2. LITERATURE REVIEW

2.1 Drug Delivery System

2.1.1 Definitions

Immediate release dosage forms are the preparations showing a release of the active ingredient which is not deliberately modified by special formulation and/or manufacturing method. In case of a solid dosage form, the dissolution profile of the active ingredient depends essentially on the intrinsic properties of the active ingredient (EMEA 1999).

Modified release dosage forms are the preparations where the rate and/or place of release of the active ingredient(s) is/are different from that of the conventional dosage form administered by the same route. This deliberate modification is achieved by special formulation design and/or manufacturing method. Modified release dosage forms include prolonged release, extended release (controlled release), sustained release, delayed release, pulsatile release and accelerated release dosage forms (EMEA 1999).

2.1.2 Advantages of Extended Release over Conventional Dosage Form

1. Improved patient convenience and compliance due to less frequent drug administration.
2. Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduce intensity of local or systemic side effects.
3. Increase safety margin of high potency drugs due to better control plasma levels (Harrison and Keam 2007).
5. Reduction in health care cost through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.

2.1.3 Disadvantages of Extended Release over Conventional Dosage Form

1. Decrease systemic availability in comparison to immediate release conventional dosage forms; this may be due to incomplete release, increase
first pass metabolism, increase instability, insufficient residence time or complete release, site specific absorption, pH-dependent solubility, etc.

2. Poor in vitro-in vivo correlation.

3. Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulation by the patient and thus, increase risk of toxicity.

4. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitive reactions.

5. Reduced potential for dosage adjustment of drugs normally administered in varying strengths.


2.1.4 Design of Controlled Drug Delivery Systems

The basic rationale of a controlled drug delivery system is to optimize the biopharmaceutics, pharmacokinetic and pharmacodynamic properties of a drug. It is done in such a way that its utility is maximize through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug administered by the most suitable route. (Brahmankar and Jaiswal 1999; Ritschel WA, 1989; Rouge et al. 1996)

2.1.4.1 Biopharmaceutics Characteristics of the Drug

The performance of a drug presented as a controlled release system depends upon its:

1. Release from the formulation.

2. Movement within the body during its passage to the site of action.

The former depends upon the fabrication of the formulation and the physicochemical properties of drug while the latter element is dependent upon pharmacokinetics of the drug. In comparison to conventional dosage form where the rate-limiting step in drug availability is usually absorption through the biomembrane, the rate-determining step in the availability of a drug from controlled delivery system is the rate of release of drug from the dosage form which is much smaller than the intrinsic absorption rate for the drug.
The desired biopharmaceutical properties of a drug to be used in controlled drug delivery systems are:

- Molecular weight of the drug: Drugs with large molecular size are poor candidate for oral controlled release systems for e.g. peptides and proteins.
- Aqueous solubility of the drug: A drug with good aqueous solubility, especially if Ph-independent, serves as a good candidate for controlled release dosage forms.
- Apparent partition coefficient of the drug: Greater the Apparent partition coefficient of the drug greater is its rate and extent of absorption.
- Drug pKa and Ionization at Physiologic pH: Drugs existing largely in ionized forms are poor candidates for controlled delivery e.g. hexamethonium.
- Drug stability: Drugs unstable in GI environment cannot be administered as oral controlled release formulation because of bioavailability problems e.g. nitroglycerine.
- Mechanism and site of Absorption: Drugs absorbed by carrier-mediated transport processes and those absorbed through a window are poor candidates for controlled release systems e.g. several B vitamins.
- Biopharmaceutics aspects of route of administration: Oral and parenteral (i.m) routes are the most popular followed by transdermal application.
  - Oral route: For a drug to be successful as oral release formulation, it must get absorbed through the entire length of GIT.
  - Intramuscular/Subcutaneous routes: These routes are suitable when the duration of action is to be prolonged from 24 hours to 12 months.
  - Transdermal route: Low dose drugs like nitroglycerine can be administered by this route. The route is best suited for drugs showing extensive first-pass metabolism upon oral administration.

2.1.4.2 Pharmacokinetic Characteristics of the Drug

A. Absorption rate: For a drug to be administered as controlled release formulation, its absorption must be efficient since the desired rate-limiting step is rate of drug release. A drug with slow release will result in a pool of unabsorbed drug e.g. iron.
B. **Elimination half-life**: Smaller the T1/2, larger amount of drug to be incorporated in the controlled release dosage form. Drugs with half-life in the range 2 to 4 hours make good candidates for such a system e.g. propranolol.

C. **Rate of metabolism**: A drug which is extensively metabolized is suitable for controlled release system as long as the rate of metabolism is not too rapid.

D. **Dosage form index**: Since the goal of controlled release formulation is to improve therapy by reducing the dosage form index while maintaining the plasma levels within the therapeutic window, ideally its value should be as close to one as possible.

### 2.1.4.3 Pharmacodynamic Characteristics of a Drug

A. **Therapeutic Range**: A candidate drug for controlled delivery system should have a therapeutic range wide enough such that variations in the release rate do not result in a concentration beyond this level.

B. **Therapeutic Index**: The release rate of a drug with narrow therapeutic index should be such that the plasma concentration attained is within the therapeutically safe and effective range. This is necessary because such drugs have toxic concentration nearer to their therapeutic range.

C. **Plasma Concentration-Response Relationship**: Drugs such as reserpine whose pharmacologic activity is independent of its concentration are poor candidates for controlled release systems.

### 2.1.4.4 Oral Controlled Release Systems

Oral route has been the most popular and successfully used for controlled delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design (possible because of versatility of GI anatomy and physiology) and ease of production and low cost of such a system. Depending upon the manner of drug release, these systems are classified as follows:
2.1.4.5. **Continuous Release Systems**

These systems release the drug for a prolonged period of time along the entire length of GIT (especially up to the terminal region of small intestine) with normal transit of the dosage form (Singh and Kim 2000). The various systems under this category are:

1. Dissolution controlled release systems
2. Diffusion controlled release systems
3. Dissolution and diffusion controlled release systems
4. Ion-exchange resin-drug complexes
5. Slow dissolving salts and complexes
6. Ph-dependent formulations
7. Osmotic pressure controlled systems
8. Hydrodynamic pressure controlled systems (Erni and Held 1987; Sheth and Tossounian 1984)

2.1.4.6. **Delayed Release Systems**

The design of such systems involves release of drug only at a specific site in the GIT. The drugs contained in such a system are those that are:

1. Destroyed in the stomach or by intestinal enzymes
2. Known to cause gastric distress
3. Absorbed from a specific intestinal site, or
4. Meant to exert local effect at a specific GI site.

The two types of delayed release systems are:

1. Intestinal release systems
2. Colonic release systems

2.1.4.7. **Delayed Transit and Continuous Release Systems**

The gastric emptying time (GET) in humans is normally 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine. It can result in incomplete drug release from the drug delivery system leading to reduced efficacy of
the administered dose (Rouge et al. 1996; Rubinstein A, 1994). Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs (Singh et al. 2000). The advantages of gastro retentive drug delivery systems are:

1. Enhanced bioavailability
2. Enhanced first-pass biotransformation
3. Sustained drug delivery/reduced frequency of dosing
4. Targeted therapy for local ailments in the upper GIT
5. Reduced fluctuations of drug concentration
6. Improved selectivity in receptor activation
7. Extended time over critical (effective) concentration
8. Minimized adverse activity at the colon
9. Site specific drug delivery

2.2 Works on Sustained Release Dosage Form

**Basak et al. (2007)** designed sustained release tablet of metformin hydrochloride using a gas-generating agent and gel-forming hydrophilic polymer. The formulation was optimized on the basis of floating ability and in vitro drug release. The in vitro drug release test of these tablets indicated controlled sustained release of metformin hydrochloride and 96-99% released at the end of 8 h.

**Jaimini et al. (2007)** prepared floating tablets of famotidine employing two different grades of methocel K100 (HPMC K100) and methocel K15 (HPMC K15) by an effervescent technique. These grades were evaluated for their gel-forming properties. The tablets with methocel K100 were found to float for a longer duration compared with the formulation containing methocel K15M. Decrease in the citric acid level increased the floating lag time. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

**Badve et al. (2007)** developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. This approach suggested the use of hollow calcium
pectinate micro particles as promising floating pulsatile drug delivery system for site- and time-specific release of drugs for chronotherapy of diseases.

Chavanpatil et al. (2006) developed a new gastro retentive sustained release delivery system of ofloxacin with floating, swellable and bioadhesive properties. Various release retarding polymers such as psyllium husk, HPMC K100M and a swelling agent, crosspovidone, in combinations were tried and optimized to obtain release profile over 24 h. The in vitro drug release followed Higuchi kinetics and the drug release mechanism was found to be non-Fickian.

Rahman et al. (2006) established a bilayer- sustained release for captopril using direct compression technology. HPMC K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and carbopol 934, alone or in combination with the drug. The formulation followed the Higuchi release model and showed no significant change in physical appearance, drug content, floatability or in vitro dissolution pattern after storage at 45 °C/75% RH for three months.

Xiaoqiang et al. (2006) developed a sustained release tablet for phenoporlamine hydrochloride because of its short biological half life. Three floating matrix tablets based on a gas-forming agent were prepared. HPMC K4M and carbopol 971P were used in formulating the hydrogel system. Incorporation of sodium bicarbonate into the matrix resulted in the tablets floating over simulated gastric fluid for more than 6 hours. The dissolution profile of all the tablets showed non-Fickian diffusion in simulated gastric fluid.

A List of marketed modified release oral dosage forms is given in Table 2.1.
### Table 2.1 Proprietary modified release oral dosage forms in the market

