2.1. Literature on application of cyclodextrins for enhancing dissolution rate and bioavailability

Several studies reported the cyclodextrin complexation of a variety of drugs for various purposes. Exhaustive reviews\textsuperscript{1-3} on cyclodextrin complexation are available. Recent research work on cyclodextrin complexation for enhancing the dissolution rate and bioavailability is as follows:

2.1.1 Rawat, S. et al.\textsuperscript{4} studied rofecoxib-\(\beta\)-cyclodextrin inclusion complex for solubility enhancement. Solid inclusion complexes of rofecoxib and cyclodextrin were prepared by the kneading method in different molar ratios. They found that the solid complexes exhibited a higher rate of dissolution than the physical mixture and the pure drug.

2.1.2 Mora, P.C. et al.\textsuperscript{5} studied the enhancement of dehydroepiandrosterone solubility and bioavailability by ternary complexation with \(\alpha\)-cyclodextrin and glycine. Solid inclusion complexes of drug-\(\alpha\)-CD-glycine in 1:1:2 and 1:2:3 molar ratios were prepared. They found that both ternary products showed better dissolution properties than the drug alone. In vivo bioavailability studies of complexes gave higher blood levels of the drug after oral administration than the pure drug alone.

2.1.3 Vlachou et al.\textsuperscript{6} studied the preparation and characterization of the inclusion complex of furosemide with hydroxy propyl-\(\beta\)-cyclodextrin and found that the complex is characterized by acceptable water solubility and increased dissolution rate.
2.1.4 Koester L.S. et al.\textsuperscript{7} studied the influence of \(\beta\)-cyclodextrin complexation on carbamazepine release from hydroxy propyl methyl cellulose matrix tablets. It was found that the release rate of carbamazepine complexe with \(\beta\)-cyclodextrin is increased from matrix tablets.

2.1.5 Chowdary, K.P.R. et al.\textsuperscript{8} studied the physico-chemical characterization and dissolution properties of nimesulide – cyclodextrin binary systems. They found that a true inclusion of N with \(\beta\)-CD at 1 : 2M in solid state was confirmed by DSC, powder XRD and SEM studies. Dissolution properties of N-CD binary systems were superior when compared to pure nimesulide.

2.1.6 Liux et al.\textsuperscript{9} studied inclusion of acitretin into cyclodextrins by phase solubility and physico-chemical characterization. They used HP\(\beta\)CD and RM\(\beta\)CD for complexation. Phase solubility studies indicated that the solubility of acitretin was dramatically improved by formation of complexes. The physico-chemical properties of solid inclusion complexes were characterized by IR, DSC and XRD and found the structural features responsible for the enhancement of its solubility and photostability.

2.1.7 Wong, J.W. et al.\textsuperscript{10} studied the inclusion complexation of artemisinin with \(\alpha\), \(\beta\), and \(\gamma\)-cyclodextrins and found that the complexation capability of CDs with ART increased in the order of \(\alpha < \gamma < \beta\). Dissolution profiles of these three complexes demonstrated an increased rate and extent of dissolution compared with those of their respective physical mixtures and a commercial preparation. The respective estimated percentage of ART complexed by \(\gamma\)-CD, \(\beta\)-CD and \(\alpha\)-CD were 85\%, 40\% and 12\%.

2.1.8 Manolikar M.K. et al.\textsuperscript{11} studied the solubility of isoproturon by its complexation with \(\beta\)-cyclodextrin. The inclusion complexes were prepared by kneading, coevaporation and co-precipitation methods. Most of the complexes showed an increase in the dissolution rate of the
herbicide. The best results were obtained when inclusion complexes were prepared by co-
precipitation and co-evaporation methods.

2.1.9 Chowdary, K.P.R. et al.\textsuperscript{12} studied the controlled release of nifedipine from
mucoadhesive tablets of its inclusion complexes with $\beta$-CD.

2.1.10 Nasongkla N. et al.\textsuperscript{13} studied the enhancement of solubility and bioavailability
of $\beta$-lapachone using cyclodextrin inclusion complexes. Inclusion complexes were investigated.
Biologic activity and bioavailability were also investigated. They found that the solubility of $\beta$-lap
was increased linearly as a function of $\alpha$, $\beta$ and HP$\beta$CD concentrations. Maximum solubility was
achieved with HP$\beta$CD. Complex formation was proved by $^1\text{H}$ NMR and fluorescence spectroscopy.
They concluded that complexation of $\beta$-lap with HP$\beta$CD offers a major improvement in drug
solubility and bioavailability.

2.1.11 Kopecky F. et al.\textsuperscript{14} studied the dissolution of nimodipine in an aqueous
solution of hydroxy ethyl-$\beta$-cyclodextrin and solubility of nimodipine with cyclodextrins. They found
from their experiments that most efficient solubiliser of nimodipine was M-$\beta$-CD and a good
solubilizing efficiency was shown by HP$\beta$CD.

2.1.12 Koontz J.L. et al.\textsuperscript{15} studied the formation of natamycin : cyclodextrin inclusion
complexes and their characterization. They found that the water solubility of natamycin was
increased 16-fold, 73-fold and 152-fold with $\beta$-CD, $\gamma$-CD and HP$\beta$CD respectively. The natamycin :
CD inclusion complexes resulted in \textit{in vitro} antifungal activity nearly equivalent to that of natamycin
in its free state.

2.1.13 Fernandes C.M. et al.\textsuperscript{16} studied the hydrophilic and hydrophobic cyclodextrins
in a new sustained release oral formulation of nicardipine. The feasibility of using complexes with
cyclodextrins (CDs) in nicardipine (NC) controlled delivery was examined. The results indicated
that the critical combination of hydrophilic and hydrophobic CDs complexes in appropriate ratios
could be a promising drug delivery system with a prolonged therapeutic effect coupled with a more balanced bioavailability.

