CHAPTER – 3

LITERATURE REVIEW
3.1 OVERVIEW

Currently available anti-HIV agents have so many drawbacks such as relatively short half life, suffers from significant first pass effect, variation in absorption and poor or low bioavailability due to poor solubility, poor CNS penetration and retention, degradation in the GIT due to enzymes and extreme pH conditions and undesirable side effects. For example, the oral bioavailability of NNRTIs is restricted due to their low aqueous solubility. The development of a successful formulation is dependent on the physicochemical and physico-technical properties of the active pharmaceutical ingredient (API), which has a direct impact on the manufacturing processes, stability, and bioavailability of the final drug product.98

Most of the anti-HIV drugs belongs to BCS Class II and suffer from poor aqueous solubility and consequently low bioavailability. Thus the variability in bioavailability of ARVs may be a significant factor in the failure of some of the drug regimens and also lead to formulation difficulties.99,100 It is for this reason various attempts have been initiated in order to overcome the drawbacks associated with the formulation of effective dosage form of ARVs in treating the AIDS. Numerous researchers around the globe have carried out extensive research work on SDs as well as inclusion complexes with CDs. Both techniques have attracted considerable interest as a means of improving the dissolution rate, and hence bioavailability of wide range of hydrophobic drugs.101-103
Solubility enhancement is part of strategies to improve the oral bioavailability especially for BCS Class II drugs. It is reported that magnificent increase in bioavailability (up to 600%) by using SDs and inclusion complexation is confirmed in many in vivo studies.\(^{104-108}\)

### 3.2 PAST RESEARCH WORK ON SDs

Jafari MR et al.\(^{109}\) examined the feasibility of preparing fast-release SDs of miconazole nitrate (MN), using three different water-soluble excipients such as PEG-6000, PVP 10,000 and urea. SDs of miconazole was prepared by fusion or co-precipitation from ethanol. Solubilization and wetting of the drug, both favoured PEG and urea over PVP in promoting the dissolution of MN. Accordingly, a 7-fold increase in the dissolution rate of MN was achieved with both PEG and urea, while the dispersion of MN in PVP resulted in only a two-fold enhancement.

Chowdary KPR and Ramesh VRNS\(^{110}\) investigated the SDs of nifedipine in combined carriers, PVP-MCC and HPC-MCC which markedly enhanced the dissolution rate and efficiency of nifedipine. About, 30-37 fold increase in the dissolution rate was observed with SDs. The enhanced dissolution rate was attributed to (i) the conversion of nifedipine into amorphous form and (ii) the enhancing effect of PVP and HPC on the solubility of nifedipine. The results revealed that dissolution of nifedipine from SDs obeyed Hixson-Crowell's cube root dissolution rate equation.
Arias MJ et al\textsuperscript{111} prepared triamterene SD system with D-mannitol employing spray-drying and melting carrier method and studied by SEM, XRD and DSC. All these studies showed a strong drug-carrier interaction existed in the SDs. In contrast, SDs prepared by the melting carrier method showed only weak interactions between triamterene and D-mannitol. This observation helped to explain the much better dissolution rates obtained for the spray-dried outputs. The results indicated that dissolution rates were much better from spray-dried products, which could attributed to decrease in particle size and partial amorphization.

Chutimaworapan S et al\textsuperscript{112} prepared SDs of nifedipine with polyethylene glycols (PEG 4000 and PEG 6000), HPβCD, and poloxamer 407 (PXM 407) in four mixing ratio by melting, solvent, and kneading methods in order to improve the dissolution of NP. The enhancement of the dissolution rate and the time for 80\% NP dissolution (T\textsubscript{80\%}) depended on the mixing ratio and the preparation method. The highest dissolution rate and the T\textsubscript{80\%} as short as 15 min were obtained from PXM 407 SDs prepared by the melting method at the mixing ratio of 1:10.

