CHAPTER 3

OBJECTIVE

OF THE

STUDY
3.0 Objectives of the proposed project

❖ To increase the bioavailability of poorly bioavailable drugs by preparation of solid solutions (solid dispersions).
❖ To investigate the physico-chemical nature of solid dispersions for an understanding of changes within these system during preparation and storage.
❖ To investigate the solid dispersions in vitro in compendial and biorelevant dissolution media and comparison of drug release.
❖ To investigate solid dispersions for increased or more effective absorption of drugs during specific gastrointestinal situations (fasted or fed states).
❖ To compare our formulation with the marketed dosage form of the same drug.

3.1 Rationale of the study:

The poor solubility of drug substances in water and their low dissolution rate in the aqueous gastrointestinal fluids often lead to insufficient bioavailability. Improvement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Besides permeability, the solubility behaviour of a drug is a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. With recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

The dissolution rate of the active ingredient, which is very poorly soluble in the gastrointestinal liquid, is the rate limiting factor for the absorption of the drug. Dissolution rate of such drugs might be improved to minimize the limitations to oral availability. A large number of possibilities have been used including polymorphs, complexation/ solubilization, chemical modification (soluble prodrugs/salts) and particle size etc. but possess limitations. The lack of efficacy of certain drugs due to poor solubility has prompted the examination of solid dispersions as a formulation aspect. Solid dispersion technique has been widely accepted as a method for improving bioavailability of dissolution dependent poorly soluble drugs. A recent application is presenting the drug as a molecular dispersion combining the benefits of a local increase in the solubility (with in solid solution) and maximizing the surface area of the drug that comes in
contact with the dissolution medium as the carrier dissolves. Thus find application in optimization of oral delivery of poorly soluble drugs increasing bioavailability. The advantages of solid dispersions over other approaches is that many of the carriers that can be applied are already extensively used in the pharmaceutical industry as excipients, so additional toxicity studies above and beyond what is required for the drug itself should not be required. The possibility of combining several carriers to produce an optimized product further extends the range of possibilities for formulation. Moreover increase in solubility and release rate that can be achieved are often much greater in orders of several magnitude. This could potentially lead to an increase in bioavailability that is so great that the dose administered could be lowered.

Solid suspensions containing metastable crystalline or amorphous drug material as well as supersaturated solid solutions represent thermodynamically unstable systems, which tend to convert into a more stable state during preparation and storage. Thus, careful investigation of the physicochemical nature of solid dispersions is essential for an understanding of changes within these systems during preparation and storage. Another aspect that must be considered is the correlation between in vitro and in vivo results. Dispersions with a rapid in vitro release rate may fail to improve the oral bioavailability, if the in vitro test conditions do not adequately simulate the gastrointestinal conditions or if there is some specific interaction between the carrier and a component of the GI fluids or a co-ingested foodstuff.

To assess food effects on drug absorption, a cross over study is usually performed in healthy volunteers. To reduce the size and number of human studies required to identify a drug product with appropriate performance in both the fed and fasted states, it would be advantageous to pre-screen formulations in vitro. Such correlations would have the benefit of reducing size and number of costly clinical studies to assess bioavailability. Bioavailability of certain drugs may be demonstrated by evidence obtained by in vitro biorelevant dissolution studies. By performing in vitro biorelevant dissolution test prediction of in vivo absorption behaviour will be possible. It is possible that the dissolution test could replace some of the in vivo studies that need to be performed during product development and registration by proper simulation of in vivo conditions. An in vitro / in vivo correlation may only be possible for those drugs where dissolution is the rate-limiting step in the absorption process. Determining dissolution profile of drugs where dissolution is the rate-limiting step in a number of different physiologically representative media will aid the understanding of the factors affecting the rate and extent of absorption in vivo. The techniques of biorelevant dissolution testing when applied on formulation will play a pivotal role in optimizing these systems suitable for human use.
3.2 Importance of study:

As the rate of infectious diseases emerging at alarming rates, the society and country are in constant need for new improved formulation of drugs (especially for the ones having low oral bioavailability), which will increase the therapeutic benefits to the patients. Drugs having low oral bioavailability not only hinders in desired performance of the drug, but also adds to the cost of the drug therapy. For example, Cephalosporin is considered as the best antibiotics to combat various infections, but due to their poor solubility and bioavailability problems are the one of the costliest option for treatment for infections. Similar is the case of the antiretroviral drugs, which are not only costly, but also its poor bioavailability results in high daily dosage resulting in patient incompliance. Drugs and formulations with potential for enhanced absorption and bioavailability find use in therapy, as the not only enhance the performance of the drug, but also results in better patient compliance and might be cheaper drug therapy.

3.3 Rationale of drug selection:

The main criterion for drug selection for the study was done on bioavailability. To increase the bioavailability of such drugs was one of the main aims. The second criterion was the low solubility of drugs; those belonging to class II and class IV were selected for the study. The aim was to increase the solubility of such drugs by formulating them as solid dispersion in order to achieve enhanced bioavailability.

On the basis of above selection criteria, two model drug candidates are selected for formulation viz. ‘Acyclovir’ – an antiretroviral protease inhibitor and ‘Cefuroxime axetil’ – a third generation cephalosporin antibiotic. Both the drug suffer from poor bioavailability due to low solubility problem.

Acyclovir has reported variable bioavailability in range of 10 to 30%. It has very poor aqueous solubility of upto 2.5 mg/ml in water at 25° C and is highly hydrophobic, as log P was reported to be -1.94. Our aim is to formulate solid dispersion, which can help in increasing the low bioavailability and thus, help in reducing the drug therapy cost. No solid dispersion formulation has been reported in literature till now.

Cefuroxime axetil also suffered from predicament of poor bioavailability, as its absolute bioavailability is reported to be 37%. However, the bioavailability of drug was reported to be increased to 52% in presence of food. It has poor solubility and is practically insoluble in water. It has a lipophilicity value of log P as 0.7, thus making it a BCS class IV drug having poor
solubility and poor permeability. There is no reported literature on cefuroxime being formulated as solid dispersion.

3.4 Drug profile

3.4.1 Acyclovir

Generic Name: Acyclovir

Chemical Name: 9-[(2-Hydroxyethoxy) methyl]guanine; 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one

Molecular formula: C$_{8}$H$_{11}$N$_{5}$O$_{3}$

Generic name abbreviations: ACV

Synonyms: Acycloguanosine; Acidovir; Zovirax®

DESCRIPTION

The discovery of acyclovir (Zovirax®) was first reported in 1977. Acyclovir is a synthetic purine nucleoside analog derived from guanine. The drug differs structurally from guanine by the presence of an acyclic side chain. Acyclovir is commercially available for parenteral use as the sodium salt and for oral use as the base.

Acyclovir is a white, crystalline powder with the molecular formula C$_{8}$H$_{11}$N$_{5}$O$_{3}$ and a molecular weight of 225 and has a maximum solubility up to 2.5 mg/mL in water at 25°C. The drug has pK$_{as}$s of 2.27 and 9.25. At physiologic pH and 37°C, the drug is almost completely unionized and has a maximum solubility of up to 2.5 mg/mL.

![Chemical structure of acyclovir](image.png)

Fig. 4: Chemical structure of acyclovir

MECHANISM OF ANTIVIRAL ACTION

Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir...
monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In vitro, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in 3 ways:

- competitive inhibition of viral DNA polymerase,
- incorporation into and termination of the growing viral DNA chain
- inactivation of the viral DNA polymerase.

The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

ANTIVIRAL ACTIVITIES

The quantitative relationship between the in vitro susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC₅₀), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC₅₀ against herpes simplex virus isolates ranges from 0.02 to 13.5 μg/mL for HSV-1 and from 0.01 to 9.9 μg/mL for HSV-2. The IC₅₀ for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 μg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC₅₀ of 1.35 μg/mL.

RESISTANCE

Herpes simplex virus develops resistance to acyclovir in vitro and in vivo by selection of mutants deficient in thymidine kinase. Other mechanisms of resistance include altered substrate specificity of thymidine kinase and reduced sensitivity of viral DNA polymerase. Resistance has also been reported with varicella-zoster virus, probably by similar mechanisms. Although occasional treatment failures have been reported, resistance has not yet emerged as a major problem in treating herpes simplex infections. However, resistant viruses are more likely to be a problem in patients with a suppressed immune response; AIDS patients may be particularly prone to acyclovir-resistant mucocutaneous herpes simplex virus infections.

Viruses resistant to acyclovir because of absence of thymidine kinase may be crossresistant to other antivirals phosphorylated by this enzyme, such as brivudine, idoxuridine, and ganciclovir. Viruses resistant because of altered substrate specificity of thymidine kinase may display crossresistance to brivudine; those with altered DNA polymerase sensitivity may be resistant to
brivudine and vidarabine. However, those viruses with altered enzyme specificity or sensitivity tend to have variable cross resistance patterns and may be relatively susceptible to acyclovir.

PHARMACOKINETICS

Absorption

Absorption of acyclovir from the GI tract is variable and incomplete. It is estimated that 10–30% of an oral dose of the drug is absorbed. In addition, steady-state peak and trough plasma acyclovir concentrations were not dose proportional over the oral dosing range of 200–800 mg 6 times daily, averaging 0.83 and 0.46, 1.21 and 0.63, or 1.61 and 0.83 μg/mL for the 200, 400, or 800 mg dosing regimens, respectively.