2.1.14 Fernandes C.M.\textsuperscript{17} studied the physico-chemical characterization and \textit{in vitro} dissolution behaviour of nicardipine - cyclodextrins inclusion compounds. Inclusion complexation between nicardipine HCl and \(\beta\)-cyclodextrin and HP\(\beta\)-cyclodextrin was evaluated. The phase solubility profiles with CDs were classified as A\(L\) type. Stability constants were found to be pH dependent. More stable complexes were formed in alkaline medium. All the combinations with HP\(\beta\)CD were more effective in achieving the enhancement of NC dissolution rate, yielding better performances than the corresponding ones with \(\beta\)-CD.

2.1.15 Fernandes C.M. et al\textsuperscript{18} studied the effect of the hydrophobic nature of triacetyl-\(\beta\)-cyclodextrin on the complexation with nicardipine HCl : physico-chemical and dissolution properties of the kneaded and spray-dried complexes. The inclusion ability of TAPCD, a hydrophobic cyclodextrin derivative was examined using NC as model drug. The binary compounds were prepared in a 1 : 1M ratio by the kneading and the spray drying process. The kneaded product presented slight modifications on the drug physico-chemical and morphological properties. But spray-drying was found to produce inclusion complexes with amorphous nature. \textit{In vitro} dissolution studies were carried out and found that NC \textit{in vitro} release was markedly retarded. However this retarding effect was more evident for the spray-dried product.

2.1.16 Bayomi M.A. et al\textsuperscript{19} studied the effect of inclusion complexation with cyclodextrins on photostability of nifedipine in solid state. Inclusion complexation is advantageous in protecting the drug against the effect of light. The effect of exposure to fluorescent lamps and sunlight on the photodegradation of uncomplexed and complexed nifedipine was tested. Inclusion complexation of nifedipine showed to retard drug photodegradation.

2.1.17 Spamer E. et al\textsuperscript{20} studied the characterization of the complexes of furosemide with 2-hydroxypropyl-\(\beta\)-cyclodextrin and sulfobutyl ether-7-\(\beta\)-cyclodextrin. The inclusion complexes were prepared and characterized by DSC, XRD, \textit{\textsuperscript{1}H} NMR spectroscopy and
found that by $^1$H NMR, furosemide fit into the cyclodextrin torus cavity with its furane ring nearest to the primary hydroxyl side.

2.1.18 Archontaki et al.\textsuperscript{21} studied the inclusion complexes of bromazepam with β- and HPβ-cyclodextrine. Inclusion complexes showed increased solubility than pure drug itself. The phase solubility diagrams were classified as of $A_4$ type in all cases.

2.1.19 Jianbin C. et al.\textsuperscript{22} studied the preparation of solid inclusion complex of ciproflaxacin with β-cyclodextrin. Solid inclusion complex of ciproflaxacin with β-CD was synthesized by the coprecipitation method. The results confirmed the existence of 1 : 1 inclusion complex of ciproflaxacin with β-CD. The formation constant of complex was determined by fluorescence method.

2.1.20 Pose-Vilamóno B. et al.\textsuperscript{23} studied the improvement of water solubility of sulfamethizole through its complexation with β- and hydroxy propyl-β-cyclodextrin. Solid inclusion complexes with β-CD and HPβCD were obtained by freeze drying. Host-guest interactions were studied by XRD, DSC. The dissolution rates of sulfamethizole increased by the complexation with β-CD and HPβCD.

2.1.21 Doliwa et al.\textsuperscript{24} studied the influence of piroxicam : hydroxy propyl-β-cyclodextrin complexation on the in vitro permeation and skin retention of piroxicam. A topical gel formulation containing piroxicam as inclusion complex with HPβCD was developed. Piroxicam complexation with HPβCD allowed the incorporation of a higher quantity of piroxicam into the gel, which resulted in a considerable increase in the piroxicam released and permeated.

2.1.22 Koester L.S. et al.\textsuperscript{25} studied the ofloxacin/β-cyclodextrin complexation. The complexes were prepared with β-cyclodextrin and showed water solubility enhancement of approximately 2.6 times but photostabilisation was not improved.
2.1.23 Chowdary, K.P.R. et al. studied the nimesulide and β-cyclodextrin inclusion complexes, their physico-chemical characterization and dissolution rate studies. Phase solubility studies indicated the formation of a 1 : 1 complex in solution. Solid complexes were prepared by kneading and coevaporation methods. Solid complexes of N-β-CD (1 : 1, 1 : 2 M) exhibited higher rates of dissolution and dissolution efficiency values than the corresponding physical mixtures and pure drug. Higher dissolution rates were observed with kneaded complexes.

2.1.24 Ozkan Y. et al. studied the improvement of water solubility and in vitro dissolution rate of glidazide by complexation with β-cyclodextrin. Inclusion complexes of glidazide with β-CD were prepared by neutralization and recrystallisation. It was found that the dissolution rates of glidazide from the inclusion complex made by neutralization was much faster than the pure drug, physical mixture of drug and cyclodextrin, recrystallisation systems.

2.1.25 Arias M.J. et al. carried out the study of omeprazole-γ-cyclodextrin complexation in the solid state. Inclusion complexes of omeprazole with γ-cyclodextrin were prepared by kneading, spray-drying, coprecipitation and freeze drying. They found that among the solid phases obtained, coprecipitated product presented the highest dissolution rate.