Ozkan Y et al\textsuperscript{113} examined the release of etodolac from various molecular weight fractions of PEG SDs. Etodolac SDs were prepared in different molar ratio of drug/carrier by using solvent and melting methods. The release rate of etodolac from the resulting complexes was determined from dissolution studies by use of USP dissolution
apparatus 2 (paddle method). The physical state and drug:PEG interaction of SDs and PMs were characterized by XRD, IR and DSC. The dissolution rate of etodolac was increased in all of the SDs compared to that of the pure drug and PMs. The SDs prepared in the molar ratio of 1:5 by the solvent method was found to have the fastest dissolution profile.

Choi HK et al\textsuperscript{114} prepared felodipine SDs using PVP, HPMC and poloxamer by solvent wetting method. The dissolution rates of felodipine in PVP, HPMC, or poloxamer SDs were much faster than the corresponding PMs and pure drug. However, dissolution profiles were found to depend on the carrier used, the dissolution rate of felodipine increased slowly for SDs prepared using HPMC, whereas rapid initial dissolution rates were observed for SDs prepared using PVP and poloxamer. It was found that the increase in dissolution rates were partly dependent on the ratio of felodipine to carrier.

Ahuja N et al\textsuperscript{115} investigated various water-soluble carriers for dissolution enhancement of rofecoxib, using solid dispersion approach. Polyethylene glycols (PEG 4000 and 6000), polyglycolized fatty acid ester (Gelucire 44/14), polyvinylpyrrolidone K25 (PVP), poloxamers, polyols (mannitol, sorbitol), organic acid (citric acid) and hydrotropes (urea, nicotinamide) were used for the purpose. Phase-solubility studies revealed A\textsubscript{L} type of curves for each carrier, indicating linear increase in drug solubility with carrier concentration. All the SDs investigated in the study enhanced the solubility and dissolution
characteristics of drug to varying degrees, as a function of carrier concentration. Solid state characterization of the drug-poloxamer binary system using XRD, FTIR, DSC and SEM techniques revealed distinct loss of drug crystallinity in the formulation, accounting for enhancement in dissolution rate.

Moneghini M et al\textsuperscript{116} prepared solvent-free SDs, employing microwave technology for the poorly soluble drug Ibuprofen (IBU) using hydrophilic carriers like PVP/VA 60/40 and HP\(\beta\)CD. The physico-chemical characteristics and dissolution properties of SDs were compared with the corresponding PMs and the drug alone. The results showed that remarkable enhancement of the \textit{in vitro} dissolution rate of the drug suggesting that the microwave technique could be considered as a new and interesting method to prepare SDs.

Shah J et al\textsuperscript{117} prepared and investigated valdecoxib SDs with the objective of dissolution enhancement by melt granulation technique using PVP K30 and PEG 4000 alone (1:1) and in combination (1:0.5:0.5). Phase solubility studies showed a linear increase in valdecoxib solubility with increase in polymer concentration in both the cases. The FTIR studies showed absence of well defined valdecoxib and polymer interaction. PXRD and DSC studies indicated a complete transformation of drug from crystalline to amorphous form. \textit{In vitro} dissolution studies performed in 0.1N HCl showed a significant enhancement in dissolution rate when PEG 4000 and PVP K30 were used in combination.
Joe JH et al\textsuperscript{118} prepared and investigated three SDs containing poorly water-soluble tacrolimus were with HP\textbeta CD and dioctyl sulfosuccinate (DOSS) using a spray drying technique, solvent wetting method with ethanol and the surface-attached method with water. Their physicochemical properties were investigated using SEM, DSC and PXRD. The solubility and dissolution of the drug were significantly improved in the order of the tacrolimus loaded SDs prepared by: solvent evaporation method > solvent wetting method > surface attached method. Among the SDs tested, the SD prepared by the solvent evaporation method gave the highest solubility and dissolution.

