate for amorphous ritonavir compared with the crystalline counterpart. In vitro dissolution of ritonavir depended on the solid phase as well as drug loading of the dispersion. In vivo study results indicate that amorphous solid dispersions containing 10-30% drug exhibited significant increases in area under the curve of concentration versus time (AUC) and maximum concentration (Cmax) over crystalline drug. For example, 10% amorphous dispersion exhibited increases of 22- and 13.7-fold in AUC and Cmax, respectively. However, both in vitro dissolution and bioavailability decreased with increasing drug load, which led to the construction of a multiple Level C in vitro-in vivo relationship for this Class IV compound. The established relationship between in vitro dissolution and in vivo absorption can help guide formulation development.