2.1.26 Veiga M.D. et al. studied the influence of surfactants (present in the dissolution media) on the release behaviour of tolbutamide from its inclusion complex with β-cyclodextrin. The possible competitive displacement of a drug from its cyclodextrin based inclusion complex by a third substance was investigated by studying the dissolution behaviour of tolbutamide-β-cyclodextrin inclusion complex in D.M. water and in aqueous solution of different surfactants. Results of this study suggest that the simultaneous presence of β-cyclodextrin and surfactants of proper molecular structure in a pharmaceutical formulation can give rise to an unexpected dissolution of the drug.

2.1.27 Bodor N. et al. carried out the effect of cyclodextrin on the solubility and stability of a novel soft corticosteroid, leupeptinol etabonate. Drug complexation was carried out with various cyclodextrins such as γ-CD, HPβCD, maltoyl-β-cyclodextrin (MBCD) and heptakis
Results suggested that a stronger complex formed between LE and DMCD, resulting in higher solubility and stability of LE in DMCD than in HPβCD.

2.1.28 Jarho P. et al.31 found that hydroxypropyl-β-cyclodextrin increases aqueous solubility and stability of anandamide.

2.1.29 Ammar H.O. et al.32 observed the improvement of some pharmaceutical properties of Ampicillin by cyclodextrin complexation. Complexation of Ampicillin with β-CD was found to increase both the solubility as well as the dissolution rate of the drug on the other hand. Assessment of bioavailability in human subjects depicted highly significant increase in both the rate and extent of absorption of the drug. Allopurinol was complexed with β-cyclodextrin by the same researchers and found that both solubility and dissolution rate was increased with complexation.

2.1.30 Tasic L.M. et al.33 studied the influence of β-cyclodextrin on the solubility and dissolution rate of paracetamol solid dispersions. They found that the improvement in solubility was influenced by complexation with β-CD.
2.2. Literature on application of cyclodextrins for controlled release

To diversify the use of the natural CDs, various kinds of derivatives have been prepared to improve their physico-chemical properties and inclusion capacity to enable them to become novel drug carriers\(^\text{34}\). The hydrophobic CD derivatives are useful as sustained-release drug carriers for water soluble drugs and peptides because they tend to decrease the solubility of the guest molecule\(^\text{35}\). Natural CDs such as β-CD have 21-hydroxyl groups that can be exploited for the structural modifications of CDs by introducing various functional groups into the CD molecules. Such structural modifications can optimize the desirable properties of CDs\(^\text{36}\).

Ethylation of the hydroxyl groups of β-CDs decreases their aqueous solubility, which in turn is proportional to the degree of substitution\(^\text{37}\). The available hydrophobic ethylated derivatives are heptakis-(2,6-di-o-ethyl)-β-cyclodextrins (diethyl β-cyclodextrins) and heptakis-(2,3,6-tri-o-ethyl) β-cyclodextrins (Triethyl β-cyclodextrins)\(^\text{34}\). Studies have shown that these derivatives sustain the release of various drugs from the inclusion complexes with varying effects. Thus, a desirable release profile can be obtained by using these derivatives either alone or in combination for the formation of inclusion complexes\(^\text{38}\).

The diethyl derivatives of β-CD were prepared by partially ethylating the C\(_2\) secondary and C\(_6\) primary hydroxyl group of β-CD; the C\(_3\) secondary hydroxyl group was left unsubstituted. For preparing triethyl-β-cyclodextrin (TE-β-CD), the primary and secondary hydroxyl groups of β-CD were perethylated. Steric hindrance offered by these groups imparts low solubility and acid-stability characteristics to these derivatives\(^\text{34}\).

In addition to ethylation, acylation has been used to prepare derivatives with differing chain lengths\(^\text{35}\). Peracylated β-CD derivatives with various alkyl chains (from acetyl to octanoyl) were prepared by acylating all hydroxyl groups of β-CD using corresponding acid anhydrides in a pyridine solution. Table 1 shows the solubility behaviour of these derivatives. The derivatives retard drug release in proportion to their alkyl chain lengths. Among all the peracylated derivatives,
perbutanoyl-β-cyclodextrin induced sufficient plasma levels as compared with the other derivatives that had shorter or longer chain lengths.

**TABLE 2.1**

**SOLUBILITY OF β-CYCLODEXTRIN AND ITS HYDROPHOBIC DERIVATIVES**

<table>
<thead>
<tr>
<th>Cyclodextrin</th>
<th>Solubility</th>
<th>Solvent system</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-cyclodextrin</td>
<td>1.6 g/100 ml</td>
<td>Water</td>
<td>34</td>
</tr>
<tr>
<td>Diethyl-β-CD</td>
<td>5.0 x 10⁻³ g/100 ml</td>
<td>Water</td>
<td>34</td>
</tr>
<tr>
<td>Triethyl-β-CD</td>
<td>1.8 x 10⁻³ g/100 ml</td>
<td>Water</td>
<td>34</td>
</tr>
<tr>
<td>Triacyetyl-β-CD</td>
<td>823.0 mg/100 ml</td>
<td>80% ethanol/water</td>
<td>33</td>
</tr>
<tr>
<td>Tripropanoyl-β-CD</td>
<td>423.0 mg/100 ml</td>
<td>80% ethanol/water</td>
<td>33</td>
</tr>
<tr>
<td>Tributanoyl-β-CD</td>
<td>219.0 mg/100 ml</td>
<td>80% ethanol/water</td>
<td>33</td>
</tr>
<tr>
<td>Trivaleryl-β-CD</td>
<td>283.0 mg/100 ml</td>
<td>80% ethanol/water</td>
<td>33</td>
</tr>
<tr>
<td>Trihexanoyl-β-CD</td>
<td>3.7 mg/100 ml</td>
<td>80% ethanol/water</td>
<td>33</td>
</tr>
<tr>
<td>Trioctanoyl-β-CD</td>
<td>*</td>
<td>80% ethanol/water</td>
<td>33</td>
</tr>
</tbody>
</table>

*: Could not be determined because of low solubility.