Peak plasma concentrations of acyclovir usually occur within 1.5–2.5h after oral administration.

In immunocompromised individuals, steady-state peak and trough plasma acyclovir concentrations averaged 0.49–0.56 and 0.29–0.31 μg/mL, respectively, following oral administration of 200 mg every 4 h, 1.2 and 0.62 μg/mL, respectively, following oral administration of 400 mg every 4 h, and 2.8 and 1.8 μg/mL, respectively, following oral administration of 800 mg (as capsules) every 4 h.

Food does not appear to affect absorption of acyclovir.

Distribution

Acyclovir is widely distributed into body tissues and fluids including the brain, kidney, saliva, lung, liver, muscle, spleen, uterus, vaginal mucosa and secretions, CSF, and herpetic vesicular fluid. The drug also is distributed into semen, achieving concentrations about 1.4 and 4 times those in plasma during chronic oral therapy at dosages of 400 mg and 1 g daily, respectively.

The apparent volume of distribution of acyclovir is reported to be 32.4–61.8 L/1.73 m² in adults and 28.8, 31.6, 42, or 51.2–53.6 L/1.73 m² in neonates up to 3 months of age, children 1–2 years, 2–7 years, or 7–12 years of age, respectively.

In vitro, acyclovir is approximately 9–33% bound to plasma proteins at plasma concentrations of 0.41–5.2 mcg/mL.

Acyclovir crosses the placenta. Limited data indicate that the drug is distributed into milk, generally in concentrations greater than concurrent maternal plasma concentrations, possibly via an active transport mechanism.
Metabolism

Acyclovir is metabolized partially to 9-carboxymethoxymethylguanine (CMMG) and minimally to 8-hydroxy-9-(2-hydroxyethoxymethyl)guanine. In vitro, acyclovir also is metabolized to acyclovir monophosphate, diphosphate, and triphosphate in cells infected with herpesviruses, principally by intracellular phosphorylation of the drug by virus-coded thymidine kinase (TK) and several cellular enzymes.

Plasma concentrations of acyclovir appear to decline in a biphasic manner. In adults with normal renal function, the half-life of acyclovir in the initial phase (t₁/₂α) averages 0.34 h and the half-life in the terminal phase (t₁/₂β) averages 2.1–3.5 h. In adults with renal impairment, both t₁/₂α and t₁/₂β may be prolonged, depending on the degree of renal impairment.

Elimination

Acyclovir is excreted principally in urine via glomerular filtration and tubular secretion. In adults with normal renal function, approximately 30–90% of a single IV dose is excreted unchanged in urine within 72 h; approximately 8–14% and less than 0.2% are excreted in urine as CMMG and 8-hydroxy-9-(2-hydroxyethoxymethyl)guanine, respectively, within 72 h.

INDICATIONS

Mucocutaneous, Ocular, and Systemic Herpes Simplex Virus (HSV) Infections

Acyclovir is considered the drug of choice for the treatment of mucocutaneous herpes HSV, HSV encephalitis, neonatal HSV infections, orolabial HSV infections, including gingivostomatitis and eczema herpeticum infections in immunocompromised adults, adolescents, and children and also is considered the drug of choice for the treatment of severe HSV infections such as:

Hematopoietic Stem Cell Transplant Recipients

Acyclovir prophylaxis is initiated at the beginning of the conditioning regimen and continued until engraftment occurs or mucositis resolves (approximately 30 days after HSCT). Routine prophylaxis for longer than 30 days is not recommended.

Genital Herpes

Acyclovir is used in the treatment of initial episodes of genital herpes at higher dosages (400 mg 5 times daily) for the treatment of first episodes of herpes proctitis and given episodically to
ameliorate or shorten the duration of lesions or can be given continuously as suppressive therapy to reduce the frequency of recurrences.

Varicella-Zoster Infections

- Varicella (Chickenpox)

Oral acyclovir is used in the treatment of varicella (chickenpox) in both healthy and immunocompetent adults and children to reduce the severity and duration of the illness.

- Herpes Zoster (Shingles, Zoster)

Oral acyclovir may prevent the appearance of new lesions, decrease viral shedding, decrease the severity and/or duration of pain, promote healing and crusting of lesions, and reduce the prevalence of localized zoster-associated neurologic manifestations (paresthesia, dysesthesia, or hyperesthesia).

Epstein-Barr Virus Infections and Disorders:

Because acyclovir exhibits in vitro activity against Epstein-Barr virus (EBV), the drug has been used in the treatment of uncomplicated or complicated infectious mononucleosis, chronic infectious mononucleosis, and various disorders (e.g., oral hairy leukoplakia) associated with EBV infections.

DOSAGE AND ADMINISTRATION

Acute Treatment of Herpes Zoster: 800 mg every 4 h orally, 5 times daily for 7 to 10 days.

Treatment of Initial Genital Herpes: 200 mg every 4 h, 5 times daily for 10 days.

- Chronic Suppressive Therapy for Recurrent Disease: 400 mg 2 times daily for up to 12 months, followed by re-evaluation. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

- Intermittent Therapy: 200 mg every 4 h, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Treatment of Chickenpox

- Children (2 years of age and older): 20 mg/kg per dose orally 4 times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

- Adults and Children over 40 kg: 800 mg 4 times daily for 5 days.
Patients With Acute or Chronic Renal Impairment & on Hemodialysis

For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 h. This results in a 60% decrease in plasma concentrations following a 6 h dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.

SIDE EFFECTS

Acyclovir is generally well tolerated. Renal impairment may be associated with systemic use of acyclovir in some patients; it is usually reversible and is reported to respond to hydration and/or dosage reduction or withdrawal, but may progress to acute renal failure. The risk of renal toxicity is increased by conditions favouring deposition of acyclovir crystals in the tubules such as when the patient is poorly hydrated, has existing renal impairment, or when the drug is given at a high dosage or by rapid or bolus injection. Nausea, vomiting, and diarrhea are among the most common adverse effects of oral acyclovir. Occasional adverse effects include increased serum bilirubin and liver enzymes, haematological changes, skin rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), fever, headache and dizziness. Anaphylaxis has been reported. Hepatitis and jaundice have been reported rarely. Reversible neurological effects including lethargy, somnolence, confusion, hallucinations, agitation, tremors, psychosis, convulsions, and coma have been reported in a small number of patients, particularly in those given intravenous acyclovir and with predisposing factors such as renal impairment; these effects may be more marked in older patients. Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, sometimes resulting in death, have occurred in immunocompromised patients given high parenteral doses of acyclovir. Accelerated diffuse hair loss has also been reported. Topical application of acyclovir may produce transient stinging, burning, itching, or erythema. Eye ointments may occasionally produce transient stinging, superficial punctate keratopathy, blepharitis, or conjunctivitis.

PRECAUTIONS

Systemic acyclovir should be used with caution and in reduced doses in patients with renal impairment. The elderly and patients with existing renal impairment should be closely monitored for neurological adverse effects. Adequate hydration should be maintained in patients given parenteral or high oral doses of acyclovir. Intravenous doses should be given by infusion over 1 h to avoid precipitation of acyclovir in the kidney; rapid or bolus injection should be avoided. The risk of renal impairment is increased by use with other nephrotoxic drugs.
Intravenous acyclovir should also be used with caution in patients with underlying neurological abnormalities, with significant hypoxia, or with serious hepatic or electrolyte abnormalities.

**Geriatrics:** Acyclovir plasma concentrations are higher in geriatric patients compared to younger adults, in part due to age-related changes in renal function. Dosage reduction may be required in geriatric patients with underlying renal impairment.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. Acyclovir did not impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). No testicular abnormalities were seen in dogs given 50 mg/kg/day, IV for 1 month (21 to 41 times human levels) or in dogs given 60 mg/kg/day orally for 1 year (6 to 12 times human levels). Testicular atrophy and aspermatogenesis were observed in rats and dogs at higher dose levels.

Mutagenic changes and chromosomal damage have occurred in vitro in human lymphocytes and mouse lymphoma cells at acyclovir concentrations at least 25 times greater than plasma drug concentrations achievable with usual dosage in humans. Evidence of mutagenicity or carcinogenicity in humans has not been reported to date.

**DRUG INTERACTIONS**

**Antifungal Agents**

Amphotericin B has been shown to potentiate the antiviral effect of acyclovir against pseudorabies virus in vitro when both drugs are added to the culture medium. Ketoconazole and acyclovir have shown dose-dependent, synergistic, antiviral activity against herpes simplex virus types 1 and 2 (HSV-1 and -2) in in vitro replication studies.

**Probenecid**

Concomitant administration of probenecid and acyclovir has reportedly increased the mean plasma half-life and area under the plasma concentration-time curve (AUC) and decreased urinary excretion and renal clearance of acyclovir. This interaction may result from competitive inhibition of the renal secretion of acyclovir by probenecid.
Interferon
The manufacturer states that acyclovir should be used with caution in patients receiving interferon, as the drugs have an additive or synergistic antiviral effect; however, the clinical importance of this interaction is not known.