Khattab IS and co-workers\textsuperscript{119}, investigated the SDs of gliclazide with different molecular weights of PEG 4000, 10,000, and 20,000 using different drug:carrier weight ratio (1:1, 1:2, 1:5, and 1:10). The solid-state interaction between the drug and the carrier was examined by DSC and FT-IR studies. It was evident from phase solubility studies that the drug solubility increased linearly with increasing PEG concentrations. The results confirmed that \textit{in vitro} dissolution of gliclazide improved significantly in the SDs prepared by fusion method as compared with the original drug and PMs.
3.3 PAST RESEARCH WORK ON CD INCLUSION COMPLEXATION

The natural and chemically modified cyclodextrins (CDs) have been extensively utilized for complexation with wide category of poorly soluble drugs by many scientists to improve drug bioavailability due to increased solubility, and also to improve rate and extent of drug dissolution\textsuperscript{120-122}. 

Kedzierewicz et al\textsuperscript{123} studied the inclusion complex of tolbutamide with βCD. Comparison of the complex was carried out with PEG 6000 SDs prepared by either the co-melting or co-precipitation method, using XRD, FT-IR and DSC. The results revealed that drug dissolution rate was faster from inclusion complexes compared to SDs and drug alone.

Ahmed SM et al\textsuperscript{124} prepared inclusion complex of bropirimine with βCD and SDs with PEG 6000 by co-precipitation method. \textsuperscript{1}H-NMR was employed to confirm the inclusion of the drug within the βCD cavity. Comparative dissolution studies revealed that the solid complex exhibited a markedly faster dissolution rate compared to the PEG 6000 SDs and corresponding PMs in water and phosphate buffer (pH 7.4) in 0.1N HCl.

Guyot et al\textsuperscript{125} investigated inclusion complexes with βCD and HPβCD (freeze drying) and also SDs with PEG 6000 (fusion method) to improve the solubility and dissolution rate of norfloxacin. FT-IR, XRD, and DSC studies showed differences between norfloxacin/CD
complexes and their corresponding PMs, but not between norfloxacin/PEG 6000 SDs and corresponding PMs. However, the results of the dissolution study showed that norfloxacin/CD complexes and norfloxacin/PEG SDs had a faster dissolution rate than norfloxacin itself.

Ozkan Y and co-workers\textsuperscript{126}, studied inclusion complexes of gliclazide with βCD using neutralization and re-crystallization method. Host–guest interactions were studied in the solid state by XRD and IR spectroscopy. Authors observed that dissolution rates of gliclazide from the inclusion complex made by neutralization were much faster than the re-crystallization system, corresponding physical mixtures and pure drug.

Veiga et al\textsuperscript{127} prepared the tolbutamide (TBM) and βCD inclusion complexes by kneading, co-precipitation, freeze drying and spray drying method. They studied the influence of preparation method on physicochemical properties of solid binary systems. The phase solubility studies revealed a $B_5$-type diagram with an inclusion complex of 1:2M. Characterization of inclusion complexes was performed using DSC, Raman spectroscopy, and XRD and by application of so-called ether washes method. The authors found that inclusion systems investigated led to a significant improvement in the dissolution rate over free TBM. Further the result showed that dissolution rate of the drug was found to be independent of the preparation method.
Pose-Vilarnovo B et al\textsuperscript{128} attempted to increase the solubility of sulfamethizole in water by complexing it with βCD and HPβCD by freeze drying (1:1M). NMR studies showed that stoichiometry was 1:1 for the sulfamethizole–βCD complex and 2:3 for the sulfamethizole–HPβCD complex. In both cases the sulfamethizole moiety included in the cyclodextrin was the thiadiazole group. Their experimental results revealed that the dissolution rates of sulfamethizole increased by complexation with βCD or HPβCD.

Mura P et al\textsuperscript{129} studied the combined effect of HPβCD and PVP on the solubility of naproxen (NAP). Phase solubility analysis at different temperatures was used to investigate interactions in aqueous solution between NAP and the carriers, either alone or in combination. Equimolar NAP–HPβCD solid systems, in the presence or the absence of 15% (w/w) PVP, were prepared by co-grinding, kneading, coevaporation or freeze drying and characterized by DSC, XRD, IR and dissolution rates. The combined use of PVP and HPβCD resulted in a synergistic increasing effect of the aqueous solubility of NAP (120 times that of the pure drug). The positive effect of PVP also reflected on NAP dissolution rates from solid preparations, because all ternary systems, with the exception of PMs, dissolved faster than the corresponding NAP–HPβCD binary systems.