In addition to these derivatives, an insoluble aluminium salt of β-cyclodextrin sulphate was prepared from sodium -cyclodextrin sulphate. Aluminium β-cyclodextrin sulphate was prepared by dissolving sodium β-cyclodextrin sulphate and aluminium chloride in water at a pH value of 4.5 adjusted using 2M sodium hydroxide. After the solution was stirred at 25°C for 2 hr. the precipitate obtained was washed with water and vacuum dried at 60°C for 24 hr. The prepared derivative was used as a stabilizer and as a sustained release carrier molecule.

Another derivative, o-carboxymethyl-o-ethyl-β-cyclodextrin (CME-β-CD) has proved to be an ideal candidate for the development of delayed - release formulations. Uekama et al. combined the carboxy methyl substituent with an ethylated CD to produce 6-o-(carboxy-methyl)-o-ethyl-β-cyclodextrin. This derivative was slightly soluble at low pH values and freely soluble in
neutral and alkaline regions as the result of ionization of the carboxyl group. Thus CME-β-CD could serve as an enteric-type drug carrier similar to carboxymethyl ethyl cellulose, with the additional advantage of stabilizing the labile drugs because of its inclusion ability.41

Sustained release formulations of diltiazem47, flufenamic acid48, nitroglycerin49, isosorbide dinitrate44, salbutamol45 and captopril46 were developed employing cyclodextrin derivatives.
2.3 Literature on sparflloxacin

2.3.1 Sparflloxacin - A profile

Sparflloxacin is a recently developed fluoroquinolone drug which is extremely useful in treating many infections. It has broad spectrum of activity against gram +ve and gram -ve organisms. Chemically it is 5-amino-1-cyclopropyl-7 (cis, 3,5-dimethyl-1-piperazinyl) 6,8-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid and is not yet official in any pharmacopoeia. It acts by inhibiting DNA synthesis in sensitive organisms by blocking their DNA gyrase activity. Its structure is:

Sparflloxacin

\[
\begin{align*}
\text{CH}_3 \\
\text{H}_3\text{C} \\
\text{HN} & \text{N} \\
\text{F} & \text{N} \\
\text{F} & \text{O} \\
\text{NH}_2
\end{align*}
\]

Sparflloxacin is a difluorinated quinolone. The fluorine at position 8 increases absorption and plasma half life and C₅-amino group confers enhanced in vitro activity against gram +ve bacteria. The cyclopropyl group at position 1 and the fluorine atom at position 6 in the quinolone ring provides activity against gram +ve bacteria, gram -ve while association of the C₅ amino group and C-7 dimethyl piperazine group of the molecule improves in-vivo antibacterial activity particularly against streptococcal infections.
2.3.1.1 Brief history

Sparfloxacin represents the fourth step in the development of the quinolone antibacterial agents. The antibacterial spectrum of sparfloxacin is wider than those of the third step quinolones having limited activity against staphylococci, pneumococci, and mycoplasma. Sparfloxacin is 10-20 times more potent than ciprofloxacin, ofloxacin and lomefloxacin against common pathogens.

It is a synthetic broad spectrum antimicrobial agent for oral administration. Its empirical formula is $C_{19}H_{22}F_2N_4O_3$. It is very sparingly soluble in water like other fluoroquinolone agents. The very poor aqueous solubility and wettability of the sparfloxacin give rise to difficulties in pharmaceutical formulations of oral dosage forms and may lead to poor bioavailability. To overcome these drawbacks, increasing the aqueous solubility is an important goal and hence in the present investigation, sparfloxacin was complexed with β-CD and HPβCD's with the aim to improve its pharmaceutical properties like aqueous solubility, dissolution rate and oral bioavailability.

2.3.1.2 Sparfloxacin

<table>
<thead>
<tr>
<th>Mol. Wt.</th>
<th>392.41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. Formula</td>
<td>$C_{19}H_{22}F_2N_4O_3$</td>
</tr>
<tr>
<td>Description</td>
<td>Sparfloxacin is a yellow crystalline powder in appearance.</td>
</tr>
<tr>
<td>Solubility</td>
<td>6.7 mg/lit. Very sparingly soluble in H$_2$O, sparingly soluble in glacial acetic acid and chloroform very slightly soluble in ethanol, soluble in methanol. It dissolves in dilute acetic acid, 0.1N NaOH.</td>
</tr>
<tr>
<td>Category</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>Meltion point</td>
<td>266-269°</td>
</tr>
</tbody>
</table>
2.3.1.3 Pharmacokinetic profile

Absorption

It is slowly absorbed following oral administration with an absolute oral bioavailability of 52%. The mean maximum plasma sparflloxacin concentration following a single 400 mg oral dose was approximately 1.3 (± 0.2) μg/ml. The AUC following a single 400 mg oral dose was approximately 34 (± 6.8) μg.hr/ml.

Steady state plasma concentration was achieved on the first day by giving a loading dose that was double the daily dose.

Maximum plasma concentrations were achieved between 3 to 6 hrs following administration with a mean value of approximately 4 hrs. Oral absorption of sparflloxacin is unaffected by administration with milk or food, including high fat meals. Concurrent administration of antacids containing magnesium hydroxide and aluminium hydroxide reduces the oral bioavailability of sparflloxacin by as much as 50%.

Distribution

Upon reaching general circulation, sparflloxacin distributes well into the body as reflected by the large mean steady-state volume of distribution (Vdss) of 3.9 (± 0.8) L/kg. It exhibits low plasma protein binding in serum.