<table>
<thead>
<tr>
<th>Drug &amp; form</th>
<th>Manufacturer</th>
<th>Marketed Name</th>
<th>Drug Name</th>
<th>Characteristics</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed release Tablets</td>
<td>Knoll</td>
<td>E-Mycin</td>
<td>Erythromycin tablet</td>
<td>Tablets enteric coated with cellulose acetate phthalate, carnauba wax, and cellulose polymer.</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>Delayed release Tablets</td>
<td>Procter &amp; Gamble</td>
<td>Asacol</td>
<td>Mesalamine tablet</td>
<td>Tablets coated with Eudragit S (methyl acrylic acid copolymer B), a resin that bypasses the stomach and dissolves in the ileum and beyond.</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Delayed release capsules</td>
<td>Astra-Merck</td>
<td>Prilosec</td>
<td>Omeprazole capsules</td>
<td>Enteric coated granules of omeprazole placed in capsules</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td>Extended Release coated particles and Beads</td>
<td>Astra-Merck</td>
<td>Toprol-XL</td>
<td>Metoprolol succinate tablets</td>
<td>Drug pellets coated with cellulose polymers compressed into tablets</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Extended Release coated particles</td>
<td>Astra-Merck</td>
<td>IndocinSR</td>
<td>Indomethacin capsule</td>
<td>Coated pellets for SR formulation includes polyvinyl acetate-crotonic acid copolymer and hydroxypropyl methyl cellulose</td>
<td>Analgesic Anti-inflammatory</td>
</tr>
<tr>
<td>Extended Release coated particles</td>
<td>Smithline Beecham</td>
<td>compazine</td>
<td>prochlorperazine capsule</td>
<td>Coated pellets in capsule formulated to release initial dose promptly with addition drug for prolonged release</td>
<td>Anti-nausea, Anti-vomiting</td>
</tr>
<tr>
<td>Extended Release Inert Matrix</td>
<td>Abbott</td>
<td>Desoxyn</td>
<td>Methamphetamine HCI tablet</td>
<td>Drug impregnated in an inert, porous, plastic matrix, drug leaches out as it passes slowly through the GI tract.</td>
<td>Attention deficit disorder</td>
</tr>
<tr>
<td>Extended Release Inert Matrix</td>
<td>Parke-Davis</td>
<td>Procanbid</td>
<td>procanamide</td>
<td>Extended-release tablets with core tablets of a non-erodible wax matrix coated with cellulose polymers</td>
<td>Ant arrhythmic</td>
</tr>
<tr>
<td>Drug product &amp; form</td>
<td>Manufacturer</td>
<td>Marketed Name</td>
<td>Drug Name</td>
<td>Characteristics</td>
<td>Use</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------</td>
<td>---------------</td>
<td>-------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Extended-Release Hydrophilic/Eroding Matrix</td>
<td>Robins</td>
<td>quinidex</td>
<td>Quinidine sulfate</td>
<td>Extended-release provided by hydrophilic matrix that swells and slowly erodes</td>
<td>Ant arrhythmic</td>
</tr>
<tr>
<td>Extended-Release Hydrophilic/Eroding Matrix</td>
<td>Roxane</td>
<td>Oramorph SR</td>
<td>Morphine sulfate</td>
<td>Sustained-release hydrophilic matrix system, based on polymer hydroxypropyl methylcellulose</td>
<td>Analgesic for severe pain</td>
</tr>
<tr>
<td>Extended-Release Microencapsulated K-Dur</td>
<td>Key</td>
<td>K-Dur</td>
<td>Potassium chloride</td>
<td>Immediately dispersing drug microcapsulated with ethyl cellulose and hydroxypropyl cellulose</td>
<td>Potassium depletion</td>
</tr>
<tr>
<td>Extended-Release osmotic Glucotrol XL</td>
<td>Pfizer</td>
<td>Glipizide tablet</td>
<td></td>
<td>Controlled-release GITOS osmotic system. Ingredients include polyethylene oxide, hydroxypropylcellulose, and cellulose acetate</td>
<td>Anti hyperglycemic</td>
</tr>
<tr>
<td>Extended-Release osmotic Verapamil HCl</td>
<td>Searle</td>
<td>Covera-HS</td>
<td>Verapamil HCl</td>
<td>A COER osmotic system</td>
<td>Antihypertensive, Antianginal</td>
</tr>
<tr>
<td>Extended release Tramadol HCL tablet</td>
<td>Biovail</td>
<td>ultramer®ER</td>
<td>Tramadol HCL tablet</td>
<td>Controlled-release tablet with ethyl cellulose polymer</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Extended release film coat Flurbiprofen tablet</td>
<td>Mylan</td>
<td>Ansaid</td>
<td>Flurbiprofen tablet</td>
<td>Tablets film coated, Enteric coated with, carnauba wax, and microcrystalline cellulose polymer.</td>
<td>Analgesic Anti inflammatory</td>
</tr>
<tr>
<td>Extended release film coat Nabumetone tablet</td>
<td>Merck</td>
<td>Relafen</td>
<td>Nabumetone tablet</td>
<td>Tablet film coated with microcrystalline cellulose polymer.</td>
<td>Analgesic</td>
</tr>
</tbody>
</table>
### Chapter 2

#### Literature Review

<table>
<thead>
<tr>
<th>Drug &amp; Form</th>
<th>Manufacturer</th>
<th>Marketed Name</th>
<th>Drug Name</th>
<th>Characteristics</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended release(sodas)</td>
<td>GlaxoSmithKline</td>
<td>Innopran XL</td>
<td>Propranolol HCL</td>
<td>Microencapsulation (beads) (Sodas) speroidal oral drug absorption system</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Extended Release</td>
<td>Merck</td>
<td>Dolobid</td>
<td>Diflunisal tablet</td>
<td>Tablet hydrophilic matrix system, based on polymer hydroxypropyl methylcellulose</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Hydrophilic/Eroding Matrix</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended Release coated</td>
<td>Noven</td>
<td>Ritalin LA</td>
<td>Methylphenidate hydrochloride capsule</td>
<td>Extended-Release Microencapsulation (beads)</td>
<td>CNS stimulant</td>
</tr>
<tr>
<td>particle beads</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended-Release film coat</td>
<td>AstraZeneca</td>
<td>Seroquel XR</td>
<td>Quetiapine fumarate</td>
<td>Tablets film coated with microcrystalline cellulose polymer</td>
<td>Psychotropic agent</td>
</tr>
</tbody>
</table>
2.3 Rationale of the Study

Cefpodoxime proxetil is available as an immediate release (IR) formulation in tablet and is administered to patients two times a day.

Patients receiving Cefpodoxime proxetil or other drugs which are administered twice or thrice daily would likely to benefit from once daily dosing. The convenience of OD dosing generally:

2.3.1 Improves Patient Compliance

To maintain antimicrobial activity, frequent administration of conventional formulations of many antibiotics with short half-life is necessary. Otherwise, concentration under MIC occurs frequently in the course of anti-infective treatment, which induces antibiotic resistance (Liu et al. 2002). By maintaining a constant plasma drug concentration over MIC for a prolonged period, extended-release dosage forms maximize the therapeutic effect of antibiotics while minimizing antibiotic resistance. Another undoubted advantage of extended-release formulation is improved patient compliance (Gao et al. 2011). Compliance improves dramatically as prescribed dose frequency decreases (Pullar et al. 1988; Eisen et al. 1990; Brun J, 1994; Claxton et al. 2001).

Extended (modified)-release formulation of ciprofloxacin provides higher maximum plasma concentrations with lower inter-patient variability than the conventional, immediate-release, twice-daily formulation. Additionally, therapeutic drug levels with extended-release ciprofloxacin are achieved rapidly and maintained over the course of 24 h, allowing once-daily dosing. These studies have also confirmed good tolerability and safety of extended-release ciprofloxacin, similar to the immediate-release formulation. Therefore, extended-release ciprofloxacin is a convenient, well-tolerated and effective therapy for UTIs that may improve patients’ compliance with treatment and thus decrease the risk of treatment failure and the spread of antibiotic resistance (Talan et al. 2004).

Kadian™/Kapanol™ (K), extended release capsule formulation of morphine designed for 12- or 24-hourly dosing. In a double-blind study comparing the efficacy and safety of morphine capsule every 24 hr to morphine every 12 hr and MS Contin® tablets
(MSC) every 12 hr, it was found that there were no statistically significant differences among the treatments for any morphine-related side effects when adjusted for baseline. K had efficacy and safety profiles similar to MSC every 12 hr but had the advantage of 12- or 24-hourly administration that ultimately leads to increased patient compliance (Broomhead et al. 1997).

In case of Cefpodoxime proxetil decreasing the dose frequency leads to increase in patient compliance; patients prefer to take the drug once daily. It also improves the rate of bacterial killing and hastens the cure from the indications, and therefore increases compliance (Merchant et al. 2006).

Especially for elderly patients and for patients taking multiple medications poor compliance is a recognized factor related to the inadequate control. Numerous studies have demonstrated that poor medication compliance poses a significant impediment to the effective treatment of a wide variety of illnesses.

2.3.2 Reduction in Fluctuation in Steady State Levels

The sustained release formulations draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Under ideal conditions, a sustained-release formulation maintains therapeutic blood level of a drug for a specific period of time. Oral controlled-release dosage forms have been developed and studied to restrict these systems to specific regions of the gastrointestinal tract as well as to improve the pharmacological activity and to reduce toxic effects (Bravo et al. 2002; Talan et al. 2004; Hilton and Deasy 1992; Timmins et al. 2005).

Extended-release formulations maintained a constant plasma drug concentration over MIC and maximize the therapeutic effect of antibiotics while minimizing antibiotic resistance (Gao et al. 2011).

Side effects for sustained release formulations are often more favorable because controlled-release formulations exhibit lower peak plasma drug concentrations when compared with immediate-release formulations. Venlafaxine extended-release (XR), bupropion sustained-release (SR), and paroxetine controlled-release (CR) are 3 commonly utilized controlled-release antidepressants that have demonstrated
improvement over their immediate-release predecessors in reducing certain adverse
effects (Charles and Nemeroff 2003; Dupon et al. 1996).

Sustained release (SR) mode of drug administration has certain features that have an
important impact on the magnitude of the pharmacologic response: (a) it minimizes
fluctuation in blood drug concentrations (i.e. between peak and trough). However, due
to the pronounced non-linear relationship between drug concentration and
pharmacologic effect (i.e. pharmacodynamics) the impact of this property differs
considerably as a function of the shape of the pharmacodynamic profile and the
position of the specific range of concentrations on the curve of this profile; (b) it
produces a slow input rate which tends to minimize the body's counteraction to the
drug’s intervening effect on regulated physiological processes; and (c) it provides a
continuous mode of drug administration. For many drugs with non-concentration-
dependent pharmacodynamics, the exposure time, rather than the AUC, is the relevant
parameter and it can therefore be optimized by SR preparations (Hoffman et al. 1998;
CPMP 1999).

In a study comparing sustained-release tablets with ordinary tablets of procaineamide
ten patients with acute myocardial infarction were recruited. During treatment it was
found that the average fluctuation of plasma concentrations was 3.5±0.1 µg/ml with
sustained-release tablets (dosage interval 8 h) and 4.2±0.4 µg/ml with ordinary tablets
(dosage interval 4 h), i.e. it was 20% greater during treatment with the conventional
preparation. There was no difference between the two preparations in recovery of the
drug from urine (sustained-release tablets 85.4±3.0%; and conventional tablets
90.3±5.4%). Thus, the new sustained-release preparation of procaineamide
administered 3 times daily produced the same range of plasma levels as the identical
dose of conventional tablets given 6 times a day (Karlsson E, 1973).

2.3.3 Other Advantages of Sustained Release Dosage Form

Following oral administration of 100 mg of Cefpodoxime proxetil to fasting subjects,
approximately 50% of the administered Cefpodoxime dose was absorbed
systemically. (Vantin 2012) Over the recommended dosing range (100 to 400 mg),
approximately 29 to 33% of the administered Cefpodoxime dose was excreted
unchanged in the urine in 12 hours. Over the recommended dosing range (100 to 400
mg), the rate and extent of Cefpodoxime absorption exhibited dose-dependency; dose-normalized Cmax and AUC decreased by up to 32% with increasing dose. Over the recommended dosing range, the Tmax was approximately 2 to 3 hours and the T1/2 ranged from 2.09 to 2.84 hours, there is minimal metabolism of Cefpodoxime in vivo. (Vantin 2012) These pharmacokinetic characteristics of Cefpodoxime are conducive to the slow and sustained release formulation of Cefpodoxime. Sustained release formulation causes slow release with absorption over the length of intestine as most sustained release formulation systems functions by delivering the drug for absorption over an extended period and along the length of gastro intestinal tract following administration.