Methotrexate
The manufacturer states that acyclovir should be used with caution in patients receiving intrathecal methotrexate.

Zidovudine
Acyclovir has been used concomitantly with zidovudine in some patients with human immunodeficiency virus (HIV) infections without evidence of increased toxicity; however, neurotoxicity (profound drowsiness and lethargy), which recurred on rechallenge, has been reported in at least one patient with acquired immunodeficiency syndrome (AIDS) during concomitant therapy with the drugs. Because use of acyclovir for the treatment and prevention of opportunistic infections may be necessary in patients receiving zidovudine, such patients should be monitored closely during combined therapy.

OVERDOSAGE
Overdoses involving ingestion of up to 100 capsules (20 g) have been reported. Adverse events that have been reported in association with overdosage include agitation, coma, seizures, and lethargy. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. This has resulted in elevated BUN and serum creatinine and subsequent renal failure. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored.

STABILITY
Acyclovir should be stored at 25°C, but can be exposed to temperatures ranging from 15–30°C.

3.4.2 CEFUROXIME AXETIL

Generic Name: Cefuroxime axetil
Chemical Name: \([6R-[\text{6a},7p(Z)]-3-[[2\text{-Aminocarbonyl}]\text{oxy}][\text{methyl}]\text{-7-[2 furanyl (methoxyimino) acetyl][ amino]}-8\text{-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2- carboxylic acid}}\)
Molecular Formula: \( \text{C}_{16}\text{H}_{16}\text{N}_{4}\text{O}_8\text{S} \)

Generic name abbreviations: CFA, CXM-AT

Synonyms: Ceftin®

DESCRIPTION:

Cefuroxime is a semisynthetic, second generation cephalosporin antibiotic containing a methoxyimino group at position 7 on the \( \beta \)-lactam ring and a carbamate group at position 3 on the ring. The methoxyimino group results in stability against hydrolysis by many \( \beta \)-lactamases and the carbamate group results in metabolic stability.

![Chemical structure of Cefuroxime axetil](image)

Fig. 5: Chemical structure of Cefuroxime axetil

MECHANISM OF ACTION:

Cefuroxime like any cephalosporin are usually bactericidal in action. The antibacterial activity of the cephalosporins, like penicillins, carbacephems, and cephemycins, results from inhibition of mucopeptide synthesis in the bacterial cell wall. Although the exact mechanisms of action of cephalosporins have not been fully elucidated, \( \beta \)-lactam antibiotics bind to several enzymes in the bacterial cytoplasmic membrane (e.g., carboxypeptidases, endopeptidases, transpeptidases) that are involved in cell-wall synthesis and cell division. It has been hypothesized that \( \beta \)-lactam antibiotics act as substrate analogs of acyl-d-alanyl-d-alanine, the usual substrate for these enzymes. This interferes with cell-wall synthesis and results in the formation of defective cell walls and osmotically unstable spheroplasts. Cell death following exposure to \( \beta \)-lactam antibiotics usually results from lysis, which appears to be mediated by bacterial autolysins such as peptidoglycan hydrolases.

The target enzymes of \( \beta \)-lactam antibiotics have been classified as penicillin-binding proteins (PBPs) and appear to vary substantially among bacterial species. The affinities of various \( \beta \)-lactam antibiotics for different PBPs appear to explain the differences in morphology that occur in susceptible organisms following exposure to different \( \beta \)-lactam antibiotics and may also
explain differences in the spectrum of activity of β-lactam antibiotics that are not caused by the presence or absence of β-lactamases.

SPECTRUM:

Based on its spectrum of activity, cefuroxime is classified as a second generation cephalosporin. Like other currently available second generation cephalosporins (e.g., cefadroxil, cefamandole, cefprozil), cefuroxime generally is more active in vitro against Gram-negative bacteria than first generation cephalosporins but has a narrower spectrum of activity against Gram-negative bacteria than third generation cephalosporins.

RESISTANCE:

Because cefuroxime contains a methoxyimino group that protects the β-lactam ring from hydrolysis by many penicillinases and cephalosporinases, the drug is more resistant to hydrolysis by β-lactamases than are first generation cephalosporins or cefamandole.

PHARMACOKINETICS

Absorption

Following oral administration of CFA, the drug is absorbed as the 1-(acetyloxy)ethyl ester from the GI tract and rapidly hydrolyzed to cefuroxime by nonspecific esterases in the intestinal mucosa and blood. Cefuroxime remaining within the intestinal lumen following hydrolysis of the ester is not absorbed appreciably. The drug has little, if any, microbiologic activity until hydrolyzed in vivo to cefuroxime. Following oral administration in adults of a single 125, 250, 500 or 1000 mg dose of commercially available tablets immediately following a meal, peak serum cefuroxime concentrations are attained approximately 2–3h after the dose and average 2.1, 4.1, 7, or 13.6 µg/mL, respectively; serum concentrations 6h after the dose average 0.3, 0.7, 2.2, or 3.4 µg/mL, respectively. AUC of the drug in these individuals averaged 6.7, 12.9, 27.4, or 50 µg.h/mL, respectively.

Bioavailability following oral administration is variable and depends on the formulation used and presence of food in the GI tract. In adults, bioavailability of cefuroxime following oral administration of commercially available tablets averages about 37% when given in the fasting state and 52% when given with or shortly after food. Although film-coated tablets may be given orally without regard to meals, administration with food maximizes bioavailability of the drug.

In children aged 3 months to 12 years who are unable to swallow tablets, cefuroxime may be administered as the commercially available oral suspension. Although commercially available
tablets have been crushed and mixed with food (e.g., apple sauce, ice cream), the crushed tablets have a strong, persistent taste and the manufacturers state that the drug should not be administered in this manner. Tablets also have been allowed to disintegrate in a small amount (60-90 mL) of beverage (e.g., apple juice or milk) and the beverage stirred and ingested immediately followed by additional amounts of beverage.

Distribution

The apparent volume of distribution of cefuroxime in healthy adults ranges from 9.3–15.8 L/m². The drug is widely distributed into body tissues and fluids including the kidneys, heart, gallbladder, liver, prostatic adenoma tissue, uterine and ovarian tissue, aqueous humor, saliva, sputum, bronchial secretions, bone, bile, adipose tissue, wound exudates, peritoneal fluid, ascitic fluid, synovial fluid, pericardial fluid and pleural fluid.

Cefuroxime is 33–50% bound to serum proteins. Cefuroxime readily crosses the placenta. Amniotic fluid concentrations of cefuroxime reportedly average 17–18.6 µg/mL 3–5.5 h after a single 750 mg IM dose of the drug. Cefuroxime is distributed into milk.

Elimination

In adults, the serum or plasma half-life of cefuroxime following oral administration of commercially available tablets or oral suspension ranges from 1.2–1.6 h. In adults with normal renal function, the serum half-life of cefuroxime following IM or IV administration reportedly ranges from 1–2 h. In adults, approximately 50% of an administered dose is recovered in the urine within 12 h. In patients with renal impairment, the serum half-life of the drug is prolonged and generally ranges from 1.9–16.1 h depending on the degree of impairment.

INDICATIONS

Cefuroxime is used orally for the treatment of mild to moderate respiratory tract infections (i.e., acute maxillary sinusitis, acute exacerbations of chronic bronchitis, secondary infections of acute bronchitis, community-acquired pneumonia) caused by susceptible bacteria; acute bacterial otitis media; pharyngitis and tonsillitis caused by Streptococcus pyogenes (group A β-hemolytic streptococci); mild to moderate uncomplicated skin and skin structure infections caused by Staphylococcus aureus (including β-lactamase-producing strains) or S. pyogenes; and uncomplicated urinary tract infections caused by Escherichia coli or Klebsiella pneumoniae. Also is used orally for the treatment of uncomplicated gonorrhea and for the treatment of Lyme disease.
DOSAGE AND ADMINISTRATION

General Adult Dosage

For the treatment of uncomplicated skin and skin-structure infections in adults and adolescents 13 years of age or older, the usual oral dosage of cefuroxime given as tablets is 250 or 500 mg twice daily for 10 days.

For the treatment of uncomplicated urinary tract infections (UTIs), the usual oral dosage of cefuroxime given as tablets is 125 or 250 mg twice daily for 7-10 days.

Duration of Therapy

The duration of cefuroxime therapy depends on the type of infection but should generally be continued for at least 48-72 h after the patient becomes afebrile or evidence of eradication of the infection is obtained.