Sparflloxacin penetrates well into body fluids and tissues. Results of tissue and body fluid distribution studies demonstrated that oral administration of sparflloxacin produces sustained concentration and that sparflloxacin concentrations in lower respiratory tract tissues and fluids generally exceed the corresponding plasma concentrations. The concentration of sparflloxacin in respiratory tissues (pulmonary parenchyma, bronchial wall, and bronchial mucosa) at 2 to 6 hrs following standard oral dosing was approximately 3 to 6 times greater than the corresponding concentration in plasma. Concentrations in these tissues increase up to 24 hrs. following dosing.
**Metabolism**

Sparfloxacin is metabolized by the liver, primarily by phase II glucuronidation, to form a glucuronide conjugate. Its metabolism doesn't interfere with cytochrome – mediated oxidation.

**Excretion**

It has a long elimination half-life, 18-20 hours allowing once daily administration. The total body clearance and renal clearance of sparfloxacin were 11.4 (± 7.5) and 1.5 (± 0.5) L/hr. respectively. It is excreted in both the faeces (50%) and urine (50%). Approximately 10% of an orally administered dose is excreted in the urine as unchanged drug in patients with normal renal function.

No specific change in pharmacokinetic parameters is observed in elderly with normal renal function. The pharmacokinetics of sparfloxacin in pediatric subjects have not been studied. There are no gender differences in the pharmacokinetics of sparfloxacin. Terminal plasma elimination half life is lengthened in patients with renal impairment (creatinine clearance < 50 ml/min) at the same time the pharmacokinetics of sparfloxacin are not altered in patients with mild hepatic impairment without cholestasis.

### 2.3.1.4 Mechanism of action

Sparfloxacin is the fourth generation of the antibacterial quinolones. Due to its intensive and efficient antibacterial activity compared to the common quinolones, it has been widely used in clinical practice. It produces its effect by inhibiting the DNA gyrase enzyme and topoisomerase IV enzyme.

DNA gyrase is essential for the replication, transcription and repair of bacterial DNA and topoisomerase IV is involved in the partitioning of chromosomal DNA during cell wall division. By inhibiting these two enzymes, it keeps cellular bacterial DNA in a super coil state, thereby preventing bacterial replication.
Sparfloxacin activity is generally stable to variations of inoculum, pH and cation concentration. The activity is unchanged in the presence of 5% sodium cholate or 70% human serum.

2.3.1.5 Pharmacokinetic properties of sparfloxacin

\[ C_{\text{max}} : 1.27 \pm 0.39 \mu g/ml \]
\[ T_{\text{max}} : 4.1 \pm 1.9 \text{ hr} \]
\[ \text{AUC} : 3.5 \pm 9.7 \mu g.\text{hr/ml} \]
\[ \text{Mean residence time} : 28.5 \pm 5.7 \text{ hr.} \]
\[ \text{Half life} : 20 \pm 4 \text{ hr} \]
\[ \text{Urinary recovery} : 11% \pm 2.7\% \]

2.3.1.6 Contraindications

Sparfloxacin is contraindicated as follows.

1. It is essential to avoid exposure to the sun, bright natural light and UV rays throughout the entire duration of treatment and for 5 days after treatment is stopped due to the possibility of photosensitivity and photodermatitis.

2. In patients who are hypersensitive to fluoro-quinolone antibiotics.

3. In pregnant and lactating women

4. Concomitant use of antiarrhythmic agents or any other drugs which produce torsades de pointes is inadvisable.
2.3.1.7 Indications

Clinical situation where sparfloxacin may be used effectively and has shown promising results in respiratory tract infections including community acquired pneumonia (CAP), acute bacterial exacerbations of chronic bronchitis, acute maxillary sinusitis, mycobacterial infections in AIDS cases, leprosy, urinary tract infections, gonococcal urethritis and many complicated urinary tract infections.

2.3.1.8 Spectrum of Activity

Sparfloxacin has in vitro activity against a wide range of gram -ve and gram +ve bacteria. Quinolones differ in chemical structure and mode of action from β-lactam antibiotics. They are active against bacteria resistant to β-lactam antibiotics.

2.3.2 Past work on enhancement of dissolution and bioavailability of sparfloxacin

2.3.2.1 Chowdary K.P.R. et al.47 evaluated the pregelatinized starch as excipient for improving the dissolution rate and bioavailability of sparfloxacin. Sparfloxacin capsules were formulated employing solvent deposited systems of SPF in PGS and were evaluated for dissolution rate and bioavailability. A 21 fold increase in the dissolution rate of SPF was observed with capsule formulation containing SPF : PGS (1 : 3) SD systems. Solvent deposition has significantly enhanced the rate of absorption of SPF but the extent of absorption from the SD system remained the same as that of SPF itself.

2.3.2.2 Shirai, Y. et al.48 studied the influence of heat treatment on dissolution and masking degree of bitter taste for a novel fine granule system. They found that sparfloxacin dissolution rate from coated fine granules in water was increased by heat treatment. Dissolution percentage at 30 min in water after heat treatment at 70 DGC for more than 4 hr reached almost 100%; whereas it was poor before heat treatment. The masking degree of the bitter taste for the coated film granules was also forced to be increased by heat treatment.
2.3.2.3 Zix, J.A. et al. investigated the pharmacokinetics of sparfloxacin and its interaction with cisapride and sucralfate. The effects of cisapride and sucralfate on the pharmacokinetics of SPF were investigated. It was found that coadministration with cisapride accelerated the absorption and increased the plasma C\textsubscript{max} of SPF without having significant effect on its bioavailability. Coadministration with sucralfate resulted in a 44% decrease in the bioavailability of SPF.

2.3.2.4 Johnson, R.D. et al. studied the effects of food on the pharmacokinetics of sparfloxacin. In their study, they determined the effects of skim milk and a high-fat breakfast without milk on the pharmacokinetic characteristics of this antibiotic. They found that despite the delay in the onset of absorption, the bioavailability of SPF in the healthy male subjects was not affected by concomitant administration with skim milk or a high-fat-meal. The results suggested that sparfloxacin can be administered without regard to the ingestion of milk or meals.