By preparing sustained release formulation we can extend the bacterial killing time by increasing the time above MIC (T>MIC). For amoxicillin and amoxicillin / clamulanate, a time above MIC (T > MIC) of 35–40% of the dosing interval (based on blood levels) is predictive of high bacteriological efficacy. This target was met by Jacobs MR 2004. They designed a unique bilayer tablet incorporating 437.5 mg of sustained-release sodium amoxicillin in one layer plus 562.5 mg of immediate-release amoxicillin trihydrate and 62.5 mg of clavulanate potassium in the second layer, with two tablets administered for each dose. This unique design extends the bacterial killing time by increasing the T > MIC to 49% of the dosing interval against pathogens with MICs of 4 mg / L, and 60% of the dosing interval against pathogens with MICs of 2 mg/L. Based on these results, this new amoxicillin/clamulanate formulation was found to be highly effective in treating respiratory tract infections due to drug-resistant S. pneumoniae as well as β-lactamase-producing pathogens, such as Haemophilusinfluenzae and Moraxella catarrhalis.

Number of days for the treatment can be reduced by using sustained release formulation in comparison to conventional immediate release formulation as shown by Takker et al. 2003. They recruited A total of 539 patients, aged 12–75 years, were randomized to receive either clarithromycin extended-release (ER) 500 mg once daily for 5 days or penicillin V 500 mg three times daily for 10 days in this multicenter, double-blind, parallel-group trial. Bacterial eradication was sustained in both treatment groups at the follow-up visit (88% (135/153) vs 91% (112/123) respectively; 95% CI for difference (−10.0, 4.4)). Clinical cure was achieved in ≥ 94%
of patients in each treatment group. So it is confirmed that clarithromycin ER 500 mg once daily for 5 days is equally effective as penicillin V 500 mg three times daily for 10 days in the treatment of with streptococcal tonsillopharyngitis.

Sustained release formulations can enhance the bioavailability of the drugs which have poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract (Timmermans and Moes 1994; Moursy et al. 2003; Oth et al. 1992). Menon et al, 1994 developed the monolithic sustained release (SR) dosage form of furosemide with prolonged gastric residence time and the bioavailability was increased. AUC obtained with the SR tablets was approximately 1.8 times those of conventional furosemide tablets. Similarly, Ichikawa et al, 1991 developed a multiparticulate system that consisted of floating pills of a drug (p- amino benzoic acid) having a limited absorption site in the gastrointestinal tract. It was found to have 1.61 times greater AUC than the control pills.

Sustained drug delivery system is also beneficial for the site specific drug action. In case of amoxicillin conventional immediate release formulation which has short residence time in stomach and amoxicillin being degraded by gastric acid resulting in lesser concentration requiring frequent dosing for treatment of Helicobacter pylori in stomach (Pandit et al.2010). This delivery system enabled the release of the drug in stomach for longer period with sustained high levels in gastric blood required for Helicobacter pylori eradication. Similarly Yang et al. 1999 has shown sustained formulation of triple drug regimen (Tetracycline, Metronidazole, Clarithromycin) for Helicobacter pylori associated peptic ulcers has caused sustained delivery of tetracycline and metronidazole over 6-8 hours and concluded that this system has the potential to increase the efficacy of therapy and patient compliance.

2.4 Bioavailability Studies

21 CFR 320.1 defines bioavailability as “the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action”.

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Chapter 2  
Literature Review  
Dept. of Pharmaceutical Medicine  20  Jamia Hamdard
A new product is said to be suprabioavailable when it displays larger bioavailability than the approved comparative product. For these suprabioavailable products, a lower dosage strength should be reformulated to assure therapeutic equivalence. Finally, a comparative bioavailability study of the reformulated new product with the old approved product is required for submission.

In bioavailability studies, the primary question is to compare measures of release of drug substance between the test and reference product. Hence, bioavailability is primarily a product quality question. Because product BA and BE are closely related, similar approaches for establishing BA and BE may be followed. Some of the approaches are as follows (Chow and Liu 2000).

Law often becomes a necessary control mechanism when people could be exploited and there are large potential financial gains for businesses choosing to exploit. The society, by law, has removed much of the decisions making about new drug products from the manufacturers, investigators, and physicians and vested it in the government (The Drug Regulatory Agencies). The regulations require the Regulatory Agencies to assess safety, efficacy and quality of all new drug formulations, before they are marketed. The fundamental mission of the Drug Regulatory Agencies is protection of the consumers.

2.4.1 BA/BE for First Entry Products

BA/BE studies may be useful during drug development and registration for a first entry product during the Investigational New Drug (IND) or New Drug Application (NDA) period to establish links between (i) early and late clinical trial formulations (ii) formulations used in clinical trial and stability studies, if different (iii) Clinical trial formulations and to be marketed drug products (iv) other comparisons as appropriate. In each comparison, the new formulation or new method of manufacture is the test product and the prior formulation or method of manufacture is the reference product.

2.4.2. BA/BE for Interchangeable Multi-Source Products

BE studies are a critical component of abbreviated new drug applications. The purpose of these studies is to compare relative BA measures between a
pharmaceutically equivalent multi-source test product and the corresponding reference pioneer product (ANDA 2010). The pioneer product is termed as reference listed drug (RLD). Together with the determination of pharmaceutical equivalence, demonstrating BE allows a regulatory conclusion of therapeutic equivalence and interchangeability between the test and reference product (CDER 1999).

2.4.3. BA/BE for Post Approval Changes

Generally specifications are adequate to assure product quality on the assumption that no important change occurs post-approval. In the presence of major changes in components and composition, and/or method of manufacture of a drug product after approval, BE may need to be re-demonstrated. For approved first-entry products, the drug product after the change should be compared to the drug product before change. For approved interchangeable multi-source products, the drug product after the change should be compared to the reference listed drug.

2.5 Types of Bioavailability

Bioavailability can be classified into four different types (Ritschel and Kearns 1998), depending on the purpose of the study and scientific questions to be solved.

2.5.1 Absolute Bioavailability

Absolute bioavailability is the ratio of the total area under the blood level - time curve upon extra vascular route of administration to the area under the blood level - time curve upon intravenous administration, corrected for the difference in the dose size.

$$\text{Absolute bioavailability} = \frac{\text{AUC}_{\text{extravascular}} \times \text{dose}_{\text{i.v.}}}{\text{AUC}_{\text{i.v.}} \times \text{dose}_{\text{extravascular}}}$$

2.5.2 Relative Bioavailability

The relative bioavailability is the extent (EBA) and rate (RBA) of the bioavailability of a drug from two or more different dosage forms given by the same route of administration. For determination of EBA or RBA blood level or urinary excretion data upon single or multiple dosing can be used. According to the FDA regulation the standard used in this procedure is an approved marketed drug product, a solution of the drug or suspension of the micronized drug.
Relative bioavailability = \( \frac{\text{AUC of } A}{\text{AUC of } B} \)

Where B is the reference standard

2.5.3 Bioavailability in Presence of First-Pass Effect

Drugs showing a first-pass effect may result in considerably lower blood level time curves. Even though the entire parent drug was absorbed from the site of administration, it did not reach systemic circulation in unchanged form.

The fraction of a per oral (po) or in part, rectal dose reaching systemic circulation F, under the assumption of linear kinetics can be described by following equation

\[ F = 1 - \text{Dose}_{iv} \times f_{m} / \text{LBF} \times \text{AUC}_{iv} \times 60 \times \lambda \]

\( f_{m} \) - fraction of drug metabolised in liver

\( \text{LBF} \) - liver blood flow

\( \lambda \) - ratio of the concentration of the drug in whole blood to that in plasma

2.5.4. Relative Optimal Bioavailability

This term was suggested for optimizing extent and rate of bioavailability for a drug product during the development phase. For determination of \( \text{EBA}_{\text{rel. opt.}} \), the active drug is administered in aqueous solution without the addition of any further excipient by the same route which is intended for the drug product under development.

\[ \text{EBA}_{\text{rel. opt.}} = \frac{\text{AUC}_{(\text{drug + vehicle; granules; tablets})}}{\text{AUC}_{\text{solution}}} \times 100 \]

2.6 Bioavailability Measurement

There are several direct and indirect methods for the measurement of bioavailability in humans. The selection of method depends on the purpose of the study, analytical method and nature of the drug product. The methods useful in quantitative evaluation of bioavailability can be broadly divided into two categories: (a) Pharmacokinetic methods (b) Pharmacodynamic methods.
2.6.1 Pharmacokinetic Methods

These are very widely used and are based on the assumption that the pharmacokinetic profile reflects the therapeutic effectiveness of a drug. Thus, these are indirect methods. The two major pharmacokinetic methods are:

2.6.1.1 Plasma level-Time Studies

Unless determination of plasma drug concentration is difficult or impossible, it is the most reliable method and method of choice in comparison to urine data. This method is based on the assumption that two dosage forms that exhibit super imposable plasma level-time profiles in a group of subjects should result in identical therapeutic activity. The three parameters of plasma level-time studies, which are considered important for determining bioavailability, are:

1. $C_{\text{max}}$: The peak plasma concentration that gives an indication whether the drug is sufficiently absorbed systemically to provide a therapeutic response.

2. $T_{\text{max}}$: The time of peak plasma concentration corresponds to the time required to reach maximum drug concentration after drug administration. At $T_{\text{max}}$, absorption is maximized and the rate of drug absorption equals the rate of drug elimination. When comparing drug products, $T_{\text{max}}$ can be used as an approximate indication of the drug absorption rate.

3. AUC: The area under the plasma level-time curve that gives a measure of the extent of absorption or the amount of drug that reaches the systemic circulation.

The extent of bioavailability can be determined by equation:

$$F = \frac{\text{AUC}_{\text{oral}}D_{\text{iv}}}{\text{AUC}_{\text{iv}}D_{\text{oral}}}$$

2.6.1.2 Urinary Excretion Studies

This method of assessing bioavailability is based on the principle that the urinary excretion of unchanged drug is directly proportional to the plasma concentration of drug. This method is particularly useful for drugs extensively excreted unchanged in the urine. The method involves collection of urine at regular intervals for a time span
equal to 7-10 biological half-lives, analysis of unchanged drug in the collected sample and determination of the amount of drug excreted in each interval and cumulative amount excreted. The three major parameters examined in urinary excretion data obtained with a single dose study are:

1. \((dx_u/dt)_{\text{max}}\): The maximum urinary excretion rate, is obtained from the peak of plot between rate of excretion versus midpoint time of urine collection period. It is analogous to \(C_{\text{max}}\) derived from plasma level studies since the rate of appearance of drug in the urine is proportional to its concentration in systemic circulation.

2. \((t_u)_{\text{max}}\): The time for maximum excretion rate, is analogous to the \(T_{\text{max}}\) of plasma level data. Its value decreases as the absorption rate increases.

3. \(X_u\): The cumulative amount of drug excreted in the urine, is related to the AUC of plasma level data and increases as the extent of absorption increases.

The extent of bioavailability can be calculated using equation:

\[
F = \frac{(X_u)_{\text{oral}}D_{\text{iv}}}{(X_u)_{\text{iv}}D_{\text{oral}}}
\]

2.6.2 Pharmacodynamic Methods

These methods are complimentary to pharmacokinetic approaches and involve direct measurement of drug effect on a physiologic process as a function of time. The two pharmacodynamic methods involve determination of bioavailability from: (a) Acute pharmacologic response (b) Therapeutic response.