Fernandes CM et al\textsuperscript{130} studied inclusion complexation between nicardipine hydrochloride with βCD or HPβCD. Stability constants (K) calculated from the phase solubility diagrams were found to be pH
dependent. More stable drug:CDs complexes were formed in alkaline medium in which the drug is in its non-ionized form. Binary systems prepared by kneading, evaporation, freeze-drying and spray-drying were investigated by DSC, FT-IR, XRD and SEM analysis. Inclusion complexes were found produce by evaporation, freeze-drying and spray-drying method. In contrast, kneading method did not originate true inclusion complexes. Both the preparation method and nature of carrier played an important role in the dissolution performance of the system. However, the results showed that complexes obtained with HPβCD were more effective in achieving the enhancement of the drug dissolution rate than the corresponding ones with βCD.

Peeters J and co-workers\textsuperscript{131}, investigated the complexation behaviour of HPβCD using itraconazole at pH 2, 4 and 7. They used phase solubility technique to assess the effect of pH on itraconazole complexation. They found that complexation of drug with the HPβCD was dependent on the CD/drug ratio as well as the pH of the system. It was found that at pH 2, 1:2 complex formation was observed whereas at pH 4 and at pH 7, 1:3 complexation occurred.

Archontaki HA et al\textsuperscript{132} studied soluble enhancement of water insoluble bromazepam during the formation of its inclusion complexes with βCD and HPβCD. They used phase solubility technique and UV spectrophotometric methods to measure the changes introduced in this chemical system. Their studies found that solubility of
bromazepam increased linearly as a function of concentration for both \( \beta \)CD and HP\( \beta \)CD.

Wong JW and Yuen KH\(^{133}\) investigated the inclusion complexation of artemisinin (ART) with natural CDs, namely \( \alpha \), \( \beta \), and \( \gamma \)-CDs with the aim of improving its solubility and dissolution rate. Complex formation in aqueous solution and solid state was studied by solubility analysis, dissolution, and thermal analysis. Solubility diagrams indicated that the complexation of ART and the three CDs at 1:1M showed a remarkable increase in ART solubility. Complexation capability of CDs with ART increased in the order of \( \alpha \)-CD \(<\gamma\)-CD \(<\beta\)-CDs and could be ascribed to the structural compatibility between the molecular size of ART and the diameter of the CD cavities. Dissolution profiles of the three complexes demonstrated an increased rate and extent of dissolution compared with those of their respective physical mixtures and a commercial preparation.

Buchi Naidu et al\(^{134}\) prepared meloxicam–cyclodextrin (using \( \alpha \), \( \beta \) and \( \gamma \)-CD) binary systems by kneading method and co-evaporation method to improve the dissolution properties of drug. Detection of inclusion complexation was done in solution state by means of phase solubility analysis, mass spectrometry and \(^1\)H NMR studies. And these studies revealed 1:1M complexation of meloxicam with all CDs. A true inclusion of drug \( \gamma \)-CD was confirmed by DSC, powder XRD and SEM studies. \textit{In vitro} dissolution studies showed improved dissolution rate in all binary systems compared to pure drug.
Saetern AM and his research group\textsuperscript{135} studied the effect of HPβCD complexation and therapeutically relevant pH values (pH 5.5–7.0) on solubility of camptothecin (CTP). The authors reported that solubility of CPT was increased with both increasing pH as well as increase in HPβCD concentration indicating the formation of a 1:1 complex. Further they found that, the apparent complexation constant ($K_C$) was decreased with increasing pH ($245M^{-1}$ at pH 5.5; $184M^{-1}$ at pH 7.0).

Rawata S and Jain SK\textsuperscript{136}, observed the formation of the inclusion complex of celecoxib with βCD both in aqueous and in solid state which was confirmed by phase solubility, spectral shift and DSC studies. It was also observed that the complexes exhibit higher dissolution rates than the pure drug and physical mixture.