SIDE EFFECTS

Hypersensitivity reactions include rash (e.g., morbilliform), fever, pruritus, erythema, urticaria, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, serum sickness-like reactions, angioedema, and anaphylaxis. It have been reported in less than 1% of patients receiving cefuroxime. Nausea and vomiting have been reported in 2.6-6.7% and diarrhea or loose stools have been reported in 3.7-10.6% of patients receiving oral cefuroxime. A strong, persistent, bitter taste has been reported when was administered as crushed tablets. Gagging, epigastric burning, GI bleeding, abdominal pain, flatulence, GI infection, ptyalism, indigestion, mouth ulcers, swollen tongue, anorexia, thirst, dyspepsia, and stomach cramps. It also has been reported in patients receiving the drug orally. Decreased hemoglobin concentration and decreased hematocrit have been reported in about 10% of patients receiving cefuroxime. Transient eosinophilia occurs less frequently and transient neutropenia, pancytopenia, thrombocytopenia, and leukopenia occur rarely. Thrombocytosis, lymphocytosis, hemolytic anemia, and increased prothrombin time also have been reported. Headache, dizziness, somnolence or sleepiness, hyperactivity, irritable behavior, seizures, myoclonic jerks and generalized hyperexcitability have been reported rarely. Transient increases in serum AST (SGOT), ALT (SGPT), alkaline phosphatase, LDH, and bilirubin concentrations have been reported in less than 5% of patients receiving oral or parenteral cefuroxime. Jaundice has been reported rarely. Acute renal failure and interstitial nephritis have also been reported rarely in patients receiving cefuroxime.
Overgrowth with nonsusceptible organisms (e.g., perianal, oral, or vaginal candidiasis; pseudomembranous colitis; superinfection) has occurred in patients receiving cefuroxime.

**PRECAUTIONS**

Prior to initiation of cefuroxime therapy, careful inquiry should be made concerning previous hypersensitivity reactions to cephalosporins, penicillins, or other drugs.

Patients should be advised that antibacterials (including cefuroxime) should only be used to treat bacterial infections and not used to treat viral infections (e.g., the common cold). Patients also should be advised about the importance of completing the full course of therapy, even if feeling better after a few days, and that skipping doses or not completing therapy may decrease effectiveness and increase the likelihood that bacteria will develop resistance and will not be treatable with cefuroxime or other antibacterials in the future.

Patients should be advised that diarrhea is a common problem caused by anti-infectives and usually ends when the drug is discontinued; however, they should contact a clinician if watery and bloody stools (with or without stomach cramps and fever) occur during or as late as 2 months or longer after the last dose.

Cefuroxime should be used with caution in patients with a history of GI disease, particularly colitis.

**Mutagenicity and Carcinogenicity**

No evidence of mutagenicity was observed with cefuroxime in various *in vitro* and *in vivo* test systems, including the mouse lymphoma assay, micronucleus test, and bacterial mutation tests. Studies have not been performed to date to evaluate the carcinogenic potential of cefuroxime.

**Lactation**

Because cefuroxime is distributed into milk and cefuroxime sodium should be used with caution in nursing women.

**DRUG INTERACTIONS**

**Aminoglycosides**

Concurrent use of aminoglycosides and certain cephalosporins reportedly may increase the risk of nephrotoxicity during therapy, due to synergistic effect.
Estrogens or Progestins

Cefuroxime may affect gut flora, leading to decreased estrogen reabsorption and reduced efficacy of oral contraceptives containing estrogen and progestin.

Probenecid

Oral probenecid administered shortly before or concomitantly with cefuroxime usually slows the rate of tubular secretion of cefuroxime and produces higher and more prolonged serum concentrations of cefuroxime. This effect is usually used to therapeutic advantage in the treatment of gonorrhea. Peak serum concentrations of cefuroxime and the half-life of the drug are reportedly increased by up to 30% when probenecid is administered concomitantly; the area under the concentration-time curve (AUC) of cefuroxime is increased by about 50%. Concomitant administration of probenecid also reportedly decreases the apparent volume of distribution of cefuroxime by about 20%.

Laboratory Test Interferences

Immunohematology Tests

Positive direct antiglobulin (Coombs') test results have been reported in a few patients receiving cefuroxime. This reaction may interfere with hematologic studies or transfusion cross-matching procedures.

Tests for Glucose

Like most other cephalosporins, cefuroxime reportedly causes false-positive results in urine glucose determinations using cupric sulfate solution (Benedict's reagent, Clinistix®); however, glucose oxidase tests (Clinistix®) are unaffected by the drug. Cefuroxime may cause false-negative results when ferricyanide methods are used to determine blood glucose concentrations.

Tests for Creatinine

Although some cephalosporins reportedly cause falsely elevated serum or urine creatinine values when the Jaffé reaction is used, cefuroxime does not appear to interfere with this laboratory test.

OVERDOSAGE

Limited information is available on the acute toxicity of cefuroxime in humans. Overdosage of cephalosporins can cause CNS irritation leading to seizures. If acute overdosage of cefuroxime
occurs, hemodialysis and/or peritoneal dialysis can be used to enhance elimination of the drug from the body.

STABILITY

Tablets should be stored in tight containers at 15–30°C. The drug should be protected from excessive moisture. When tablets are allowed to disintegrate in apple juice, the drug is stable for 24 h at room temperature. Commercially available powder for oral suspension should be stored at 2–30°C. Following reconstitution, oral suspensions of containing 125 mg/5 mL or 250 mg/5 mL should be stored immediately at 2–8°C in a refrigerator. Any unused oral suspension should be discarded after 10 days.

3.5 CARRIERS SELECTED

3.5.1 POLYETHYLENGLYCOL (PEG)

Nonproprietary Names
- BP: Macrogols
- JP: Macrogol 400, 1500, 4000, 6000, 20000
- PhEur: Macrogols
- USP-NF: Polyethylene Glycol

Synonyms:
- Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG; Pluriol E; polyoxyethylene glycol.

Chemical Name: Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)

Empirical Formula: \( \text{HOCH}_2(\text{CH}_2 \text{OCH}_2)_n \text{CH}_2 \text{OH} \)

where \( m \) represents the average number of oxyethylene groups.

Alternatively, the general formula \( \text{H(OC}_{n+1}\text{C}_{n+1})_n \text{OH} \) may be used to represent polyethylene glycol, where \( n \) is a number \( m \) in the previous formula.

Description: The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol (PEG) grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures. Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. The grades of PEG 6000 and above are available as free-flowing milled powders.
All grades of PEG are soluble in water and miscible in all proportions with other PEG (after melting, if necessary). Aqueous solutions of higher molecular-weight grades may form gels. Liquid PEGs are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid PEGs are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

PEGs are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.

Adverse reactions to PEGs have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low.

Applications in Pharmaceutical Formulation or Technology: PEGs are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations. Aqueous PEG solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, PEGs can act as emulsion stabilizers.

PEGs can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate PEG.

Rationale for the selection: PEGs are one the most studied carrier for dissolution enhancement by solid dispersion technique for poorly soluble drugs. Its readily solubility in aqueous solutions is one of main reason for which it has been a carrier of choice for formulation of solid dispersions. Its proven ability to enhance aqueous solubility and bioavailability was a reason for its selection for the study.

3.5.2 POLYVINYLPYRROLIDONE

Nonproprietary Names

- BP: Povidone
- JP: Povidone
- PhEur: Povidone
- USP: Povidone

Synonyms: E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1-vinyl-2-pyrrolidinone polymer.

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula: \((\text{C}_4\text{H}_4\text{NO})_n\)
Description: PVP occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder, with melting point at 150°C with sudden decomposition. PVP is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

PVP are freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

PVP darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Unlike other polymers such as PEG, melted PVP is almost not used as an embedding matrix for drugs, except in melt extrusion, because of its high melting point (over 180°C with decomposition). PVP has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran. PVP is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. PVP additionally has no irritant effect on the skin and causes no sensitization.

Applications in Pharmaceutical Formulation or Technology: Although, PVP is used in a variety of pharmaceutical formulations such as disintegrant, dissolution enhancer, suspending agent and tablet binder, it is primarily used in solid-dosage forms. In tableting, PVP solutions are used as binders in wet-granulation processes. PVP is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. PVP is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. PVP solutions may also be used as coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads. PVP is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with PVP. PVP K30 has no disintegrant effect whatsoever, but it can be used to improve the dissolution of many drugs by forming a soluble complex with them.
Different grades of PVP can also be used as lyophilizing agents. They act as a binder in the same way as mannitol, holding the powder together during the freeze-drying process and preventing splashing, and also as a solubilizer or suspension stabilizer that facilitates reconstitution with the solvent prior to use by the patient.

PVP dissolves in the continuous phase of a suspension as a polymer, separating the drug particles without lowering their zeta potential. It can act as redispersing agents by increasing the sediment volume.

**Rationale for the selection:** The PVPs are excellent auxiliaries for the manufacture of effective solid solutions and dispersions as they possess excellent hydrophilization properties, form water-soluble complexes with many drugs, in contrast to most other carrier materials, and are almost universally soluble. This is why more than 150 drugs in solid solutions and dispersions with povidone have been described in the literature between 1960 and 2002. Their excellent solubility in water and in other solvents used in pharmaceutical production is an advantage in almost all dosage forms and making it an obvious choice as carrier in formulating solid dispersions.

### 3.5.3 POLOXAMER

**Nomenclature:**
- BP: Poloxamers
- PhEur: Poloxamers
- USP-NF: Poloxamer

**Synonyms:** Lutrol; Monolan; Pluronic; poloxalkoi; poloxamera; polyethylene–propylene glycol copolymer; polyoxyethylene–polyoxypropylene copolymer; Supronic; Synperonic.