2.6.2.1 Acute Pharmacologic Response

In some cases quantitative measurement of a drug is difficult, inaccurate or non reproducible. In such cases an acute pharmacologic effect such as effect on pupil diameter, heart rate or blood pressure can be a useful index of drug bioavailability. Bioavailability can be determined by construction of pharmacologic effect-time curve as well as dose-response graphs. The method requires measurement of responses for at least 3 biological half-lives of drug in order to obtain a good estimate of AUC.
2.6.2.2 Therapeutic Response

Theoretically the most definite, this method is based on observing the clinical response to a drug formulation given to patients suffering from disease for which it is intended to be used. Bioequivalent drug products should have the same systemic drug bioavailability and therefore the same predictable drug response. However, variable clinical responses among individuals that are unrelated to bioavailability might be due to differences in the pharmacodynamics of the drug. Various factors affecting pharmacodynamics drug behavior may include age, drug tolerance, drug interactions and unknown pathophysiologic factors.

2.6.3 In Vitro Methods

Under certain circumstances, product quality BA and BE can be documented using in vitro approaches. For highly soluble, highly permeable, rapidly dissolving, orally administered drug products, documentation of BE using an in vitro approach (dissolution studies) is appropriate based on the biopharmaceutics classification system (BCS) (CDER, 2000). The preferred dissolution apparatus is USP apparatus I (basket) or II (paddle), used at compendially recognized rotation speeds (e.g., 100 rpm for the basket and 50-75 rpm for the paddle). In other cases, the dissolution properties of some ER formulations may be determined with USP apparatus III (reciprocating cylinder) or IV (flow through cell).

2.7 Factors Affecting Bioavailability

The various factors affecting bioavailability of drugs can be classified as shown in Table 2.2.

2.7.1 Physicochemical Properties of Drug Substances

2.7.1.1 Drug Solubility and Dissolution Rate

Dissolution is the rate-determining step (RDS) for hydrophobic, poorly aqueous soluble drugs like griseofulvin and spironolactone; absorption of such drugs is said to be dissolution rate-limited. If the drug is hydrophilic with high aqueous solubility e.g. cromolyn sodium or neomycin, then dissolution is rapid and the RDS in the absorption of such drugs is rate of permeation through the biomembrane. Adsorption
Chapter 2

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of such drugs is said to be permeation rate limited or transmembrane rate limited. Fig. 2.1 shows a schematic representation of this concept.

Table 2.2 Factors affecting absorption of a drug from its dosage form

(Shargel L, 1999).

<table>
<thead>
<tr>
<th>Factors affecting bioavailability of drugs</th>
<th>PHARMACEUTICAL FACTORS</th>
<th>PATIENT RELATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicochemical properties of drug substances</td>
<td>Dosage form related factors</td>
<td></td>
</tr>
<tr>
<td>Drug solubility and dissolution rate</td>
<td>Disintegration time</td>
<td>Age</td>
</tr>
<tr>
<td>Particle size and effective surface area</td>
<td>Dissolution time</td>
<td>Gastric emptying time</td>
</tr>
<tr>
<td>Polymorphism and amorphism</td>
<td>Manufacturing variables</td>
<td>Intestinal transit time</td>
</tr>
<tr>
<td>Hydrates / solvates</td>
<td>Pharmaceutical ingredients</td>
<td>GIT pH</td>
</tr>
<tr>
<td>Salt form of the drug</td>
<td>Nature and type of dosage form</td>
<td>Disease states</td>
</tr>
<tr>
<td>Lipophilicity of the drug</td>
<td>Product age and storage conditions</td>
<td>Blood flow through GIT</td>
</tr>
<tr>
<td>pKa of the drug and pH</td>
<td></td>
<td>Gastrointestinal contents: Other drugs, Food, Fluids, Other normal GI contents</td>
</tr>
<tr>
<td>Drug stability</td>
<td></td>
<td>Presystemic metabolism by: Luminal enzymes, Gut wall enzymes, Bacterial enzymes, Hepatic enzymes</td>
</tr>
</tbody>
</table>
2.7.1.2 Particle Size and Effective Surface Area

Particle size and surface area of a solid drug are inversely related to each other. Particle size is of importance for drugs of low solubility. The critical point seems to be if the solubility is less than 0.3 percent. With decreasing particle size, the surface area increases, thus increasing the area of solid matter being exposed to the dissolution media and, hence, dissolution rate increases. However, the actual solubility does not significantly change with particle size reduction (micronization) in the range used in pharmaceutical manufacture. The following equation describes the dissolution rate:

\[ \frac{dc}{dt} = k \cdot a \cdot (C_s - C_t) \]

- \( dc/dt \) = dissolution rate (amount per unit time) (Noyes Whitney equation)
- \( a \) = surface area of undissolved solute
- \( C_s \) = solubility of drug in solvent
- \( C_t \) = concentration of dissolved drug at time \( t \)
- \( k \) = constant depending on intensity of agitation, temperature, structure of solid surface and diffusion coefficient

Examples of drugs for which therapeutic differences have been found depending on particle size are: amphotericin, aspirin, bishydroxycoumarin, chloramphenicol, digoxin, acetonide, griseofulvin, meprobamate, nitrofurantoin, phenobarbital, phenothiazine, prednisolone, procaine penicillin, reserpine, spironolactone, sulfadiazine and tolbutamide (Ritschel and Kearns 1998).
2.7.1.3 Polymorphism and Amorphism

Polymorphism is the phenomenon that a drug may exist in different crystalline forms, polymorphs. Polymorphism exists only in solid state. The most stable form has highest stability but lowest dissolution rate. The least stable form usually has the most rapid dissolution rate. The unstable (metastable) forms convert more or less slowly into the more stable form, e.g. chloramphenicol palmitate appears in three different polymorphs, but only polymorph B is biologically active, since the other forms do not dissolve and are not hydrolyzed. The polymorphs differ from each other with respect to their physical properties such as solubility, melting point, density, hardness and compression characteristics.

Some drugs can exist in amorphous form (i.e. having no internal crystal structure). In general, the amorphous state is more soluble and has a higher dissolution rate than the crystalline form. The crystalline form requires a higher amount of energy to free a molecule of drug from it than does the amorphous form, e.g. amorphous novobiocin and amorphous chloramphenicol esters are biologically active while their crystalline forms are inactive.

2.7.1.4 Salt Form of a Drug

Most drugs are either weak acids or weak bases. One of the easiest approaches to enhance the solubility and dissolution rate of such drugs is to convert them into their salt forms. At a given pH, the solubility of a drug, whether acidic/basic or its salt form, is a constant.

2.7.1.5 Drug pKa, lipophilicity and GI pH (pH Partition hypothesis)

The pH Partition theory explains in simple terms, the process of drug absorption from the GIT and its distribution across all biologic membranes. The theory states that for a drug compound of molecular weight greater than 100, which are primarily transported across the biomembrane by passive diffusion, the process of absorption is governed by:

1. The dissociation constant (pKa) of the drug.
2. The lipid solubility of the unionised drug (a function of drug K_{o/w}).
3. The pH at the absorption site.

### 2.7.1.6 Lipophilicity and Drug Absorption

The pKa of a drug determines the degree of ionisation at a particular pH and that only the unionised drug, if sufficiently lipid soluble, is absorbed into the systemic circulation. Thus, even if the drug exists in the unionised form, it will be poorly absorbed if it has poor lipid solubility. Ideally, for optimum absorption, a drug should have sufficient aqueous solubility to dissolve in the fluids at the absorption site and lipid solubility ($K_{o/w}$) high enough to facilitate the partitioning of the drug in the lipoidal membrane and into the systemic circulation. Hence, a perfect hydrophilic-lipophilic balance (HLB) should be there in the structure of the drug for optimum bioavailability.

### 2.7.2 Patient Related Factors

#### 2.7.2.1 Age

In infants, the gastric pH is high and intestinal surface and blood flow to the GIT is low resulting in decreased absorption in comparison to adults. In elderly persons, causes of impaired drug absorption include altered gastric emptying, decreased intestinal surface area and GI blood flow.

#### 2.7.2.2 Gastric Emptying

Apart from dissolution of a drug and its permeation through the biomembrane, the passage from stomach to the small intestine, called as gastric emptying can also be rate limiting step in drug absorption because the major site of drug absorption is intestine. Thus generally speaking, rapid gastric emptying increases bioavailability of a drug.

Rapid gastric emptying is desired where:

1. A rapid onset of action is desired e.g. sedatives
2. Dissolution of drug occurs in the intestine e.g. enteric coated dosage forms
3. The drugs are not stable in the gastric fluids e.g. penicillin G, and erythromycin

4. The drugs is best absorbed from the distal part of the small intestine e.g. vitamin B$_{12}$

### 2.7.2.3 Intestinal Transit

Since small intestine is the major site for absorption of most drugs, long intestinal transit time is desirable for complete drug absorption. The residence time depends upon the intestinal motility or contractions. The mixing movement of the intestine that occurs due to peristaltic contractions promotes drug absorption, firstly, by increasing the drug-intestinal membrane contact, and secondly, by enhancing the drug dissolution especially of poorly soluble drugs, through induced agitation.

### 2.7.2.4 Blood Flow to the GIT

GIT is extensively supplied by blood capillary network and the lymphatic system. The absorbed drug can thus be taken by the blood or the lymph. Since the blood flow rate to the GIT (splanchnic circulation) is 500 to 1000 times (28% of cardiac output) more than the lymph flow, most drugs reach the systemic circulation via blood whereas only a few drugs, especially low molecular weight, and lipid soluble compounds are removed by lymphatic system. The high perfusion rate of GIT ensures that once the drug has crossed the membrane, it is rapidly removed from the absorption site thus maintaining the sink conditions and concentration gradient for continued drug absorption (Bechgaard and Ladefoged 1978).

### 2.8 Population and Individual Bioequivalence

The bioequivalence study in current use, so called average bioequivalence approach, judges bioequivalence between the test formulation and reference formulation by verifying that the confidence interval for the ratio of average bioavailability values of the two formulations is in a given acceptance range. However, the average bioequivalence approach has been indicated to be insufficient to warrant bioequivalence of the test formulation and the reference formulation, since it compares the average bioavailability values of the test and the reference formulations.
and does not consider differences in variance of test and reference formulation (Nakai et al. 2002). Due to these concerns raised over the years, on the use of average bioequivalence for evaluation of comparability between formulations, scientists from academia, industry and regulatory agencies, propose the use of concepts of individual and population bioequivalence (Chen et al. 2000). The FDA also has proposed replacing the 1992 average bioequivalence (ABE) approach with population and individual bioequivalence (CDER, 1997).

### 2.8.1 Individual Bioequivalence (IBE)

In the IBE criterion, replicate designs are required, in which at least the R, and commonly both R and T drug products, are each administered on two separate occasions. The individual criteria may be utilized for equivalence questions when some change occurs in a stable dosage form. Examples include substitution of a generic for a pioneer product and, for both a pioneer and interchangeable equivalent, when re-documentation of BE is needed in the presence of specified post-approval changes in component/composition and/or method of manufacture (Banahan and Kolassa 1997; Meredith P, 2003). A regulatory objective is to encourage bioequivalent formulations over an extended period of time that clearly relate, in terms of performance, to the pivotal clinical trial material on which safety and efficacy were based. The proposed new criteria include variance as well as mean terms (Williams R, 1997; Williams et al, 2000). The variance term for population BE is total variance, which is the sum of between and within-subject variances. For individual BE, a subject-by-formulation interaction variance, and within-subject variance for both T and R products are estimated. Both PBE and IBE criteria allow scaling of the BE limit (goal post) by R product variability (Williams et al. 2000).