Wen X et al\textsuperscript{137} prepared the inclusion complex of βCD with carvedilol using a convenient new method of microwave irradiation. They used phase solubility studies to demonstrate the ability of βCD to complex with carvedilol and increase drug solubility. The structure of inclusion complex was determined by fluorescence spectroscopy and $^1$H-NMR, $^{13}$C-NMR measurement in solution further solid inclusion complex was characterized by IR, differential spectroscopy and element analysis. Their experimental results confirmed the existence of 1:2 inclusion complex of carvedilol with βCD.

Pralhad T and co workers\textsuperscript{138}, studied the inclusion behaviour of HPβCD and βCD with poorly water soluble bioflavonoid, quercetin in
solution and solid-state. They prepared drug:CD solid systems by freeze drying. Phase solubility study was used to evaluate the complexation in solution of βCD and HPβCD and the formation of inclusion complexes with βCD and HPβCD in the solid state were confirmed by IR spectroscopy, DSC, XRD, and SEM.

Ruan LP et al\textsuperscript{139} aimed to increase the solubility of ampelopsin (AMP) in water by two systems: SDs with PEG 6000 or PVP K30 and inclusion complexes with βCD and HPβCD. All preparations were evaluated by DSC, FTIR, SEM studies. The influence of various factors (pH, temperature, type of polymer, ration of the drug to polymer) on the solubility and dissolution rate of the drug were evaluated. Results revealed that solubility and dissolution rates of AMP were significantly increased and it was found that improvement of solubility using different polymers was in the following order: HPβCD ≈ βCD > PVP K30 > PEG 6000.

Chowdary KPR and Srinivas SV\textsuperscript{140} studied the complexation of celecoxib with hydroxypropyl β-cyclodextrin (HPβCD) in the presence and absence of 3 hydrophilic polymers PVP, HPMC, and PEG with an objective of evaluating the effect of hydrophilic polymers on the HPβCD complexes. The phase solubility studies indicated the formation of celecoxib-HPβCD inclusion complexes at a 1:1M ratio in solution in both the presence and the absence of hydrophilic polymers. Addition of hydrophilic polymers markedly enhanced the complexation and solubilizing efficiencies of HPβCD. Solid inclusion
complexes of celecoxib-HPβCD were prepared in 1:1 and 1:2 ratio by the kneading method, with and without the addition of hydrophilic polymers. The solubility and dissolution rate of celecoxib were significantly improved by complexation with HPβCD. The addition of hydrophilic polymers markedly enhanced the dissolution rate of celecoxib from HPβCD complexes. DSC and XRD studies indicated that stronger drug amorphization and entrapment in HPβCD because of the combined action of HPβCD and the hydrophilic polymers.

Al Omari MM and co-workers\textsuperscript{141}, studied guest–host interactions of ibuprofen tromethamine salt with native and modified CDs using several techniques, namely phase solubility diagrams \textsuperscript{1}H NMR, DSC, FT-IR, XRPD, SEM and molecular mechanics (MM). All data obtained from the above studies confirmed the ibuprofen tromethamine salt/βCD inclusion complex formation in solution as well as in the solid state.

Nicolescu C et al\textsuperscript{142} studied the inclusion complexes between repaglinide βCD, HPβCD and randomly methylated-β cyclodextrin (RAMEB)) to enhance the drug solubility. The inclusion complexes were prepared by lyophilisation, co-precipitation and kneading method and characterized by means of \textsuperscript{1}H-NMR, \textsuperscript{13}C-NMR, DSC and FT-IR. The results obtained confirmed the inclusion of repaglinide into the cyclodextrins cavity.
3.4 PAST RESEARCH WORK ON ANTIRETROVIRAL SDs

Damian F et al\textsuperscript{143,144} prepared and characterized the SDs (fusion method) of the antiviral thiocarboxanilide UC-781 with PEG 6000, Gelucire 44/14 and PVP K30 as hydrophilic carriers to improve its dissolution properties. The rate of dissolution of UC-781 was considerably improved when formulated in SDs with PEG 6000, Gelucire 44/14 and PVP K30 as compared to pure UC-781. XRD and DSC confirmed that UC-781 formed a molecular dispersion when formulated with PVP K30. Further, the results from IR together with those from XRD and DSC showed the absence of well-defined drug-polymer interactions.