2.3.2.5 Johnson, R.D. et al. studied the effect of Maalox on the oral absorption of sparfloxacin. Treatment with antacids has demonstrated a reduction in the oral absorption of many quinolones. Administration of Maalox 2 hrs before, 2 hrs after, and 4 hrs after oral administration of SPF caused mean decrease in AUC and C\textsubscript{max} with C\textsubscript{max} value unaffected with Maalox administered 4 hrs after oral administration of SPF.

2.3.2.6 Kamberi, M. et al. investigated the effect of acidification and alkalization on the pharmacokinetics of SPF in healthy subjects. Acidic and alkaline conditions were achieved by repeated oral doses of ammonium chloride and sodium bicarbonate respectively. The relative bioavailability of SPF was 84.4% and 122.3% after ammonium chloride and sodium bicarbonate treatments respectively. The alteration in the environmental pH in the gastro intestinal tract produced by the concomitant ingestion of ammonium chloride or sodium bicarbonate, influences the absorption and bioavailability of SPF.

2.3.2.7 Montay, G. et al. studied the pharmacokinetics of SPF in humans after single oral administration at doses of 200, 400, 600 and 800 mg. Each dose administration was separated by a 1-week washout period. A slight decrease of SPF bioavailability with increasing
dose was observed with increased mean $C_{\text{max}}$ and $t_{\text{max}}$ values with same doses. The metabolic ratio conjugated/free drug was not modified by increasing dose.

2.3.2.8 Ludwig M. et al. studied the tissue penetration of SPF in a rat model of experimental E.Coli epididymitis. Tissue penetration of SPF was assessed in a rat model of acute epididymitis. It is concluded that the pharmacokinetic properties of SPF (good in vitro activity, high penetration into the prostate gland, testes, infected and non-infected epididymides) make this drug a recommendable choice for the initial treatment of acute epididymitis caused by E. Coli.
2.4 Literature on nifedipine

2.4.1 Nifedipine – A profile

Nifedipine was first introduced in 1975 and has become one of the major cardiovascular drugs. Chemically nifedipine is 1,4-dihydro 2,6-dimethyl-4-(2-nitrophenyl)-pyridine-3,5-dicarboxylic acid – dimethyl ester. Its structural formula is given below.

Nifedipine

![Nifedipine structure](image)

2.4.1.1 Description

It is an yellow, odorless and tasteless crystalline powder. It is thermostable and non-hygroscopic.

2.4.1.2 Solubility

Nifedipine is freely soluble at 20°C in acetone (250 g/l), in methylene chloride (180 g/l) in chloroform (140 g/l), soluble in ethyl acetate (50 g/l), slightly soluble in methanol (26 g/l) and ethanol (17 g/l) and practically insoluble in water. Further the solubility at 37°C in buffer solutions at different pH – values is as follows.

pH 4 : 0.0058 g/l; pH 7 : 0.0056 g/l; pH 9 : 0.0078 g/l; pH 13 : 0.006 g/l.

2.4.1.3 Loss on Drying

It looses not more than 0.5% of its weight when dried at 105°C to constant weight.
2.4.1.4 Melting Point

171 – 175°C.

2.4.1.5 Dissociation Constant

This is determined with tetrabutyl ammonium hydroxide in dimethyl formamide as solvent and pKa – value (acidic) > 13 is obtained. The pKa values of calcium antagonists such as nifedipine and verapamil were measured using a potentiometric, microtitration techniques. Nifedipine is not protonated and must exert its action via the unchanged form pKa value (basic) is about 0.9 owing to the extreme low basicity of the dihydropyridine nitrogen it is not possible to obtain stable salts with acids.

2.4.1.6 Distribution Co-efficient

i. Cyclohexane – aqueous buffer solution of any pH value between 0 and 13 = 95.5

ii. Octanol-water = about 10000 : 1

2.4.1.7 Light Sensitivity

The substance is sensitive to light in solid form and extremely sensitive to light in dissolved state in solution.

2.4.1.8 Sensitivity to Temperature

Should not be stored above 25°C, should be protected from frost.

2.4.1.9 Crystal Structure

In the crystal lattice the almost flat dihydropyridine ring lies at a practically perpendicular angle to the nitro phenyl group, the ortho nitro group facing away from the dihydropyridine ring.
2.4.1.10 Ultraviolet Spectrum

The ultraviolet spectra of nifedipine were taken with a Perkin-Elmer UV - Spectrophotometer Lambda 5 at a concentration of 1.00 mg in 100 ml methanol, 0.1N HCl and 0.1N NaOH, the structure showed absorption maxima at 235 nm and around 340 nm in alkaline and acid solutions respectively.

2.4.1.11 Infrared Spectrum

The major peaks and the corresponding structural assignments are as follows.

<table>
<thead>
<tr>
<th>Frequency (cm⁻¹)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3102</td>
<td>CH-aromatic</td>
</tr>
<tr>
<td>2931, 2842</td>
<td>CH-aliphatic</td>
</tr>
<tr>
<td>1689</td>
<td>C = O ester</td>
</tr>
<tr>
<td>1625</td>
<td>-C = C- aromatic</td>
</tr>
<tr>
<td>1530</td>
<td>NO₂</td>
</tr>
<tr>
<td>1380</td>
<td>-C-CH₃</td>
</tr>
<tr>
<td>1121</td>
<td>-C-O-ester</td>
</tr>
</tbody>
</table>

2.4.1.12 Stability and Degradation

Nifedipine is relatively sensitive compound. Exposure to light, high temperature and presence of oxidizing agents yield predominantly two degradation products. Under the influence of visible and ultraviolet light nifedipine in solutions is converted to nitroso compound. In diffuse day light this process goes on gradually for hours. Nifedipine is affected by light of wavelengths below 450 nm. The photo stability of a similar compound without the nitro phenyl group is remarkably good compared to nifedipine⁷. On exposure to day light its UV visible spectrum changes quickly. Yellow colored dilute alcoholic solutions of nifedipine (0.01%) turn colorless when exposed to
daylight, whereby a new absorption maxima of nitroso compound is formed at 280 nm. Nifedipine crystals are more stable than its solutions, because the light effect is a surface phenomenon; nifedipine solutions kept at 50°C for five months remained stable under complete exclusion of light. The parameters, pH between 2 and 12 and ionic strength have no influence of the stability of nifedipine.