A key concept underlying IBE criterion relates to the term switchability, which denotes the situation where a patient currently on one formulation switches to another with the expectation that the safety and efficacy of the drug will remain essentially unchanged (Covington TR, 1992). The criterion uses, in the aggregate, a distance concept that compares means and variances of T and R products. By expanding the variance terms, the proposed criterion offers many consumer and producer advantages, including: (i) assurance of switchability; (ii) rewards for reduction of
variance in the T product; (iii) scaling for highly variable and/or narrow therapeutic range drugs.

The IBE criterion encourages BE studies in subjects more representative of the general population or even in patients for whom the drug is intended, as opposed to healthy young males where detection of interaction is less likely. This feature addresses a frequently expressed concern that BE studies in healthy young males lack clinical relevance (Levy G, 1996). The re-test characteristics of replicate study design allow scrutiny of outliers.

IBE can be calculated as:

\[
\sigma_D^2 = [(\sigma_{BT}^2 - \sigma_{BR}^2)^2 + 2(1-\sigma)\sigma_{BT}\sigma_{BR}]
\]

\[
\theta_1 = \left[\left(\mu_T - \mu_R\right)^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2 \right]/\sigma_{WR}^2 \text{ when } \sigma_{WR} > 0.2
\]

\[
\theta_1 = \left[\left(\mu_T - \mu_R\right)^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2 \right]/0.2^2 \text{ when } \sigma_{WR} \leq 0.2
\]

Where,

- \(\mu_T\) = mean (test)
- \(\mu_R\) = mean (reference)
- \(\sigma_{WT}^2\) = within subject variance (test)
- \(\sigma_{WR}^2\) = within subject variance (reference)
- \(\sigma_{BT}^2\) = between subject variance (test)
- \(\sigma_{BR}^2\) = between subject variance (reference)

Again, \(\sigma_{WR}^2\) is set to 0.20 (that is, constant scaled versus reference standard) in the denominator of the formula \(\theta_1\) when the point estimate of the parameter based on the original data set falls below 0.20 (CDER, 1997).

Individual BE is demonstrated when; \(\theta_1(0.95) < 2.45\), where \(\theta_p(0.95)\) is defined as the 95th quartile of \(\theta_1\) based on the non-parametric percentile method using 2000 bootstrap samples. The bootstrap is used, as the exact distribution for the parameter \(\theta_p\) has not yet been derived.

### 2.8.2 Population Bioequivalence (PBE)

Population bioequivalence approach, which evaluates the total bioavailability variances in the in addition to the average bioavailability values, has been proposed as
a method to overcome the disadvantages of average bioequivalence approach (Hauschke and Steinijans 2000). FDA has also proposed the use of population bioequivalence as a bioequivalence study which might guarantee prescribability and which is applicable in the development stages of novel drugs (CDER, 1997). Based on earlier published reports of bioequivalence in literature, it was concluded that population bioequivalence value was affected more extensively by the bioavailability variance rather than by the average bioavailability (Nakai et al. 2002). PBE criteria aggregate the difference between the population means and variances. Both IBE and PBE criteria allow for scaling of the regulatory limits based on the variability of the reference product. Both require the use of bootstrapping methodology to derive empirical distributions of the criteria, as the exact statistical distribution has not yet been established.

2.9 Bioavailability/Bioequivalence Study: Design and Evaluation

The preferred approach is an in vivo study carried out in healthy volunteers to whom the 2 preparations (generic and innovator) are alternatively administered. The design and evaluation of well-controlled bioequivalence studies require the cooperative input from pharmacokineticists, statisticians, clinicians, bio-analytical chemists, and others.

2.9.1 Design

The design of a bioavailability and/or bioequivalence study is dependent upon the drug, dosage form and study objectives. For BE studies, both the test and reference drug formulations contain the pharmaceutical equivalent drug in the same dose and are given by the same route of administration. A pilot study in small number of subjects can be carried out before proceeding with a full BE study. This study can be used to validate analytical methodology, assess variability, optimize sample collection time intervals or provide any other information. Non replicate crossover study designs are recommended by FDA (CDER, 2003) for immediate release and modified release dosage forms. However, replicate designs can also be used. The recommended method for analysis to establish BE is average bioequivalence. The study should be of crossover design and suitably randomized, as far as possible. Some of the designs are being discussed below.
2.9.2 Two-Period Crossover Design

In case of two formulations, an even number of subjects should be randomly divided into two equal groups. In the first period, each member of one group will receive a single dose of the test formulation and each member of the other group will receive standard formulation. After a suitable washout period (not less than 5 half lives). In the second period, each member of the respective groups will receive a dose of an alternative formulation and the experiment will be repeated. The design can be depicted as follows:

<table>
<thead>
<tr>
<th>Volunteers</th>
<th>Period 1</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>

2.9.3 Latin Square Design

In case of more than two formulations, a Latin square design should be used. For example in a bioequivalence study of 3 formulations, a group of volunteers will receive formulations in the sequence shown below:

<table>
<thead>
<tr>
<th>Volunteers</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>A</td>
<td>B</td>
</tr>
</tbody>
</table>

The next group of 3 volunteers will receive formulations in the same sequence as shown above.

2.9.4 Balance Incomplete Block Design (BIBD)

In case there are more than 3 formulations, the Latin square design will not be ethically advisable, mainly because each volunteer may require the drawing of too
many blood samples. However, if each volunteer is expected to receive at least two formulations, then such a study can be carried out using Balanced Incomplete Block Design. As per this design, if there are four formulations, six possible pairs of formulations can be chosen from four formulations. Then, the first 6 volunteers will receive these six pairs of formulations and the next six volunteers will receive the same six pairs in reverse order. The design is depicted below:

<table>
<thead>
<tr>
<th>Volunteers</th>
<th>Period 1</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>D</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>D</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>9</td>
<td>D</td>
<td>A</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>B</td>
</tr>
<tr>
<td>11</td>
<td>D</td>
<td>B</td>
</tr>
<tr>
<td>12</td>
<td>D</td>
<td>C</td>
</tr>
</tbody>
</table>

The minimum acceptable number of volunteers is 18 for bioequivalence studies.

\[ n \geq \left\{ \frac{1}{2D^2} \frac{\sigma^2}{\alpha^2 + \beta^2} \right\} + 0.25 \alpha^2 \]

Where,

\[ n = \text{no. of volunteers} \]
\[ \alpha = \text{Required level of significance (0.05)} \]
\[ \beta = \text{Required power of test (0.80)} \]
\[ \sigma^2 = \text{Error mean sum of squares from ANOVA (estimated/guess)} \]

### 2.9.5 Statistical Issues in BA/BE Studies

The pharmacokinetic parameters, \( C_{\text{max}} \), \( T_{\text{max}} \) and AUC should be subjected to a three-way analysis of variance (3-way ANOVA) in order to test differences due to
formulations, period and subjects. A more complex ANOVA may be appropriate in some circumstances, e.g. if treatments are replicated. The standard parametric ANOVA assumes homogeneity of variances, normality and additivity of independent variables.

In order to ensure homogeneity of variances between treatments, Bartlett’s test or a similar test should be carried out prior to performing the ANOVA. The primary comparison of interest in a bioequivalence study is the ratio of average parameter data (AUC or C\text{max}) from the test and reference formulations rather than the difference between them. Log transformation of the data allows the general linear statistical model to draw inferences about the ratio of the two averages on the original scale. Log transformation thus achieves the general comparison based on the ratio rather than on the difference.

Moreover, plasma concentration data, including AUC and C\text{max}, tend to be skewed and their variances tend to increase with the means. Log transformation corrects this situation and makes the variances independent of the mean.

Further, the frequency distribution skewed to the left, i.e., those with a log tail to the right is made symmetrical by log transformation.

In case no suitable transformation is available, the non-parametric method should be used. Tmax values being discrete, data on Tmax should be analysed using non-parametric methods.

2.9.6 Two One-Sided Tests Procedures (TOST):

This procedure is also referred to as confidence interval approach. This method is used to demonstrate if the bioavailability of the drug from the test formulation is too high or low in comparison to the reference drug product. The 90% confidence limits are estimated for the sample means. In this test, presently required by the FDA, a 90% confidence interval about the ratio of means of the two drug products must be within ± 20% for measurement of the rate and extent of drug bioavailability. The lower 90% CI for the ratio of means cannot be less than 0.8, and the upper 90% CI for the ratio of the means cannot be greater than 1.20. The 90% CI is a function of sample size and study variability, including inter and intra subject variability (CDER, 2003).
Current DCGI requirements for bio-equivalence approval are that 90% confidence interval should be within 80-125% for log transformed $C_{\text{max}}$ and for log transformed AUC. For narrow therapeutic index drugs, the same criterion i.e., log transformed $C_{\text{max}}$ and log transformed AUCs of 80-125% is applicable. No tighter limit has been proposed for NTIs. Canadian regulatory requirements for bio-equivalence approval are that 90% confidence interval should be within 80-125% for log transformed $C_{\text{max}}$ and AUC. For narrow therapeutic index drugs, log transformed $C_{\text{max}}$ should be within 90-111% and log transformed AUCs should be within 80-125.

The T/R ratio should be as close as possible to 95-105%. Intra subject CV should be as low as possible (<15%). Table 2.3 mentions the bioequivalence criteria followed by various regulatory agencies in the world.

Table 2.3 Criteria of bio-equivalence of various regulatory agencies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CPMP (EU)</th>
<th>USFDA</th>
<th>CANADIAN FDA (CEC)</th>
<th>DCGI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log transformed $C_{\text{max}}$ using 90% CI</td>
<td>▫ 80-125% of reference &lt;br&gt;▫ 70-143% of reference (If clinically acceptable). Tighter limits for $C_{\text{max}}$ accepted for NTI drugs.</td>
<td>▫ 80-125% of reference and otherwise indicated for NTI drugs. The range is same as the wide margin drugs.</td>
<td>▫ 80-125% of reference &lt;br&gt;▫ 90-111% of reference for NTI drugs.</td>
<td>▫ 80-125% of reference &lt;br&gt;▫ 80-125% of reference for NTI drugs.</td>
</tr>
<tr>
<td>Log transformed AUC$_{0-t}$ using 90% CI</td>
<td>▫ 80-125% of reference &lt;br&gt;▫ 80-125% of reference for NTI drugs.</td>
<td>▫ 80-125% of reference &lt;br&gt;▫ 80-125% of reference for NTI drugs.</td>
<td>▫ 80-125% of reference &lt;br&gt;▫ 80-125% of reference for NTI drugs.</td>
<td>▫ 80-125% of reference.</td>
</tr>
</tbody>
</table>

*NTI- Narrow Therapeutic Index
2.10 Need of Bioavailability/Bioequivalence Studies

Regulatory authorities (FDA, CPMP) insists that generic products should compulsorily be "essential similar" (Composition, formulation and bioequivalence) with that of reference product in order to exclude any clinically significant difference. When 2 formulations of the same drug present similar bioavailabilities to the extent that they are considered bioequivalent by prescribed criteria, it is assumed that when administered in the same molar dose, they will provide the same therapeutic effect (Therapeutically equivalent). The use of generic drugs is of increasing importance, in terms of efficiency, in the selection of therapeutic alternatives (Shah HK, 1992). But their use in clinical practice depends not only on their, but mostly on the conviction of their interchangeability with their reference counterparts (Rocchi et al. 2004).