**Chemical Name:** a-Hydro-o-hydroxypoly(oxyethylene)poly(oxypropylene)-poly(oxyethylene) block copolymer.

**Empirical Formula:** The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula \( \text{HO(C}_2\text{H}_4\text{O)}_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}. \)

**Description:** Poloxamer 188 is a block polymer consisting of 81% of polyethylene glycol and 19% of polypropylene glycol. The polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. It has an average molecular weight of 8600.
The nonproprietary name 'poloxamer' is followed by a number, the first two digits of which, when multiplied by 100, correspond to the approximate average molecular weight of the polyoxypropylene portion of the copolymer and the third digit, when multiplied by 10, corresponds to the percentage by weight of the polyoxyethylene portion.

Similarly, with many of the trade names used for poloxamers, e.g. Pluronic F-68 (BASF Corp.), the first digit arbitrarily represents the molecular weight of the polyoxypropylene portion and the second digit represents the weight percent of the oxyethylene portion. The letters 'L', 'P', and 'F', stand for the physical form of the poloxamer: liquid, paste, or flakes. In the USA, the trade name Pluronic is used by BASF Corp. for pharmaceutical-grade and industrial-grade poloxamers, while in Europe the trade name Lutrol is used by BASF Corp. for the pharmaceutical-grade material.

Poloxamers generally occur as white, waxy, free-flowing prilled granules, or as cast solids. They are practically odorless and tasteless. The melting point for poloxamer 188 is 52–57 °C. Solubility varies according to the poloxamer type. Poloxamer 188 is freely soluble in 95% ethanol, and water at 20 °C.

Poloxamers are stable materials. Aqueous solutions are stable in the presence of acids, alkalis, and metal ions. Poloxamers are used in a variety of oral, parenteral, and topical pharmaceutical formulations, and are generally regarded as nontoxic and nonirritant materials. Poloxamers are not metabolized in the body.

Applications in Pharmaceutical Formulation or Technology:

Poloxamers are nonionic polyoxyethylene–polyoxypropylene co-polymers used primarily in pharmaceutical formulations as dispersing agent, emulsifying agent, solubilizing agent, tablet lubricant and wetting agent. Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents; in ointments, suppository bases, and gels; and as tablet binders and coatings.

Poloxamer 188 is primarily intended as an emulsifier, solubilizer, and suspension stabilizer in liquid oral, topical and parenteral dosage forms, as a plasticizer, and for enhancing the bioavailability in solid preparations. Poloxamer 188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes, and in the preparation of solid-dispersion systems.

More recently, poloxamers have found use in drug-delivery systems. Therapeutically,
poloxamer 188 is administered orally as a wetting agent and stool lubricant in the treatment of constipation; it is usually used in combination with a laxative such as danthron. Poloxamers may also be used therapeutically as wetting agents in eye-drop formulations, in the treatment of kidney stones, and as skin-wound cleansers.

**Rationale for the selection:** Poloxamers has been primarily used as solubilizer and suspension stabilizer and has excellent property to enhance drug wettablity by surfactant effect. Its well known role in solubilizing poorly soluble drugs and vitamins make it an ideal candidate as carrier for solid dispersion formulations.

### 3.5.4 KOLLIDON®-CL

**Nonproprietary Names:**
- BP: Crospovidone
- PhEur: Crospovidone
- USP-NF: Crospovidone

**Synonyms:**
- Crospovidonum; Crospopharm; crosslinked povidone; E1202; Kollidon® CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

**Chemical Name:** 1-Ethenyl-2-pyrrolidinone homopolymer

**Empirical Formula:** \((C_6H_9N_0)_n\)

**Description:** The USP32–NF27 describes crospovidone as a water insoluble synthetic crosslinked homopolymer of N-vinyl-2-pyrrolidinone. Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder. It is practically insoluble in water and most common organic solvents. An exact determination of the molecular weight has not been established, because of the insolubility of the material. Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

**Applications in Pharmaceutical Formulation or Technology:** Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can
also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

However, Kollidon® CL is by far the more important disintegrant, as it develops a much higher swelling pressure than Kollidon® CL-M. Crospovidone is referred to as one of the “super disintegrants” in the literature but it is also an excellent agent for the enhancement of the drug release.

The rapid disintegration of a tablet is by no means a guarantee that the active substance is released and made bioavailable quickly. Thus, the drug release rate of a tablet is a much more important criterion than its disintegration time.

In difficult cases where drug release still proves inadequate, higher concentrations of Kollidon® CL or Kollidon® CL-M can be used. Then, the active substance should be co-milled or co-evaporated with the crospovidone before addition to the other ingredients. A complex between the drug and the crospovidone forms in these intimate mixtures, which increases the solubility of the drug, thereby enhancing its bioavailability. Such mixtures generally require an excess of crospovidone, typically 2 parts per 1 part of active substance. With substances that are used in low dosages, such as hormone derivatives, this presents no problems.

One of the greatest problems in the development of formulations for suspensions is the prevention of sedimentation over the necessary period. Thickeners such as cellulose derivatives are traditionally used as sedimentation inhibitors to increase the relative sediment volume. The use of Kollidon® CL-M as a suspension stabilizer is not limited to aqueous systems. It also stabilizes suspensions in organic solvents such as paraffin.

Rationale for the selection: The ability to accelerate disintegration and therefore, also of dissolution and bioavailability of the active substances as a result of predictable swelling and hence disintegration effect; Improvement of dissolution and bioavailability of insoluble drugs by complex formation are the most important property of Kollidon CL as an auxiliary for its disintegration and dissolution enhancing effect, which can be used for improvement in the dissolution of insoluble drugs by using it as carrier in solid dispersion.

3.5.5. KOLLIDON® VA64

Nonproprietary Names BP: Copovidone
**PhEur:** Copovidone  
**USP-NF:** Copovidone  

**Synonyms:** Acetic acid vinyl ester, polymer with 1-vinyl-2-pyrrolidinone; copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a ratio of 3:2 by mass; copovidone; copovidonum; Kollidon VA 64; Luviskol VA; Plasdone S-630; poly(1-vinylpyrrolidone-co-vinyl acetate); polyvinylpyrrolidone-vinyl acetate copolymer; PVP/VA; PVP/VA copolymer.

**Chemical Name:** Acetic acid ethenyl ester, polymer with 1-ethenyl-2-pyrrolidinone  
**Empirical Formula:** \((\text{C}_4\text{H}_6\text{O}_2)_n\)  
The ratio of \(n\) to \(m\) is approximately \(n = 1.2m\).  
The average molecular weight of copovidone is usually expressed as a K-value.

**Description:** Kollidon® VA 64 is a white to yellowish-white amorphous powder. It is typically spray-dried with a relatively fine particle size. It has a slight odor and a faint taste. It melts at 140 °C and has solubility of greater than 10% in 1,4-butanediol, glycerol, butanol, chloroform, dichloromethane, ethanol (95%), glycerol, methanol, polyethylene glycol 400, propan-2-ol, propanol, propylene glycol, and water, while have solubility of less than 1% in cyclohexane, diethyl ether, liquid paraffin, and pentane.

Kollidon® VA 64 is used widely in pharmaceutical formulations and is generally regarded as nontoxic. However, it is moderately toxic by ingestion, producing gastric disturbances. It has no irritating or sensitizing effects on the skin.

Kollidon® VA 64 has low hygroscopicity, good flow characteristics, a low glass transition temperature, and it gives hard tablets, making it the best dry binder available.

**Applications in Pharmaceutical Formulation or Technology:** Kollidon® VA 64 is used as a tablet binder, a film-former, and as part of the matrix material used in controlled-release formulations. In tabletting, copovidone can be used as a binder for direct compression and as a binder in wet granulation. Kollidon® VA 64 is often added to coating solutions as a film-forming agent. It provides good adhesion, elasticity, and hardness, and can be used as a moisture barrier.

Kollidon® VA 64 can be used as a dry binder together with all fillers and practically all active ingredients. A mixture of Kollidon® VA 64 with microcrystalline cellulose has been found to be a
particularly effective combination. Kollidon® VA 64 is used in water-soluble tablet coatings to improve stability or organoleptic properties, particularly in conjunction with other film-forming agents.

Kollidon® VA 64 can also be used together with other film-forming agents such as polyvinyl alcohol, hydroxypropylcellulose, ethylcellulose or sucrose in the manufacture of soluble tablet coatings.

Particularly, Kollidon® VA 64 are suitable for use as mucoadhesives in buccal tablets.

Kollidon VA 64 can also be used as a matrix in certain rapid-dissolution dosage forms, depending on the other ingredients used. This should be of particular interest for drugs with relatively poor bioavailability, as copovidone forms complexes with these substances, increasing the dissolution rate in much the same manner, as does PVP.

**Rationale for the selection:** The applications of Kollidon VA 64 rely mainly on its good binding and film-forming properties, its affinity to hydrophilic and hydrophobic surfaces and its relatively low hygroscopicity helps Kollidon® VA 64 to use as matrix to enhance drug dissolution. Also, because of the ratio of vinylpyrrolidone to vinyl acetate in Kollidon VA 64, it is almost as universally soluble as PVP K30. It dissolves in extremely hydrophilic liquids such as water as well as in more hydrophobic solvents such as butanol. Although nowadays the use of organic solvents such as methylene chloride or chloroform is largely avoided in the production of finished drugs, most pharmaceutical companies still use small quantities of ethanol, isopropanol, propylene glycol or low-molecular PEG. Kollidon VA 64 is soluble in practically all proportions in these solvents and in water, making it an ideal candidate for its utility as carrier for solid dispersions.