Law D et al\textsuperscript{145} studied physicochemical considerations in the preparation of amorphous ritonavir-PEG 8000 SDs. The prepared ritonavir SDs in PEG revealed that amorphous ritonavir SDs in PEG showed significant improvement of \textit{in vitro} dissolution profile and also could exhibit long-term stability ( \textgreater 1.5 years at 25°C when protected from moisture).

In the next phase, Law D and his co-workers\textsuperscript{146}, prepared PEG-amorphous ritonavir SDs with different drug loadings, and performed \textit{in vitro} (in 0.1N HCl) and \textit{in vivo} evaluation. A crossover design was used to evaluate the oral bioavailability of amorphous dispersions relative to crystalline drug in beagle dogs. Intrinsic dissolution measurements of the two solid phases indicated a 10-fold
improvement in intrinsic dissolution rate for amorphous ritonavir compared with the crystalline counterpart. In vivo study results indicated that amorphous SDs containing 10-30% drug exhibited significant increases in area under the curve (AUC) of concentration versus time and maximum concentration (C_{max}) over crystalline drug.

Van den Mooter G and Goddeeris C\textsuperscript{147}, investigated SDs and PMs of poorly water-soluble drug UC 781 (thiocarboxanilide, NNRTI) using Poloxamer 407 and d-alpha-tocopheryl polyethylene glycol succinate 1000 (TPGS 1000) by spray drying. Pure drugs, PMs and SDs were characterized by DSC and XRD. The study revealed that drug release was markedly increased when formulated as a SD with Poloxamer 407 and TPGS 1000 and also variability in dissolution rates was considerably reduced upon SD formulation.

Mohammed GA et al\textsuperscript{148} co-processed two active pharmaceutical ingredients (APIs), nevirapine (NVP) and stavudine (STV), by spray drying technique to overcome the respective problems of poor solubility and poor content uniformity. The co-processed product (NVP-STV CP) and untreated APIs were characterized by PXRD, DSC, SEM, particle size, surface area analysis, compressibility, and solubility. Co-processing enhanced NVP solubility by 1.5 fold over that of the pure NVP and STV demonstrated content uniformity in the powder blend. The co-processed product was then formulated into 3 drug fixed dose combination (FDC) tablets with lamivudine (LMV),
which gave an enhanced in vitro NVP drug release compared with the control formulation to assure a quality antiretroviral formulation.

Goddeeris C et al\textsuperscript{149} studied to improve the dissolution properties of the anti-HIV drug UC 781 by preparing ternary SDs consisting of a high amount of d-alpha-tocopheryl polyethylene glycol succinate (TPGS 1000). Eudragit E100 was selected as a polymer based on supersaturation studies. DSC analysis of SDs revealed eutectic phase behaviour of the ternary TPGS 100–Eudragit E100–UC 781 mixture. The release of UC 781 in a medium simulating the gastrointestinal lumen was markedly enhanced, reaching a release of 70% w/w after 4 h. XRD results pointed to the presence of crystalline drug in the solid dispersion. NMR experiments revealed that several carbon atoms of the aromatic ring and free methyl groups of UC 781 experienced shielding and/or deshielding upon exposure to the carrier.

Sanganwar GP et al\textsuperscript{150} prepared and studied the microparticles of a poorly water-soluble model drug, nevirapine (NEV) by supercritical anti-solvent (SAS) method and simultaneously deposited on the surface of excipients such as lactose and microcrystalline cellulose in a single step to reduce drug–drug particle aggregation. Drug/excipient mixtures were characterized for surface morphology, crystallinity, physico-chemical interactions, and molecular state of drug. Further, the drug content uniformity and dissolution rates were determined. The authors reported that obtained drug/excipient mixture exhibited
significantly faster dissolution rate as compared to SAS drug microparticles alone or when physically mixed with the excipients.