Despite many advantages for consumers and health care providers, with low-priced generic formulation, these are not always as safe or effective as their counterpart (Cantor LB, 2002). Issue of the impurities in manufacturing generic drugs had been addressed by US Office of Generic Drugs and draft guideline for industry has been proposed. In the USA itself, many important drugs like diclofenac sodium (Suleman et al, 1989), theophylline (Baker et al, 1985, Weinberger et al. 1978) phenytoin (Rosenbaum et al, 1994), warfarin tablets (Hope and Havrda 2001), digoxin tablets, and levothyroxine tablets have failed bioequivalence studies. Reports of the generic drugs having different in vitro profile in comparison to innovator product and substandard quality are frequent across many countries (Nightingale CH, 2005; Lambert and Conway 2003). Nevertheless, there has always been a report of variations in the efficacy of generic drugs compared with the corresponding brand-name drugs (Kluznik et al. 2001; Hope and Havrda 2001; Ansbacher R 2000; Haas et al. 1997; Richton-Hewett et al. 1998).

The Commissioner of Food and Drugs describes following factors to assess actual or potential bioequivalence problems of drugs/products (21 CFR 320.33). These drugs can have higher risk as the absorption/bioavailability is dependent on one of the following characteristics:

1. When there is evidence that drug products do not give comparable therapeutic effects from well-controlled clinical trials or controlled observations in patients.
(2) When products are not bioequivalent in well-controlled bioequivalence studies.

(3) Narrow therapeutic ratio drugs (steep dose-response curve) for careful dosage titration and patient monitoring.

(4) Competent medical determination that a lack of bioequivalence would have a serious adverse effect in the treatment or prevention of a serious disease or condition.

(5) When physicochemical factors are important in the bioavailability of drugs like:

(a) Unfavourable physicochemical properties, e.g., low solubility, instability, metastable modifications, poor permeability etc.

(b) Slow dissolution rate of one or more such products.

(c) The particle size and/or surface area of the active drug ingredient is critical in determining its bioavailability.

(d) Certain physical structural characteristics of the active drug ingredient, e.g., polymorphic forms, conformers, solvates, complexes, and crystal modifications, dissolve poorly and this poor dissolution may affect absorption.

(e) High excipients to active ingredients ratio e.g., greater than 5 to 1.

(f) Specific inactive ingredients, e.g., hydrophilic or hydrophobic excipients and lubricants, either may be required for absorption of the active drug ingredient or therapeutic moiety or, alternatively, if present, may interfere with such absorption.

(6) Pharmacokinetic evidence that:

(a) The active drug ingredient, therapeutic moiety, or its precursor is absorbed in large part in a particular segment of the gastrointestinal tract or is absorbed from a localized site (Klausner et al. 2003).

(b) The degree of absorption of the active drug ingredient, therapeutic moiety, or its precursor is poor, e.g., less than 50 percent, ordinarily in comparison to an intravenous dose, even when it is administered in pure form, e.g., in solution.
(c) There is rapid metabolism of the therapeutic moiety in the intestinal wall or liver during the process of absorption (first-class metabolism) so the therapeutic effect and/or toxicity of such drug product is determined by the rate as well as the degree of absorption.

(d) The therapeutic moiety is rapidly metabolized or excreted so that rapid dissolution and absorption are required for effectiveness.

(e) The active drug ingredient or therapeutic moiety is unstable in specific portions of the gastrointestinal tract and requires special coatings or formulations, e.g., buffers, enteric coatings, and film coatings, to assure adequate absorption.

(f) The drug product is subject to dose dependent kinetics in or near the therapeutic range, and the rate and extent of absorption are important to bioequivalence.

WHO specifies few other categories of the drugs for which equivalence studies are necessary:

1. Sustained or otherwise modified release pharmaceutical products designed to act by systemic absorption.

2. Fixed combination products with systemic action.

3. Oral immediate release pharmaceutical products indicated for serious conditions requiring assured therapeutic response.

2.11 Studies of Cefpodoxime Extended Release Formulations

Merchant et al. (2006) studied the hydrophilic matrix of HPMC controlled the Cefpodoxime proxetil release effectively for 24 hours; hence, the formulation can be considered as a once-daily sustained-release tablet of Cefpodoxime proxetil. The formulation showed acceptable pharmacotechnical properties and assay requirements. In vitro dissolution studies indicated a sustained-release pattern throughout 24 hours of the study that was comparable to the theoretical release profile. Drug release kinetics indicated that drug release was best explained by Higuchi’s equation, as these
plots showed the highest linearity ($r^2=0.9734$), but a close relationship was also noted with zero-order kinetics ($r^2=0.9708$). Korsmeyer’s plots indicated a $n$ value of 0.57, which was indicative of an anomalous diffusion mechanism or diffusion coupled with erosion; hence, the drug release was controlled by more than one process. Hixson-Crowell plots indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time.

2.12 Various Bioavailability and Bioequivalence Studies of Cefpodoxime

Few bioavailability studies of Cefpodoxime have been carried out by various investigators. Some are listed below;

**Gregory et al. (1998)** They report the results of a randomized two-way crossover study designed to characterize the disposition of a single dose (10 mg/kg) of Cefpodoxime proxetil oral suspension in children, under fed and fasted conditions. Seventeen children (8.4 months to 12.2 years old, seven female) participated in this study. Each subject received a single 10-mg/kg dose of Cefpodoxime proxetil oral suspension, after a predose fast and again coadministered with food. Repeated blood samples ($n= 10$) were obtained during 12 h postdose and Cefpodoxime was quantified from plasma by high performance liquid chromatography. Plasma concentration vs. time data were curve fit for each subject with a nonlinear weighted least squares algorithm, and pharmacokinetic parameters were determined from the polyexponential estimates. Cefpodoxime disposition was best characterized using a one-compartment open model with first order absorption. The area under the plasma concentration vs. time curve, $C_{\text{max}}$ and $K_e$ were not significantly different between fed and fasted conditions. However, $T_{\text{max}}$ was significantly prolonged (fed $= 2.79 \pm 1.10$ h vs. fasted $= 1.93 \pm 0.54$ h) and $K_a$ was significantly smaller (fed $= 0.42 \pm 0.14$ h$^{-1}$ vs. fasted $= 0.81 \pm 0.72$ h$^{-1}$) in the fed state. They concluded that administration of Cefpodoxime in the presence of food affected the rate but not the extent of absorption. Cefpodoxime proxetil oral suspension can be administered without regard to meals in children 6 months to 12 years of age.

**Borin and Forbes (1995)** they evaluated the effect of a high-fat meal on absorption of a 200-mg dose of Cefpodoxime proxetil oral suspension in 20 healthy, male
volunteers in a randomized, two-way crossover study. The concentrations of Cefpodoxime in plasma and in urine were determined by sensitive and specific high-performance liquid chromatography methods. The area under the plasma drug concentration-time curve, time to peak concentration, and urinary excretion of Cefpodoxime were significantly greater (P < or = 0.05) after administration of Cefpodoxime proxetil oral suspension with food than under fasting conditions. However, the difference in the areas under the curve between fed and fasted treatments was only 11%, and application of the two one-sided tests procedure showed bioequivalence between treatments for this parameter. The slight increase in the extent of drug absorption and the slower rate of absorption which results when Cefpodoxime proxetil is given with food are unlikely to be of clinical importance.

**Gehanno et al. (1990)** studied seventeen patients undergoing tonsillectomy received Cefpodoxime proxetil orally in a dose equivalent to 100 mg Cefpodoxime 4, 7 or 12 h before operation. Plasma and tonsillar tissue concentrations of Cefpodoxime were assayed by a microbiological method. Tonsillar tissue concentrations after 4 and 7 h were 0.24 and 0.09 mg/kg respectively (being 23% of the plasma concentration). The tonsillar tissue concentration after 12 h was less than 0.06 mg/kg. As the MIC for Streptococcus pyogenes is less than 0.06 mg/l, Cefpodoxime proxetil may be of value in acute tonsillitis.

**Tremblay et al. (1990)** performed three pharmacokinetic studies involving single oral doses of Cefpodoxime proxetil in healthy volunteers are reported. The first study was to determine the absolute bioavailability of Cefpodoxime, the second was to study the relationship between the oral dose of Cefpodoxime proxetil and pharmacokinetic parameters of Cefpodoxime, and the third was to compare the pharmacokinetics of Cefpodoxime in healthy young and elderly volunteers. Half the dose of Cefpodoxime orally administered as Cefpodoxime proxetil in tablet form reaches the systemic circulation, while 80% of the Cefpodoxime absorbed is excreted unchanged in urine. The volume of distribution is large (32.3 l). The pharmacokinetics of Cefpodoxime was linear in young and elderly subjects after 100 and 200 mg oral doses, which are those used therapeutically. The $C_{\text{max}}$ was about 1.4mg/l (after 100 mg) and 2.6 mg/l (after 200 mg). Deviation from linearity appeared at 400 mg and the effect was confirmed at 800 mg. The differences between young and elderly subjects...
were negligible, with the exception of the half-life which increased by only 14%, from 2.67 to 3 h. Dosage adjustment is therefore not necessary in the elderly.

**Borin et al. (1991)** administered the Cefpodoxime proxetil in single doses of 100, 200, 400, 600, and 800 mg (dose expressed as Cefpodoxime equivalents) and multiple doses of 100, 200, and 400 mg twice daily to healthy volunteers. The pharmacokinetics of the active metabolite, Cefpodoxime, and tolerance of Cefpodoxime proxetil were determined. Results from the single-dose study indicate that Cefpodoxime exhibits nonlinear pharmacokinetics over the dose range of 100 to 800 mg. This nonlinearity is primarily due to differences in dose-normalized AUC and Cmax, urinary recovery, and half-life between one or more of the higher-dose treatment groups and the 100-mg dosing group. After multiple-dose (twice daily) administration for 15 days, steady state is achieved on the second day of dosing, and there is no drug accumulation. Cefpodoxime pharmacokinetics are linear with dose over the clinically relevant dosing range of 100 to 400 mg. Microbiologic and HPLC plasma assay results are highly correlated, with close agreement between HPLC- and microbiologic-determined pharmacokinetic parameter estimates. Cefpodoxime proxetil was well tolerated in both studies. The most frequent medical events were related to gastrointestinal problems and consisted of transient loose stools in three subjects in the single-dose study and antibiotic-associated diarrhea in one subject in the multiple-dose study.

**Couraud et al. (1990)** studied eighteen patients undergoing thoracotomy for suspected pulmonary neoplasia were given 200 mg Cefpodoxime equivalent by mouth, before operation. Plasma samples were obtained before dose administration, and plasma and lung tissue samples were obtained at the time of operation which was 3, 6 or 12 h after the dose. All samples were assayed for Cefpodoxime. The mean ratios for lung tissue/plasma concentrations were similar between 3 and 12 h after dose, suggesting that equilibrium between plasma and lung tissue concentrations was reached within 3 h of medication. The mean concentrations of Cefpodoxime in lung tissue were 0.63±0.16, 0.52±0.09 and 0.19±0.02 mg/kg at 3, 6 and 12 h after administration, respectively. These observations indicate good, rapid and sustained penetration into lung tissue in concentrations ≥ the MIC₉₀ for most common microorganisms found in community-acquired pneumonia.
2.13 Drug Description

Cephalosporins

Cephalosporin compounds were first isolated from cultures of *Cephalosporium acremonium* from a sewer in Sardinia in 1948 by Italian scientist Giuseppe Brotzu (Podolsky DK, 1998). He noticed that these cultures produced substances that were effective against *Salmonella typhi*, the cause of typhoid fever, which had beta-lactamase. Guy Newton and Edward Abraham at the Sir William Dunn School of Pathology at the University of Oxford isolated cephalosporin C. The cephalosporin nucleus, 7-aminocephalosporanic acid (7-ACA), was derived from cephalosporin C and proved to be analogous to the penicillin nucleus 6-aminopenicillanic acid, but it was not sufficiently potent for clinical use. Modification of the 7-ACA side-chains resulted in the development of useful antibiotic agents, and the first agent cephalothin (cefalotin) was launched by Eli Lilly and Company in 1964.