### 3.5.6 KOLLICOAT® IR

**Nonproprietary Names**
- PhEur: Macrogol Poly(vinylalcohol) Grafted Copolymer
- USP-NF: Ethylene Glycol and Vinyl Alcohol Graft Copolymer

**Synonyms:**
- Polyvinyl alcohol-polyethylene glycol graft copolymer;
- Macrogol poly(vinyl alcohol) grafted copolymer; Kollicoat® IR

**Chemical Name:** Polyvinyl alcohol-polyethylene glycol copolymer

**Description:** Kollicoat® IR is a polyvinyl alcohol-polyethylene glycol-graft copolymer consisting of 75% of polyvinyl alcohol and of 25% of polyethylene glycol with a molecular weight of around 45,000 Dalton. The solubility of the polymer is independent of the
pH-value and it is possible to achieve 40% solutions in water, 0.08N HCl, and phosphate buffer pH 6.8. Besides the high solubility in water polymer films show a very high flexibility. This property makes the product extremely suitable for film-coating applications.

Applications in Pharmaceutical Formulation or Technology: The product is mainly applied in instant-release coatings of tablets and pellets as highly flexible film-former with low viscosity. Furthermore it functions as binder for granules and film-former in sprays. Polyethylene glycol-polyvinyl alcohol graft copolymer (PEG-PVA-graft polymer) used for the instant-release coating of tablets, pellets and particulate matter. Also applicable as a binder using a binding solution for wet-granulation and as a pore former in combination with sustained-release polymers.

The instant-release film-coating polymer Kollicoat® IR (polyvinyl alcohol grafted onto polyethylene glycol) also can be used as an excellent binder in the wet granulation using a binder solution. This plastic polymer is very soluble in water and alcohol, does not form any peroxides during storage and gives good physical tablet properties.

Instant release coatings are applied to tablets or capsules with the purposes of coloring to increase the patient compliance or to identify and distinguish different types of tablets; protection of the active ingredient against oxidation or against hydrolysis or to avoid chemical interactions between the active ingredients (e.g., vitamin combinations) and masking the smell and taste of the active ingredient.

Rationale for the selection: Kollicoat® IR (polyvinyl alcohol grafted onto polyethylene glycol) can be considered as the ideal film former for instant release film coatings, since it is plastic, very soluble in water, has no significant viscosity even in a concentration of 20% and very low tackiness. Therefore high concentrated spray solutions can be applied and no plasticizer is needed. This gives simple and efficient formulations of low manufacturing costs. The ability of instant release make it good candidate as carrier for formulation of solid dispersions.

3.5.7 CREMOPHOR® EL

Nonproprietary Names: BP: Polyoxyl 35 Castor Oil
PhEur: Polyoxyl Castor Oil
USP-NF: Hydrogenated Polyoxyl Castor Oil

Synonyms: Castor oil POE-35; Cremophor EL; Cremophor ELP; Etocas 35; glycerol polyethleneglycol ricinoleate; PEG-35 castor oil; polyethoxylated castor oil; polyoxyethylene 35 castor oil;
Acconon; Arlatone; Cremophor; Etocas; Eumulgin; Jeechem; Lipocol; macrogolglyceroli hydroxystearas; macrogolglyceroli ricinoleas; Mapeg; Marlowet; Nikkol; Protachem; Simulsol.

Chemical Name: Polyethoxylated castor oil

Empirical Formula: Polyoxyethylene castor oil derivatives are complex mixtures of various hydrophobic and hydrophilic components. Members within each range have different degrees of ethoxylation (moles)/PEG units as indicated by their numerical suffix (n). The chemical structures of the polyethoxylated hydrogenated castor oils are analogous to polyethoxylated castor oils with the exception that the double bond in the fatty chain has been saturated by hydrogenation.

The PhEur 6.0 states that polyoxyl castor oil contains mainly ricinoleyl glycerol ethoxylated with 30–50 molecules of ethylene oxide (nominal value), with small amounts of macrogol ricinoleate, and of the corresponding free glycols. The PhEur 6.0 also states that polyoxyl hydrogenated castor oil contains mainly trihydroxystearyl glycerol ethoxylated with 7–60 molecules of ethylene oxide (nominal value).

In polyoxyl 35 castor oil, the relatively hydrophobic constituents comprise about 83% of the total mixture, the main component being glycerol polyethylene glycol ricinoleate. Other hydrophobic constituents include fatty acid esters of polyethylene glycol along with some unchanged castor oil. The hydrophilic part (17%) consists of free polyethylene glycols and glycerol ethoxylates.

Description: Cremophor® EL appear as pale yellow oily liquid, clear above 26 °C with faint characteristic odor. It has melting point of 19–20 °C and is freely soluble in water and all organic solvents.

Polyoxyl 35 castor oil forms stable solutions in many organic solvents such as chloroform, ethanol, and propan-2-ol; it also forms clear, stable, aqueous solutions. Polyoxyl 35 castor oil is miscible with other polyoxyethylene castor oil derivatives and on heating with fatty acids, fatty alcohols, and certain animal and vegetable oils. Solutions of polyoxyl 40 hydrogenated castor oil in aqueous alcohols and purely aqueous solutions are also stable. Solutions become cloudy as temperature increases.

On heating of an aqueous solution, the solubility of polyoxyl 35 castor oil is reduced and the solution becomes turbid. Aqueous solutions of polyoxyl hydrogenated castor oil heated for prolonged periods may separate into solid and liquid phases on cooling. However, the product
can be restored to its original form by homogenization.

Acute and chronic toxicity tests in animals have shown polyoxyethylene castor oil derivatives to be essentially nontoxic and nonirritant materials. However, there are reports of cardiovascular changes and nephrotoxicity in various species of animals. The precise mechanism of the reaction is not known.

**Applications in Pharmaceutical Formulation or Technology:** Polyoxyethylene castor oil derivatives are nonionic solubilizers and emulsifying agents used in oral, topical, and parenteral pharmaceutical formulations.

Polyoxyl 35 castor oil is mainly used as an emulsifying and solubilizing agent, and is particularly suitable for the production of aqueous liquid preparations containing volatile oils, fat-soluble vitamins, and other hydrophobic substances. Cremophor EL emulsifies or solubilizes the fat-soluble vitamins A, D, E, and K in aqueous solutions for oral and topical administration. Aqueous solutions of hydrophobic drugs (e.g. miconazole, hexetidine, clotrimazole, benzocaine) can be prepared with Cremophor EL, which has also been used as a solubilizing agent for drugs like cyclosporin A, paclitaxel, and cisplatin.

Polyoxyl 35 castor oil has also been used as a solvent in proprietary injections of diazepam, propanidid, and alfaxalone with alfadolone acetate. A self-microemulsifying drug delivery system (SMEDDS) for oral bioavailability, and the enhancement of halofantrine, and simvastatin have been prepared. Polyoxyl 35 castor oil has been used as a buffering agent for aqueous tropicamide eyedrops. It has also been used in an aqueous mixture together with caprylic/capric glyceride for mucosal vaccination, providing a potential alternative to parenteral vaccination. Polyoxyl 35 castor oil has been used to enhance the permeability of peptides across monolayers of Caco-2 cells by inhibiting the apically polarized efflux system, enhancing intestinal absorption of some drugs. Cremophor has been used as a vehicle for boron neutron-capture therapy in mice, which is a form of radiation therapy used in the treatment of glioblastoma multiforme. Polyoxyl 35 castor oil is also used in the production of glycerin suppositories. Cremophor EL can enhance the bioavailability of substances such as vitamins in feed and veterinary medicines, improving their efficacy.

**Rationale for the selection:** Cremophor® EL is an excellent solubilizers for the oral and topical use. The principle of solubilization in a microemulsion is useful for lipophilic and strongly hydrophobic substances. Surfactants such as Cremophor® EL increase the wettability of the solid particles in a suspension and reduce the surface tension of the continuous phase. This prevents,
among other things, the flotation of the particles and reduces aggregate formation, which increases the sediment volume.

They act in a similar manner to propylene glycol in preventing the dissolved part of the active ingredient from recrystallizing, stabilizing the physical properties of the suspension, making it an ideal candidate for carrier to formulate stable solid dispersions.

3.5.8 CROSSCARMALLOSE SODIUM

Nonproprietary Names:  
BP: Croscarmellose Sodium  
JP: Croscarmellose Sodium  
PhEur: Croscarmellose Sodium  
USP-NF: Croscarmellose Sodium

Synonyms:  
Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical Name: Cellulose, carboxymethyl ether, sodium salt, crosslinked

Empirical Formula: Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium; polycarboxymethyl ether of cellulose.

Description: Croscarmellose sodium occurs as an odorless, white or grayish-white powder. Its is insoluble in water, although croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Croscarmellose sodium is a stable though hygroscopic material.

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems.

In the UK, croscarmellose sodium is accepted for use in dietary supplements.
The WHO has not specified an acceptable daily intake for the related substance carboxymethylcellulose sodium, used as a food additive, since the levels necessary to achieve a desired effect were not considered sufficient to be a hazard to health.