The decomposition velocity of nifedipine in solutions under the influence of light is remarkably high. This makes it impossible to work with the nifedipine solutions in daylight. Under constant conditions nifedipine degrades by apparent first order reaction on non-radical type with a quantum frequency of $Q = 32$. All Experimental work with nifedipine solutions should be performed under red light or yellow light or sodium lamp.

The influence of various excipients such as PVP, PEG (20), sorbitanmonolaurate, ethanol and PEG 200 has been investigated. The stability of nifedipine has been markedly increased using PVP as complexing agent. The light protective effect of whole blood is very marked, allowing only an 11% decrease in nifedipine level due to photo degradation over four hours compared to a 62% decrease in plasma and 79% decrease in aqueous solution.

2.4.1.13 Pharmacokinetics

Nifedipine is completely absorbed in gastrointestinal tract after its administration as soft capsules. Following the oral administration blood concentrations are reported to occur 30 to 120 minutes with a half-life of 2-5 hours. A comparison of the absorption rates following oral administration showed marked superiority of the sublingual administration of the gelatin capsules. In sublingual mode of administration, nifedipine is present in plasma after 5 to 10 minutes. Independent of the type of enteral administration a total of 90% of the administered quantity is absorbed. The maximum plasma concentrations are reached between 60 to 120 minutes in the case of sublingual mode of administration, in case of sustained release preparations maximum plasma concentrations are obtained between 2 to 4 hours and therapeutic levels of about 11 ng/ml and present still after 12 hours.
Nifedipine undergoes first pass effect to the extent of 30 to 40% of the absorbed dose. It is reported to have a short biological half-life of 2 to 5 hours\textsuperscript{11}. Nifedipine is highly bound to proteins and is neutral compound of neither strongly lipophilic nor hydrophilic character.

2.4.1.14 Actions and uses

Nifedipine is a calcium channel-blocking agent also known as calcium antagonist it inhibits the cellular influx of calcium. Calcium channel blocker primarily effect tissues in which depolarization is dependent upon calcium and this effect is observed in vascular smooth muscle, myocardial cells, arterioventricular nodes among other cells. Administration of nifedipine results in vasodilatation with reduced peripheral resistance, blood pressure, increased coronary blood flow and a reflex increase in heart rate. This in turn results in an increase in myocardial oxygen supply and cardiac output.

Nifedipine is used in the treatment and prophylaxis of angina pectoris both stable and variant in the management of hypertension and in the treatment of Raynaud’s syndrome. Sustained release nifedipine formulations are used to reduce frequency of ischaemic episodes in patients with silent myocardial ischaemia.

2.4.1.16 Adverse effects

The most common adverse effects of nifedipine are associated with the vasodilatory action, such as dizziness, flushing, headache, hypotension and peripheral oedema. There are a few reports of abnormalities in liver function due to hypersensitivity reactions and gingival hyperplasia has been reported, gastrointestinal symptoms and lower leg oedema are also reported.

2.4.1.16 Preparations

Nifedipine Extended release tablets 10 mg and 20 mg are official in USP XXIV. A dissolution test is specified for Nifedipine Extended Release Tablets in USP XXIV\textsuperscript{12} under the following conditions.

Medium : Phosphate buffer of pH 6.8 containing 1% SLS (900 ml)
Apparatus: Paddle type

Speed: 50 rpm

Time: 3, 6, 12 hours

2.4.1.17 Tolerance: The percentage of the labelled amounts of nifedipine released and dissolved at the times specified confirm to

<table>
<thead>
<tr>
<th>Time (Hrs)</th>
<th>Amount dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>between 10% and 30%</td>
</tr>
<tr>
<td>6</td>
<td>between 40% and 65%</td>
</tr>
<tr>
<td>12</td>
<td>not less than 80%</td>
</tr>
</tbody>
</table>
2.6 Literature on nimodipine

2.6.1 Nimodipine - A profile

Nimodipine

\[
\begin{align*}
\text{Chemical Formula} & : \quad \text{C}_{21}\text{H}_{36}\text{N}_{2}\text{O}_{7} \\
\text{Molecular Weight} & : \quad 418.5 \\
\text{Category} & : \quad \text{Calcium channel blocking agent}
\end{align*}
\]

2.6.1.1 Properties

Nimodipine is one of the major cardiovascular drugs. Chemically, it is 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl) pyridine-3,5-dicarboxylic acid 2-methoxy ethyl 1-methyl ethyl ester.

Melting point : 125°C

2.6.1.2 Light sensitivity

The substance is sensitive to light in solid form and extremely sensitive to light in dissolved state in solution.

2.6.1.3 Description

It is an yellow, odorless and tasteless crystalline powder and shows polymorphism.
2.5.1.4 Solubility

It is practically insoluble in water. Its aqueous solubility is 0.23 mg/100 ml. It is freely soluble in ethyl acetate, sparingly soluble in ethanol.