2.13.1 Mechanism of Action

Cephalosporins are bactericidal and have the same mode of action as other beta-lactam antibiotics (such as penicillins) but are less susceptible to penicillinases. Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin-binding proteins (PBPs). PBPs bind to the D-Ala-D-Ala at the end of muropeptides (peptidoglycan precursors) to crosslink the peptidoglycan. Beta-lactam antibiotics mimic this site and competitively inhibit PBP crosslinking of peptidoglycan (Chocas et al. 2003).

2.13.2 Clinical Use of Cephalosporins

2.13.2.1 Indications

Cephalosporins are indicated for the prophylaxis and treatment of infections caused by bacteria susceptible to this particular form of antibiotic. First-generation cephalosporins are predominantly active against Gram-positive bacteria, and successive generations have increased activity against Gram-negative bacteria (albeit often with reduced activity against Gram-positive organisms).
2.13.2.2 Adverse effects

Common adverse drug reactions (ADRs) (≥1% of patients) associated with the cephalosporin therapy include: diarrhea, nausea, rash, electrolyte disturbances, and/or pain and inflammation at injection site. Infrequent ADRs (0.1–1% of patients) include: vomiting, headache, dizziness, oral and vaginal candidiasis, pseudomembranous colitis, superinfection, eosinophilia, and/or fever.

The commonly quoted figure of 10% of patients with allergic hypersensitivity to penicillins and/or carbapenems also having cross-reactivity with cephalosporins originated from a 1975 study looking at the original cephalosporins, (Dash CH, 1975) and subsequent "safety first" policy meant this was widely quoted and assumed to apply to all members of the group. (Pegler and Healy 2007) Hence it was commonly stated that they are contraindicated in patients with a history of severe, immediate allergic reactions (urticaria, anaphylaxis, interstitial nephritis, etc.) to penicillins, carbapenems or cephalosporins (Rossi S, 2006). This, however, should be viewed in the light of recent epidemiological work suggesting that, for many second-generation (or later) cephalosporins, the cross-reactivity rate with penicillin is much lower, having no significantly increased risk of reactivity in the studies examined (Pegler and Healy 2007; Pichichero ME 2006). The British National Formulary previously issued blanket warnings of 10% cross reactivity, but, since the September 2008 edition, suggests in the absence of suitable alternatives that oral cefixime or cefuroxime and injectable cefotaxime, ceftazidine, and ceftriaxone can be used with caution, but to avoid cefaclor, cefadrocil, cefalexin, and cefradine (BNF 2008).

Several cephalosporins are associated with hypoprothrombinemia and a disulfiram-like reaction with ethanol. (Kitson TM, 1987; Shearer et al. 1988) These include latamoxef, cefmenoxime, moxalactam, cefoperazone, cefamandole, cefmetazole, and cefotetan. This is thought to be due to the N-methylthiotetrazole (NMTT) side-chain of these cephalosporins, which blocks the enzyme vitamin K epoxide reductase (likely causing hypoprothrombinemia) and aldehyde dehydrogenase [causing alcohol intolerance] (Stork C, 2006).
2.13.3 Classification

The cephalosporin nucleus can be modified to gain different properties. Cephalosporins are sometimes grouped into "generations" by their antimicrobial properties. The first cephalosporins were designated first-generation cephalosporins, whereas, later, more extended-spectrum cephalosporins were classified as second-generation cephalosporins. Each newer generation of cephalosporins has significantly greater Gram-negative antimicrobial properties than the preceding generation, in most cases with decreased activity against Gram-positive organisms. Fourth-generation cephalosporins, however, have true broad-spectrum activity.

The classification of cephalosporins into "generations" is commonly practiced, although the exact categorization of cephalosporins is often imprecise. For example, the fourth generation of cephalosporins is not recognized as such, in Japan. In Japan, cefaclor is classed as a first-generation cephalosporin, even though in the United States it is a second-generation one; and cefbuperazone, cefminox, and cefotetan are classed as second-generation cephalosporins. Cefmetazole and cefoxitin are classed as third-generation cephems. Flomoxef, latamoxef are in a new class called oxacephems.

Most first-generation cephalosporins were originally spelled "ceph-" in English-speaking countries. This continues to be the preferred spelling in the United States and Australia: the inventor country of clinical use of penicillin (Buckley et al. 1998). European countries (including the United Kingdom) have adopted the International Nonproprietary Names, which are always spelled "cef-". Newer first-generation cephalosporins and all cephalosporins of later generations are spelled "cef-", even in the United States.

Some state that, although cephalosporins can be divided into five or even six generations, the usefulness of this organization system is of limited clinical relevance. (Weiss et al. 2007) Fourth-generation Cephalosporins as of March, 2007 were considered to be "a class of highly potent antibiotics that are among medicine's last defenses against several serious human infections" according to the Washington Post.
2.13.4. Drug Chemistry

Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic antibiotic of the cephalosporin class.


2.13.4.2. Empirical Formula: $\text{C}_{21}\text{H}_{27}\text{N}_{5}\text{O}_{9}\text{S}_{2}$ and its structural formula is represented below:

![Structural formula of Cefpodoxime proxetil]

2.13.4.3. Molecular Weight: 557.6

Cefpodoxime proxetil is a prodrug; its active metabolite is Cefpodoxime. All doses of Cefpodoxime proxetil in this insert are expressed in terms of the active Cefpodoxime moiety.

2.13.5. Clinical Pharmacology

2.13.5.1 Absorption and Excretion

Cefpodoxime proxetil is a prodrug that is absorbed from the gastrointestinal tract and de-esterified to its active metabolite, Cefpodoxime. Following oral administration of 100 mg of Cefpodoxime proxetil to fasting subjects, approximately 50% of the administered Cefpodoxime dose was absorbed systemically. Over the recommended
dosing range (100 to 400 mg), approximately 29 to 33% of the administered Cefpodoxime dose was excreted unchanged in the urine in 12 hours. There is minimal metabolism of Cefpodoxime in vivo.

2.13.5.2 Effects of Food:

The extent of absorption (mean AUC) and the mean peak plasma concentration increased when film-coated tablets were administered with food. Following a 200 mg tablet dose taken with food, the AUC was 21 to 33% higher than under fasting conditions, and the peak plasma concentration averaged 3.1 mcg/mL in fed subjects versus 2.6 mcg/ml in fasted subjects. Time to peak concentration was not significantly different between fed and fasted subjects.

When a 200 mg dose of the suspension was taken with food, the extent of absorption (mean AUC) and mean peak plasma concentration in fed subjects were not significantly different from fasted subjects, but the rate of absorption was slower with food (48% increase in Tmax).

2.13.5.3 Pharmacokinetics of Cefpodoxime Proxetil

Over the recommended dosing range (100 to 400 mg), the rate and extent of Cefpodoxime absorption exhibited dose-dependency; dose-normalized Cmax and AUC decreased by up to 32% with increasing dose. Over the recommended dosing range, the Tmax was approximately 2 to 3 hours and the T½ ranged from 2.09 to 2.84 hours. Mean Cmax was 1.4 mcg/mL for the 100 mg dose, 2.3 mcg/mL for the 200 mg dose, and 3.9 mcg/mL for the 400 mg dose (Table 2.4). In patients with normal renal function, neither accumulation nor significant changes in other pharmacokinetic parameters were noted following multiple oral doses of up to 400 mg Q 12 hours.

2.13.5.4. Distribution

Protein binding of Cefpodoxime ranges from 22 to 33% in serum and from 21 to 29% in plasma.
Table 2.4 Cefpodoxime plasma levels (mcg/ml) in fasted adults (Single Dose)

<table>
<thead>
<tr>
<th>Dose (Cefpodoxime equivalents)</th>
<th>1hr</th>
<th>2hr</th>
<th>3hr</th>
<th>4hr</th>
<th>6hr</th>
<th>8hr</th>
<th>12hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>0.98</td>
<td>1.4</td>
<td>1.3</td>
<td>1.0</td>
<td>0.59</td>
<td>0.29</td>
<td>0.08</td>
</tr>
<tr>
<td>200 mg</td>
<td>1.5</td>
<td>2.2</td>
<td>2.2</td>
<td>1.8</td>
<td>1.2</td>
<td>0.62</td>
<td>0.18</td>
</tr>
<tr>
<td>400 mg</td>
<td>2.2</td>
<td>3.7</td>
<td>3.8</td>
<td>3.3</td>
<td>2.3</td>
<td>1.3</td>
<td>0.38</td>
</tr>
</tbody>
</table>

2.13.5.5. Skin Blister

Following multiple-dose administration every 12 hours for 5 days of 200 mg or 400 mg Cefpodoxime proxetil, the mean maximum Cefpodoxime concentration in skin blister fluid averaged 1.6 and 2.8 mcg/mL, respectively. Skin blister fluid Cefpodoxime levels at 12 hours after dosing averaged 0.2 and 0.4 mcg/mL for the 200 mg and 400 mg multiple-dose regimens, respectively.

2.13.5.6. Tonsil Tissue

Following a single, oral 100 mg Cefpodoxime proxetil film-coated tablet, the mean maximum Cefpodoxime concentration in tonsil tissue averaged 0.24 mcg/g at 4 hours post-dosing and 0.09 mcg/g at 7 hours post-dosing. Equilibrium was achieved between plasma and tonsil tissue within 4 hours of dosing. No detection of Cefpodoxime in tonsillar tissue was reported 12 hours after dosing. These results demonstrated that concentrations of Cefpodoxime exceeded the MIC\textsubscript{90} of \textit{S. pyogenes} for at least 7 hours after dosing of 100 mg of Cefpodoxime proxetil.

2.13.5.7. Lung Tissue

Following a single, oral 200 mg Cefpodoxime proxetil film-coated tablet, the mean maximum Cefpodoxime concentration in lung tissue averaged 0.63 mcg/g at 3 hours post-dosing, 0.52 mcg/g at 6 hours post-dosing, and 0.19 mcg/g at 12 hours post-dosing. The results of this study indicated that Cefpodoxime penetrated into lung tissue and produced sustained drug concentrations for at least 12 hours after dosing at levels that exceeded the MIC\textsubscript{90} for \textit{S. pneumoniae and H. influenzae}. 
2.13.5.8. Cerebro Spinal Fluid (CSF)

Adequate data on CSF levels of Cefpodoxime are not available.

2.13.5.9. Effects of Decreased Renal Function

Elimination of Cefpodoxime is reduced in patients with moderate to severe renal impairment (< 50 mL/min creatinine clearance). In subjects with mild impairment of renal function (50 to 80 mL/min creatinine clearance), the average plasma half-life of Cefpodoxime was 3.5 hours. In subjects with moderate (30 to 49 mL/min creatinine clearance) or severe renal impairment (5 to 29 mL/min creatinine clearance), the half-life increased to 5.9 and 9.8 hours, respectively. Approximately 23% of the administered dose was cleared from the body during a standard 3-hour hemodialysis procedure.