**Applications in Pharmaceutical Formulation or Technology:** Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules.

In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extra-granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

**Rational for the selection:** Croscarmellose sodium was primarily used for its disintegrant role in solid dosage forms thus, been main reason for its selection as carrier for formulating solid dispersion with an objective to utilize its disintegrant effect. It also swells to form matrix, which was postulated to release dispersed drug.

### 3.5.9 SODIUM STARCH GLYCOLATE

**Nonproprietary Names:**
- BP: Sodium Starch Glycolate
- PhEur: Sodium Starch Glycolate
- USP-NF: Sodium Starch Glycolate

**Synonyms:**
- Carboxymethyl starch, sodium salt; carboxymethylamylose amelim; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

**Chemical Name:** Sodium carboxymethyl starch

**Empirical Formula:** The USP32–NF27 describes two types of sodium starch glycolate, Type A and Type B, and states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch or of a crosslinked carboxymethyl ether of starch.

The PhEur 6.0 describes three types of material: Type A and Type B are described as the sodium salt of a crosslinked partly O-carboxymethylated potato starch. Type C is described as the sodium salt of a partly O-carboxymethylated starch, crosslinked by physical dehydration. Types A, B, and C are differentiated by their pH, sodium, and sodium chloride content.
The PhEur and USP–NF monographs have been harmonized for Type A and Type B variants. Sodium starch glycolate may be characterized by the degree of substitution and crosslinking.

**Description:** Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. The PhEur 6.0 states that when examined under a microscope it is seen to consist of: granules, irregularly shaped, ovoid or pear-shaped, 30–100 mm in size, or rounded, 10–35 mm in size; compound granules consisting of 2–4 components occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum; small crystals are visible at the surface of the granules. The granules show considerable swelling in contact with water. It does not melt, but chars at approximately 200 °C. It is practically insoluble in methylene chloride. It gives a translucent suspension in water.

Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

**Applications in Pharmaceutical Formulation or Technology:** Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

Although, the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired.

Sodium starch glycolate has also been investigated for use as a suspending vehicle.

**Rationale for the selection:** Similarly like crosscarmallose sodium, sodium starch glycolate also posses disintegrant properties and thus been the main reason to be used as carrier for formulating solid dispersions.
3.5.10 MICROCRYSTALLINE CELLULOSE

Nonproprietary Names:  
BP: Microcrystalline Cellulose  
JP: Microcrystalline Cellulose  
PhEur: Cellulose, Microcrystalline  
USP-NF: Microcrystalline Cellulose  

Synonyms:  
Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Celenus KG; crystalline cellulose; E460; Emcocel; Ethilospheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

Chemical Name: Cellulose  
Empirical Formula: \((\text{C}_6\text{H}_{10}\text{O}_5)_n\)

Description: Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications. It chars at 260–270 °C, and is slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents. Microcrystalline cellulose is a stable though hygroscopic material. Microcrystalline cellulose is incompatible with strong oxidizing agents.

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

Applications in Pharmaceutical Formulation or Technology: Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some
lubricant and disintegrant properties that make it useful in tableting.

Rationale for the selection: Similarly like selection of crosscarmellose sodium and sodium starch glycolate, the super disintegrant property was the main reason to select microcrystalline cellulose as carrier for the study.

3.5.11 PROSOLV® SMCC 90

Nonproprietary Names: None adopted.
Synonyms: ProSolv®.
Chemical Name: Silicified cellulose; cellulose with silicon dioxide
Empirical Formula: \( (C_{6}H_{10}O_{5})_{n} \text{ with SiO}_2 \)
Description: Silicified microcrystalline cellulose is a synergistic, intimate physical mixture of two components: microcrystalline cellulose and colloidal silicon dioxide. Silicified microcrystalline cellulose contains 2% w/w colloidal silicon dioxide. Microcrystalline cellulose component chars at 260-270 °C. It is practically insoluble in water, dilute acids, and most organic solvents. The microcrystalline cellulose component is slightly soluble in 5% w/w sodium hydroxide solution.

Applications in Pharmaceutical Formulation or Technology: Silicified microcrystalline cellulose is used as a filler in the formulation of capsules and tablets. It has improved compaction properties in both wet granulation and direct compression compared to conventional microcrystalline cellulose. Silicified microcrystalline cellulose was specifically developed to address the loss of compaction that occurs with microcrystalline cellulose after wet granulation. Silicified microcrystalline cellulose also appears to have beneficial properties for use in the formulation of powder-filled capsules.

Rationale for the selection: Similarly like selection other disintegrant for the study as carrier for poorly soluble drugs for formulating solid dispersion, silicified microcrystalline cellulose as carrier was selected for the study.

3.6 SURFACTANT SELECTED

3.6.1 SOLUTOL®

Nonproprietary Names
BP: Macrogol 15 Hydroxystearate
PhEur: Macrogol 15 Hydroxystearate
Synonyms: 12-Hydroxyoctadecanoic acid polymer with α-hydroxy-o-hydroxy-
poly(oxy-1,2-ethanediyl); 12-hydroxyoleic acid polyethylene
glycol copolymer; macrogol 15 hydroxystearate; polyethylene
glycol-15-hydroxystearate; polyethylene glycol 660 12-
hydroxystearate; Solutol HS 15.

Chemical Name: 2-Hydroxyethyl-12-hydroxyoctadecanoate [70142-34-6]

Empirical Formula: \( \text{C}_2\text{O}_4\text{H}_{40}\text{O}_4 \)

The PhEur 6.0 describes macrogol 15 hydroxystearate as a mixture of mainly monoesters and
diesters of 12-hydroxystearic acid and macrogols obtained by the ethoxylation of 12-
hydroxystearic acid. The number of moles of ethylene oxide reacted per mole of 12-
hydroxystearic acid is 15 (nominal value). It contains about 30% free macrogols.

Description:

Macrogol 15 hydroxystearate is a yellowish-white, almost odorless waxy mass or paste at room
temperature, which becomes liquid at approximately 30 °C. It is soluble in organic solvents
such as ethanol (95%), propan-2-ol, and very soluble in water to form clear solutions. The
solubility in water decreases with increasing temperature. It is insoluble in liquid paraffin.

Macrogol 15 hydroxystearate has a high chemical stability. The prolonged action of heat may
induce physical separation into a liquid and a solid phase after cooling, which can be reversed
by subsequent homogenization. Macrogol 15 hydroxystearate is stable for at least 24 months if
stored in unopened airtight containers at room temperature (maximum 25 °C). Aqueous
solutions of macrogol 15 hydroxystearate can be heat-sterilized (121 °C, 0.21 MPa). The pH
may drop slightly during heating, which should be taken into account. Separation into phases
may also occur, but agitating the hot solution can reverse this. Aqueous solutions can be
stabilized with the standard preservatives used in pharmaceuticals.

Macrogol 15 hydroxystearate should be stored in tightly sealed containers in a dry place.
Macrogol 15 hydroxystearate is reported not to be mutagenic in bacteria, mammalian cell
cultures and mammals.

As is the case with oral solutions, nonionic surfactants are also used as solubilizers in parenteral
preparations. However, because of side effects such as the release of histamine, their suitability
for use in an injectable formulation must be carefully checked. The only solubilizer that did not
trigger the release of histamine in an animal trial was macrogol hydroxystearate 15 (Solutol® HS
15), so that this product can be particularly recommended for parenterals.
Applications in Pharmaceutical Formulation or Technology

Macrogol 15 hydroxystearate is frequently used in preclinical testing of drugs, mainly for IV and other parenteral applications. The solubilizing capacity for some tested drugs (clotrimazole, carbamazepine, 17b-estradiol, sulfathiazole, and piroxicam) increases almost linearly with increasing concentration of solubilizing agent. This is due to the formation of spherical micelles even at high concentrations of macrogol 15 hydroxystearate. Similarly, tests have revealed that viscosity increases with increasing amount of solubilizer, but the amount of solubilized drugs does not have any additional influence on the kinematic viscosity. Lipid nanocapsules comprising macrogol 15 hydroxystearate and soybean phosphatidylcholine containing 3% docetaxel have been successfully prepared by a solvent-free inversion process.

Macrogol 15 hydroxystearate has been used in the manufacture of aqueous parenteral preparations with vitamin A, D, E and K, and a number of other lipophilic pharmaceutical active agents, such as propanidid, miconazole, alfadolone, and alfaxalone. It is very efficient at solubilizing substances like fat-soluble vitamins and active ingredients of hydrophobic nature. It is also an excellent solubilizer for parenteral use, at a concentration of 20%, and the water solubility of different drugs may be enhanced by a factor of 10–100, depending on the structure of the drug molecule.

Rationale for the selection:

Solutol® HS 15 is frequently used to solubilize lipophilic substances, in particular vitamins and liponic acid. But, they can also be used to solubilize other hydrophobic substances. It is also recommended as a sedimentation inhibitor and redispersing agent. They act in a similar manner to propylene glycol in preventing the dissolved part of the active ingredient from recrystallizing, stabilizing the physical properties of the suspension. The use of nonionic solubilizers as a means of improving the bioavailability of active ingredients is of interest above all for lipophilic substances and thus been selected for the study.