2.5.1.5 Actions

This dihydropyridine derivative inhibits the voltage and receptor-operated channels of vascular smooth muscle. It preferentially relaxes the cerebral vasculature especially when 5-hydroxytryptamine is used as an agonist to constrict isolated blood vessels. It has a more pronounced effect than other calcium channel blocking agents on cerebral blood vessels. In healthy subjects and in patients with ischemic stroke, nimodipine increases cerebral blood flow without affecting the systolic and diastolic pressure and heart rate.

2.5.1.6 Uses

Several uncontrolled and controlled studies on the use of nimodipine in patients with subarachnoid hemorrhage have been performed. The results were variable (drug evaluation 1995, p. 594).

2.5.1.7 Adverse reactions and precautions

Nimodipine has been well tolerated by patients with subarachnoid hemorrhage. Hypotension is the most prevalent adverse effect.

Following i.v. administration, elevated serum concentrations of γ-glutamyl transferase and transaminase enzymes were reported in a number of studies. These returned to normal at the end of the treatment period and did not require early withdrawal of nimodipine. The mechanism underlying the rise in serum level of liver enzymes is not clear.
2.5.1.8 Pharmacokinetics

Absorption and fate

Nimodipine is slowly absorbed from the gastrointestinal tract following oral administration. The oral bioavailability is reported to be about 13%. It readily crosses the blood brain barrier. Nimodipine is extensively metabolized in the liver. It is excreted in faeces via the bile and in urine almost entirely as metabolites. The terminal elimination half-life is reported to be as long as 9 hrs but the initial decline in plasma concentrations is very much more rapid, equivalent to a half-life of 1 to 2 hrs. Nimodipine is about 95% bound to plasma protein.

Bioavailability (%) : 13
Half-life (hrs) : 5
Protein binding (%) : 95
Volume of distribution (l/kg): 0.9 – 2.3
Urinary excretion of unchanged drug (%) : 0.1
Active metabolites : --

2.5.1.9 Dosage and preparations

Oral

For subarachnoid hemorrhage, oral administration should be started as soon as possible: 60 mg is given every four hours for 21 consecutive days. Alternatively, the contents of the capsule can be aspirated into a syringe and emptied into a nasogastric tube, followed by washing with 30 ml of normal saline (0.9%); for patients with hepatic cirrhosis, the dosage is reduced by 50% and the blood pressure and heart rate are monitored closely.

Nimotop capsules : 30 mg
2.5.2 Past work on controlled release and enhancement of bioavailability of nimodipine

2.5.2.1 Lu, FQ et al.\textsuperscript{56} investigated the effects of chitosan alginate microcapsules on controlled release of nimodipine. The preparation and release characteristics of nimodipine microcapsule formulations prepared with chitosan and alginic acid are reported. Results showed that the chitosan-alginate microcapsules could sustain release of nimodipine.

2.5.2.2 Fuhr, U. et al.\textsuperscript{58} studied the effect of grape fruit juice on the oral bioavailability of nimodipine. To assess the effects of grape fruit juice on the pharmacokinetics of nimodipine and its metabolites, a randomized, crossover study was conducted in 8 healthy men, ages 23-29 year, who received a single 30 mg nimodipine (nimotop) tablet with either 250 ml water or 250 ml grape fruit juice. By the results obtained it was concluded that nimodipine should not be taken with grape fruit juice.

2.5.2.3 Li, XF et al.\textsuperscript{57} performed a study on relative bioavailability of nimodipine tablets. The relative bioavailability of 2 different brand name preparations of tablets of nimodipine was studied in 10 healthy volunteers. Drug concentration was measured in plasma, the results showed that there were no significant differences between the pharmacokinetic parameters of both brand name preparations of nimodipine.

2.5.2.4 Yan, XF et al.\textsuperscript{59} carried out the studies on the bioavailability and pharmacokinetics of nimodipine tablets in the human body. To compare the pharmacokinetics and bioavailability of 2 nimodipine tablets, 6 healthy volunteers received a single oral dose of one of the formulations, pharmacokinetics were compared with a reference solution. Results indicated that the bioavailability of the tablet were 16.01 and 82.39% compared to the reference.

2.5.2.5 Chowdary, K.P.R. et al.\textsuperscript{60} performed the work on solid dispersions of nimodipine and its physico-chemical and dissolution rate studies. To improve the dissolution rate and efficiency of nimodipine by solid dispersion in individual and combined carriers and to study the physiochemical nature of the dispersions, solid dispersions of nimodipine in povidone, HPMC, PEG
6000, and cellulose microcrystalline (Avicel) were prepared and evaluated for content uniformity, drug-carrier interactions, dissolution rate and efficiency. A marked increase in the dissolution rate and efficiency of nimodipine was observed with all solid dispersions. Solid dispersions in combined carriers gave much higher improvement in the dissolution rate and efficiency than was possible with individual carriers. Among the carriers studied, they found that cellulose microcrystalline – povidone combination gave the highest improvement in dissolution rate and efficiency of nimodipine.

2.5.2.6 Lu, JW et al. studied about the preparation and dissolution of nimodipine – PEG solid dispersion. For this nimodipine – polyethylene glycol solid dispersion was prepared by the melting method and evaluated. The formation of a eutectic mixture between drug and carrier was demonstrated by DSC and dissolution studies. They found that the dissolution rate of the solid dispersion was greater than that of pure drug.

2.5.2.7 Lu, W. Sun, YC et al. developed a dissolution model for slightly soluble drugs. A simple and practical kinetic dissolution model developed for interpretation of the dissolved/time plots derived from the in vitro testing of conventional solid preparations of nimodipine is described. A model was developed that consisted of 3 drug states namely the solid preparation, the fine particles and the dissolved solution. The dissolution curves were well fitted and it was evident that the values of the parameters in this model can reflect the characteristics of the preparation.
REFERENCES