2.13.5.10. Effect of Hepatic Impairment (Cirrhosis)

Absorption was somewhat diminished and elimination unchanged in patients with cirrhosis. The mean Cefpodoxime T½ and renal clearance in cirrhotic patients were similar to those derived in studies of healthy subjects. Ascites did not appear to affect values in cirrhotic subjects. No dosage adjustment is recommended in this patient population.

2.13.5.11. Pharmacokinetics in Elderly Subjects

Elderly subjects do not require dosage adjustments unless they have diminished renal function. In healthy geriatric subjects, Cefpodoxime half-life in plasma averaged 4.2 hours (vs. 3.3 in younger subjects) and urinary recovery averaged 21% after a 400 mg dose was administered every 12 hours. Other pharmacokinetic parameters (Cmax, AUC, and Tmax) were unchanged relative to those observed in healthy young subjects.

2.13.6. Microbiology

Cefpodoxime is active against a wide spectrum of Gram-positive and Gram-negative bacteria. Cefpodoxime is stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and cephalosporins, due to their
production of beta-lactamase, may be susceptible to Cefpodoxime. Cefpodoxime is inactivated by certain extended spectrum beta-lactamases.

2.13.6.1. Aerobic Gram-Positive Microorganisms

*Staphylococcusaureus* (including penicillinase-producing strains).

NOTE: Cefpodoxime is inactive against methicillin-resistant, staphylococci, *Staphylococcus saprophyticus*, *Streptococcus pneumoniae* (excluding penicillin-resistant strains), *Streptococcus pyogenes*

2.13.6.2. Aerobic Gram-Negative Microorganisms

*Escherichia coli*, *Klebsiellapneumonia*, *Proteus mirabilis*, *Haemophilus influenzae*, including beta-lactamase producing strains), *Moraxella* (Branhamella) catarrhalis *Neisseria gonorrhoeae* (including penicillinase-producing strains).

Cefpodoxime exhibits in vitro minimum inhibitory concentrations (MICs) of ≤ 2.0 mcg/mL against most (≥ 90%) of isolates of the following microorganisms (NCCLS 1997; 1998). However, the safety and efficacy of Cefpodoxime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

2.13.6.3. Aerobic Gram-Positive Microorganisms

*Streptococcusagalactiae*

*Streptococcus spp.* (Groups C, F, G)

NOTE: Cefpodoxime is inactive against enterococci.

2.13.6.4. Aerobic Gram-Negative Microorganisms

*Citrobacterdiversus*

*Klebsiellaoxytoca*

*Proteus vulgaris*

*Providenciarettergeri*

*Haemophilusparainfluenzae*
NOTE: Cefpodoxime is inactive against most strains of Pseudomonas and Enterobacter.

2.13.6.5. Anaerobic Gram-Positive Microorganisms

Peptostreptococcus magnus

2.13.7. Indications
Cefpodoxime proxetil is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

2.13.7.1. Acute Otitis Media
Caused by Streptococcus pneumoniae (excluding penicillin-resistant strains), Streptococcus pyogenes, Haemophilus influenzae (including beta-lactamase-producing strains), or Moraxella (Branhamella) catarrhalis (including beta-lactamase-producing strains).

2.13.7.2. Pharyngitis and/or Tonsillitis
Caused by Streptococcus pyogenes.

2.13.7.3. Community-Acquired Pneumonia
Caused by S. pneumoniae or H. Influenzae (including beta-lactamase-producing strains).

2.13.7.4. Acute Bacterial Exacerbation of Chronic Bronchitis
Caused by S. pneumoniae, H. influenzae (non-beta-lactamase-producing strains only), or M. catarrhalis. Data are insufficient at this time to establish efficacy in patients with acute bacterial exacerbations of chronic bronchitis caused by beta-lactamase-producing strains of H. influenzae.

2.13.7.5. Acute, Uncomplicated Urethral and Cervical Gonorrhea
Caused by Neisseriagonorrhoeae (including penicillinase-producing strains).
2.13.7.6. Acute, Uncomplicated Ano-rectal Infections in Women

Due to *Neisseria gonorrhoeae* (including penicillinase-producing strains).

2.13.7.7. Uncomplicated Skin and Skin Structure Infections

Caused by *Staphylococcus aureus* (including penicillinase-producing strains) or *Streptococcus pyogenes*. Abscesses should be surgically drained as clinically indicated.

2.13.7.8. Acute Maxillary Sinusitis

Caused by *Haemophilus influenzae* (including beta-lactamase-producing strains), *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.

2.13.7.9. Uncomplicated Urinary Tract Infections (cystitis)

Caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Staphylococcus saprophyticus*.

2.13.8. Dosage and Administration

The recommended dosages, durations of treatment, and applicable patient population are as described in the Table 2.5.

2.13.8.1 Patients with Renal Dysfunction:

For patients with severe renal impairment (< 30 mL/min creatinine clearance), the dosing intervals should be increased to Q 24 hours. In patients maintained on hemodialysis, the dose frequency should be 3 times/week after hemodialysis.

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to estimate creatinine clearance (mL/min). For this estimate to be valid, the serum creatinine level should represent a steady state of renal function.

\[
\text{Males (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinin (mg/100 ml)}}
\]
Females (ml/min) = 0.85 x above value

Table 2.5 Dose, frequency and duration of Cefpodoxime for different kind of diseases

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Total Daily Dose</th>
<th>Dose Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharyngitis and/or tonsillitis</td>
<td>200 mg</td>
<td>100 mg Q 12 hours</td>
<td>5 to 10 days</td>
</tr>
<tr>
<td>Acute community-acquired pneumonia</td>
<td>400 mg</td>
<td>200 mg Q 12 hours</td>
<td>14 days</td>
</tr>
<tr>
<td>Acute bacterial exacerbations of chronic bronchitis</td>
<td>400 mg</td>
<td>200 mg Q 12 hours</td>
<td>10 days</td>
</tr>
<tr>
<td>Uncomplicated gonorrhea (men and women) and rectal gonococcal infections (women)</td>
<td>200 mg</td>
<td>single dose</td>
<td></td>
</tr>
<tr>
<td>Skin and skin structure</td>
<td>800 mg</td>
<td>400 mg Q 12 hours</td>
<td>7 to 14 days</td>
</tr>
<tr>
<td>Acute maxillary sinusitis</td>
<td>400 mg</td>
<td>200 mg Q 12 hours</td>
<td>10 days</td>
</tr>
<tr>
<td>Uncomplicated urinary tract infection</td>
<td>200 mg</td>
<td>100 mg Q 12 hours</td>
<td>7 days</td>
</tr>
</tbody>
</table>

2.13.8.2. Patients with Cirrhosis

Cefpodoxime pharmacokinetics in cirrhotic patients (with or without ascites) are similar to those in healthy subjects. Dose adjustment is not necessary in this population.

2.13.9. Side Effects

In clinical trials using multiple doses of Cefpodoxime proxetil film-coated tablets, 4696 patients were treated with the recommended dosages of Cefpodoxime (100 to 400 mg Q 12 hours). There were no deaths or permanent disabilities thought related to drug toxicity. One-hundred twenty-nine (2.7%) patients discontinued medication due
to adverse events thought possibly or probably related to drug toxicity. Ninety-three (52%) of the 178 patients who discontinued therapy (whether thought related to drug therapy or not) did so because of gastrointestinal disturbances, nausea, vomiting, or diarrhea. The percentage of Cefpodoxime proxetil-treated patients who discontinued study drug because of adverse events was significantly greater at a dose of 800 mg daily than at a dose of 400 mg daily or at a dose of 200 mg daily. Adverse events thought possibly or probably related to Cefpodoxime in multiple-dose clinical trials (N=4696 Cefpodoxime-treated patients) were diarrhea, headache and abdominal pain.

2.13.10. Drug Interactions

Antacids: Concomitant administration of high doses of antacids (sodium bicarbonate and aluminum hydroxide) or H₂ blockers reduces peak plasma levels by 24% to 42% and the extent of absorption by 27% to 32%, respectively. The rate of absorption is not altered by these concomitant medications. Oral anti-cholinergics (e.g., propantheline) delay peak plasma levels (47% increase in Tmax), but do not affect the extent of absorption (AUC).

2.13.10.1 Probenecid

As with other beta-lactam antibiotics, renal excretion of Cefpodoxime was inhibited by probenecid and resulted in an approximately 31% increase in AUC and 20% increase in peak Cefpodoxime plasma levels.

2.13.10.2. Nephrotoxic drugs

Although nephrotoxicity has not been noted when Cefpodoxime proxetil was given alone, close monitoring of renal function is advised when Cefpodoxime proxetil is administered concomitantly with compounds of known nephrotoxic potential.

2.13.11. Warnings

Before therapy with Cefpodoxime proxetil is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to Cefpodoxime, other cephalosporins, penicillins, or other drugs. If Cefpodoxime is to be administered to penicillin sensitive patients, caution should be exercised because cross hypersensitivity among beta-lactam antibiotics has been clearly documented and
may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Cefpodoxime proxetil occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamine, and airway management, as clinically indicated.

2.13.12. Precautions

2.13.12.1. General

In patients with transient or persistent reduction in urinary output due to renal insufficiency, the total daily dose of Cefpodoxime proxetil should be reduced because high and prolonged serum antibiotic concentrations can occur in such individuals following usual doses. Cefpodoxime, like other cephalosporins, should be administered with caution to patients receiving concurrent treatment with potent diuretics.

As with other antibiotics, prolonged use of Cefpodoxime proxetil may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

2.13.12.2. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenesis studies of Cefpodoxime proxetil have not been performed. Mutagenesis studies of Cefpodoxime, including the Ames test both with and without metabolic activation, the chromosome aberration test, the unscheduled DNA synthesis assay, mitotic recombination and gene conversion, the forward gene mutation assay and the in vivo micronucleus test, were all negative. No untoward effects on fertility or reproduction were noted when 100 mg/kg/day or less (2 times the human dose based on mg/m²sup) was administered orally to rats.

2.13.12.3. Pregnancy - Teratogenic Effects

2.13.12.3.1. Pregnancy Category B
Cefpodoximeproxetil was neither teratogenic nor embryocidal when administered to rats during organogenesis at doses up to 100 mg/kg/day (2 times the human dose based on mg/m$^2$) or to rabbits at doses up to 30 mg/kg/day (1-2 times the human dose based on mg/m$^2$). There are, however, no adequate and well-controlled studies of Cefpodoxime proxetil use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

2.13.12.3.2. Labor and Delivery

Cefpodoxime proxetil has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

2.13.12.3.3. Nursing Mothers

Cefpodoxime is excreted in human milk. In a study of 3 lactating women, levels of Cefpodoxime in human milk were 0%, 2% and 6% of concomitant serum levels at 4 hours following a 200 mg oral dose of Cefpodoxime proxetil. At 6 hours post-dosing, levels were 0%, 9% and 16% of concomitant serum levels. Because of the potential for serious reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

2.13.13. Overdose

In acute rodent toxicity studies, a single 5 g/kg oral dose produced no adverse effects. In the event of serious toxic reaction from overdosage, hemodialysis or peritoneal dialysis may aid in the removal of Cefpodoxime from the body, particularly if renal function is compromised. The toxic symptoms following an overdose of beta-lactam antibiotics may include nausea, vomiting, epigastric distress, and diarrhea.

2.13.14. Contraindication

Cefpodoxime proxetil is contraindicated in patients with a known allergy to Cefpodoxime or to the cephalosporin group of antibiotics (Vantin, 2012).