3.6.2 LABRASOL®

Nonproprietary Names:
- BP: Caprylocaproyl Macrogolglycerides,
- PhEur: Caprylocaproyl Macrogolglycerides
- USP-NF: Caprylocaproyl Polyoxylglycerides

Synonym:
- Caprylocaproyl polyoxylglycerides; Labrasol;
- macrogolglyceridorum caprylocaprates; PEG 400 caprylic/capric glycerides
Chemical name: Decanoic acid, mixed monoesters with glycerol and octanoic acid; poly(oxy- 1,2-ethanediyl), a-hydro-o-hydroxy-, mixed decanoate and octanoate
Empirical Formula: Polyoxylglycerides are mixtures of monoesters, diesters, and triesters of glycerol, and monoesters and diesters of polyethylene glycols (PEG).

Caprylocaproyl polyoxylglycerides: Mixtures of monoesters, diesters, and triesters of glycerol and monoesters and diesters of polyethylene glycols with mean relative molecular mass between 200 and 400. They are obtained by partial alcoholysis of medium-chain triglycerides using polyethylene glycol or by esterification of glycerin and polyethylene glycol with caprylic (octanoic) acid and capric (decanoic) acid or a mixture of glycerin esters and condensates of ethylene oxide with caprylic acid and capric acid. They may contain free polyethylene glycols.

Description: Polyoxylglycerides are inert liquid or semi-solid waxy materials and are amphiphilic in character. Caprylocaproyl polyoxylglycerides are pale-yellow oily liquids, which may give rise to a deposit after prolonged periods at 20 °C. It is dispersible in hot water and freely soluble in methylene chloride.

Applications in Pharmaceutical Formulation or Technology: Labrasol can be used as dissolution enhancer; emulsifying agent; nonionic surfactant; penetration agent; solubilizing agent and sustained-release agent. Polyoxylglycerides are used as self-emulsifying and solubilizing agents in oral and topical pharmaceutical formulations. They are also used in cosmetic and food products.

Rationale for the selection: Labrasol® is a known dissolution enhancer for many poorly soluble compounds. Its penetration enhancing properties can be utilized to enhance bioavailability of drugs in consideration in the study. Thus, its surfactant and penetration enhancing properties make it suitable candidate for the study.

3.6.3 LABRAFIL®

Nonproprietary Names: BP: Linoleoyl Macrogolglycerides
PhEur: Linoleoyl Macrogolglycerides
USP-NF: Linoleoyl Polyoxylglycerides

Synonyms: Linoleoyl polyoxylglycerides, Corn oil PEG 300 esters; Labrafil M2125CS; macrogolglyceridorum linoleates, Oleoyl
polyoxylglycerides: Apricot kernel oil PEG 300 esters; Labrafil M1944CS; macrogolglyceridorm oleates; peglicol-5-oleate

Chemical Name:
- Linoleoyl polyoxylglycerides: Corn oil, ethoxylated; 9,12-octadecadienoic acid (9E,12E)-monoester with 1,2,3-propanetriol
- Oleoyl polyoxylglycerides: 9-Octadecenoic acid (9Z), monoester with 1,2,3-propanetriol; poly(oxy-1,2-ethanediyl), a-[(9Z)-1-oxo-9-octadeceny]-o-hydroxy-

Empirical Formula: Polyoxylglycerides are mixtures of monoesters, diesters, and triesters of glycerol, and monoesters and diesters of polyethylene glycols (PEG). Linoleoyl polyoxylglycerides Mixtures of monoeesters, diesters, and triesters of glycerol and monoesters and diesters of polyethylene glycols. They are obtained by partial alcoholysis of an unsaturated oil mainly containing triglycerides of linoleic (cis,cis-9,12-octadecadienoic) acid, using polyethylene glycol with mean relative molecular mass between 300 and 400, or by esterification of glycerol and polyethylene glycol with unsaturated fatty acids, or by mixing glycerol esters and condensates of ethylene oxide with the fatty acids of this unsaturated oil.

Description: Polyoxylglycerides are inert liquid or semi-solid waxy materials and are amphiphilic in character. Linoleoyl polyoxylglycerides occur as amber oily liquids, which may give rise to a deposit after prolonged periods at 20 °C. Linoleoyl polyoxylglycerides are practically insoluble but dispersible in water and freely soluble in methylene chloride.

Polyoxylglycerides are very stable and inert. However, preventive measures against the risk of oxidation or hydrolysis may be taken to ensure stability during handling.

Polyoxylglycerides are used in oral and topical pharmaceutical formulations, and also in cosmetics and food products. They are generally regarded as relatively nonirritant and nontoxic materials.

Applications in Pharmaceutical Formulation or Technology: Labrafil® is known to be used as dissolution enhancer; emulsifying agent; nonionic surfactant; penetration agent; solubilizing agent and sustained-release agent. Polyoxylglycerides are used as self-emulsifying and solubilizing agents in oral and topical pharmaceutical formulations. They are also used in cosmetic and food products.

Rationale for the selection: Labrafil® is a known dissolution enhancer for many poorly
soluble compounds with properties of being penetration enhancer. Its surfactant properties enhance solubility of hydrophobic drugs and make it ideal candidate for the study.

3.6.4 TRANSCUTOL®

Nonproprietary Names:  
BP: Monoethyl ether of diethylene glycol  
PhEur: Diethylene glycol monoethyl ether  
USP-NF: Diethylene Glycol Monoethyl Ether

Synonyms:  
3.6.4 TRANSCUTOL®
Nonproprietary Names:  
BP: Monoethyl ether of diethylene glycol  
PhEur: Diethylene glycol monoethyl ether  
USP-NF: Diethylene Glycol Monoethyl Ether

Chemical name:  
2-(2-ethoxyethoxy)ethanol

Emperical formula:  
C₈H₁₄O₃

Description: Transcutol® offers as a grade of purity greater than 99.8%. It appears as pale yellowish liquid, which is soluble in both water and oil. It appears as liquid at normal room temperature.

Applications in Pharmaceutical Formulation or Technology: Transcutol® is a high performance solubilizer/solvent for many poorly soluble compounds. It acts as solubilizers, emulsifiers, co-emulsifiers and dispersants for the poorly soluble drug. This grade is suitable for topical, rectal and vaginal formulations. It is also quite versatile, can be formulated in gels, creams and lotions.

Rationale for the selection: Transcutol® can act as solubilizer for many poorly soluble compounds. Its surfactant properties with ability to enhance permeation and thus having effect on bioavailability makes it perfect candidate for the study.
3.7 WORK PLAN

The research work will be divided in three main steps i.e. optimization of the formulation, its in vitro evaluation and stability studies. The year wise division of the work proposed is as follows:

First Year

I. Choice of drug

Drugs that have poor water solubility and related poor bioavailability would be selected on the basis of biopharmaceutical classification system of drugs.

II. Analytical methodology

A suitable analytical method will be designed for the analysis of the drug and the following steps will be undertaken.

i. Absorption spectra of the selected drugs will be taken in various solvents and in media (compendial and biorelevant media) in which in vitro studies will be performed to determine $\lambda_{\text{max}}$.

ii. Calibration curves will be prepared in different solvents at the respective $\lambda_{\text{max}}$ of the drugs.

iii. A study will be carried out to see the interference of the polymers with the analysis of the drug and methods will be devised to eliminate the interference if any.

III. Characterisation of the drugs and carriers

Drug carrier compatibility studies would be performed in order to select appropriate carriers for preparation of solid dispersions.

IV. Formulation of solid dispersions

It is planned that various carriers compatible with the drugs will be used in different ratios for formulation of solid dispersions and will be evaluated on the basis of

- Yield
- Solubility studies
- Comparative dissolution in different buffers
V. Design of appropriate methods for in vitro dissolution testing for oral absorption forecasting:

Appropriate biorelevant dissolution media will be prepared/ designed for performing in vitro release methods.

Second Year

I. Optimization of formulae for solid dispersions:

On the basis of yield, solubility and dissolution characteristics solid dispersions will be selected for optimization. They will be optimized on the basis of

- Fourier transform infrared spectroscopy
- X-ray diffraction analysis
- Differential scanning calorimetry

The formulation which will give satisfactory/promising results would be selected as optimized formulation.

II. Mechanism for establishing improved solubility:

Comparison of results of pure drug powder and physical mixtures of the drug and carrier will help to indicate the mechanism by which the carrier improved dissolution via solubilization and wetting effects which could be affected by a simple mixture of the components, or by formation of a solid dispersion/solution.

III. Interaction studies:

These studies will be performed to ascertain that no interaction has occurred between the drug and polymers or other additives or due to conditions of the formulation process. It will be done on the basis of TLC, DSC, I.R. and UV scans.

IV. Comparison of drug release from conventional/modified products with solid dispersions

Third year

I. Accelerated stability studies

Stability studies will be carried out to determine the effect of the presence of polymers, excipients and also to determine the physical stability of the formulations under accelerated storage conditions of temperature and humidity.
II. Pharmacokinetic studies:

*In vivo* studies in suitable animal model will be conducted and various pharmacokinetic parameters will be calculated.

III. *In vivo-in vitro* correlation:

Based on the results obtained, *in vitro-in vivo correlation* would be established using suitable statistical methods.