Ahire BR et al\textsuperscript{151} prepared and investigated nevirapine SDs using polyvinylpyrrolidone K 30 (PVP K 30) as carrier to improve solubility of model drug. The SDs prepared by solvent evaporation and kneading method was investigated by FT-IR, DSC and XRD. The results from the FTIR and XRD analyses showed that SD might exist in the amorphous form. A DSC result showed that the nevirapine was molecularly dispersed in an amorphous form. Saturation solubility and dissolution studies indicated that dissolution rate was remarkably increased in SDs as compared to the physical mixture and drug alone.

3.5 \textbf{PAST RESEARCH WORK ON ANTIRETROVIRAL INCLUSION COMPLEXATION}

Ahmed SM et al\textsuperscript{152} prepared inclusion complex of bropirimine (ABPP) with $\beta$CD and SDs with PEG 6000 by co-precipitation method. $^1$H-NMR was employed to confirm the inclusion of the drug within the $\beta$CD cavity. Comparative dissolution studies shown that the solid complex exhibited a markedly faster dissolution rate compared to the PEG 6000 SDs and corresponding physical mixtures in water and phosphate buffer (pH 7.4) in 0.1N HCl.

Echezarreta-Lopez M et al\textsuperscript{153} studied the complexation of interferon inducer bropirimine with several CD derivatives like $\alpha$, $\beta$, $\gamma$ and
HPβCD with a degree of substitution 2.7 and the effect of the complexation process on the water solubility of the drug was evaluated. The best results were obtained with the HPβCD (1:1M). The inclusion complex ABPP:HPβCD was characterized in solution by ¹H NMR studies. The solid inclusion complex obtained by freeze-drying was characterized by DSC, XRD and mass spectrometry. The results indicated that the complexation of ABPP with HPβCD enhanced solubility and the dissolution rate of the drug in aqueous media and could be used to develop new oral formulations which improves the bioavailability of the model drug.

Boudad and his coworkers¹⁵⁴ prepared HPβCD and saquinavir inclusion complex to improve the solubility of saquinavir in water. At a concentration of 10%, cyclodextrin increased the apparent solubility to 15.8 and 9.3 mg/ml at pH values of 7.0 and 2.0, respectively.

Buchanan CM et al¹⁵⁵ extensively investigated to solubilize saquinavir free base and mesylate salt (a more soluble derivative, intrinsic solubility 2.1 mg/ml) with the HPβCD. Solubility levels increased to 6–12 and 3.8–12 mg/ml for the free base and the salt, respectively, with 10% CD. Then, an increase in the concentration of CD resulted in a gradual increase in solubility. Dissolution studies indicated that 95–100% complexed saquinavir dissolved within 30 min in a 1.2–6.8 pH range.
Yang H and co-workers\textsuperscript{156}, have examined the ability of several classes of CDs, βCD, methyl-β-cyclodextrin (MβCD) and 2-HPβCD, to enhance the aqueous solubility of UC781 (anti HIV, NNRTI). They evaluated inhibitory potency of UC781 and its HPβCD inclusion complex using an \textit{in vitro} HIV-1 reverse transcriptase inhibition assay. The inhibitory potency of the complex was found to be 30-fold greater than that of UC781 alone. Complexations of the drug within the nanocarrier were found to enhance the aqueous solubility significantly and thus the inhibitory potential of the drug, which is essential for the development of a useful vaginal microbicide drug delivery system.

Sathigar S and his research group\textsuperscript{157}, prepared different efavirenz inclusion complexes with βCD, HPβCD, and randomly methylated βCD (RMβCD) by kneading and freeze-drying method aiming to improve the drug solubility and dissolution rate. \textit{In vitro} dissolution studies showed a slight increase in solubility in PMs due to the higher wettability of the drug. Kneaded and freeze-dried HPβCD and RMβCD complexes showed the highest dissolution extents compared to βCD complexes.

Pathak SM et al\textsuperscript{158} prepared saquinavir inclusion complexes with Methyl βCD (MβCD) and subjected for \textit{in vitro} and \textit{in vivo} evaluation. Their result suggests that MβCD is particularly useful in designing oral preparations of saquinavir with an enhanced bioavailability and a reduced variability in absorption due to improved solubility of the drug.