FORMULATION DEVELOPMENT OF BCS CLASS II DRUGS
EMPLOYING CYCLODEXTRIN COMPLEXATION – A REVIEW OF
RECENT RESEARCH

K. P. R. Chowdary* and M. Gowthami

Vikas Institute of Pharmaceutical Sciences, Nidigatla Road, Rajahmundry- 533103.

ABSTRACT

BCS class II drugs pose challenging problems in their pharmaceutical product development process because of their low solubility and dissolution rates. They require enhancement in solubility and dissolution rate in their formulation development especially solid dosage forms such as tablets and capsules. Several conventional methods and new emerging technologies have been developed for formulation development of BCS class II drugs. These methods and literature on cyclodextrin complexation along with recent research work on cyclodextrin complexation is reviewed in this article.

KEYWORDS: BCS class II drugs, Formulation development, Cyclodextrin complexation, Recent research.

INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility and dissolution rate of drug molecules. Solubility and dissolution rate are the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The Biopharmaceutical Classification System (BCS) is an experimental model that measures permeability and solubility under prescribed conditions.

Biopharmaceutical Classification System

Biopharmaceutical Classification System (BCS) guidance was provided by US Food and Drug Administration (FDA), to improve the efficiency of drug product development process. According to which drugs are grouped into four major classes basing on their solubility and permeability.
Class I: High Permeability and High Solubility
Propranolol, Metoprolol, Diltiazem, Verapamil

Class II: High Permeability and Low Solubility
Ketoconazole, Mefenamic acid, Nifedipine, Nicardipine, Felodipine, Piroxicam

Class III: Low permeability and High solubility
Acyclovir, Neomycin B, Captopril, Enalaprilate, Alendronate

Class IV: Low permeability and Low solubility
Chlorthiazide, Furosemide, Tobramycin, Cefuroxime

A drug substance is considered highly soluble when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5 and it is considered highly permeable when the extent of absorption in humans is determined to be > 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose. A drug product is considered to be rapidly dissolving when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.

The rate limiting process for drug absorption and bioavailability (rate and extent of absorption) is either the release (or dissolution) of drug substances from the dosage form or its permeation through the intestinal membrane. If permeation through intestinal membrane is rate limiting, dissolution properties may be of negligible importance. Class I drugs behave in vivo like an oral solution. Dissolution and bioavailability is very rapid for these drugs. If the Class I drug substance is released from the dosage form very rapidly in vivo, gastric emptying will become the rate limiting process for drug absorption. Whereas for drugs having high permeability and low solubility (Class II), dissolution or release from the dosage form occurs slowly and the dissolution rate will become the rate limiting factor for drug absorption. These drugs exhibit variable bioavailability and need enhancement in dissolution rate for increasing bioavailability. Permeation through the intestinal membrane forms the rate-limiting step for absorption of drugs of Class III and bioavailability is independent of drug release from the dosage form. These drugs generally exhibit low bioavailability and need enhancement in permeability. Class IV drugs exhibit poor and variable bioavailability. Several factors such as dissolution rate, permeability, gastric emptying form rate limiting steps for absorption of these drugs.
Formulation Development Techniques for BCS Class II Drugs

BCS class II drugs pose challenging problems in their pharmaceutical product development process. As the dissolution rate forms the rate limiting step in their bioavailability, enhancement of dissolution rate and achieving the target dissolution is a critical step in their formulation development. Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, micro emulsion and self-emulsifying systems are available to enhance the bioavailability of BCS Class II drugs. The more industrially useful techniques are as follows.

Particle size reduction

Particle size reduction can be achieved by micronisation and nanosuspension. Each technique utilizes different equipments for reduction of the particle size.

Micronization

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronisation is used to increase surface area for dissolution. Micronisation increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

Nano suspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor. Techniques for the production of nanosuspensions include Homogenization and wet milling. Active drug in the presence of surfactant is defragmented by milling. Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants. The nanosuspension
approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone. All the formulations are in the research stage. One major concern related to particle size reduction is the eventual conversion of the high energy polymorph to a low energy crystalline form, which may not be therapeutically active one. Drying of nanosuspensions can be done by lyophilisation or spray drying.

**Sonocrystallisation**

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation. Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallisation. It’s not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 kHz-5 MHz.

**Supercritical fluid process**

A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids). Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points. Hence, it is possible to fine tune a unique combination of properties necessary for a desired application. These unique processing capabilities of SCFs, long recognized and applied in the food industry, have recently been adapted to pharmaceutical applications.

**Lipid-based formulations**

Lipid-based delivery systems like emulsions, microemulsions, liposomes, microspheres, solid-lipid nanoparticles, etc have ability to avoid resistant chemical and physical barriers to oral absorption and are most successful in enhancing the bioavailability of molecules that are poorly water-soluble but highly permeable drug molecules (BCS class II). Some proposed mechanisms of action of lipid-based systems to enhance oral bioavailability of compounds include.
a) Particle size reduction to molecular size yielding a solid-state solution within the carrier.

b) Enhanced wetting of hydrophobic solids resulting in enhanced dissolution.

c) Increased rate of dissolution into aqueous environment from oil droplets of high surface area.

d) Promotion of absorption via intrinsic lipid pathways.

e) Enhanced thermodynamic activity via supersaturation of the aqueous environment of the gastrointestinal tract.

**Melt-Granulation**

In this technique powdered drugs are efficiently agglomerated by the use of a meltable binder which can be a molten liquid, a solid or a solid that melts during the process usually in high shear mixers, where the product temperature is raised higher than the melting point of the binder either by a heating jacket or, when the impeller speed is high enough, by the heat of friction generated by the impeller blades. In this technique no water or organic solvents are needed and there is no drying step therefore the process is environmentally safe, less time consuming and uses less energy than conventional wet granulation. Polyethylene glycol is widely used as a molten binder due to its complimentary solution properties, low melting point, rapid solidification rate, low toxicity and little cost. The increase in dissolution rate can be described to the hydrophilic character of the system due to the presence of water-soluble carriers and the fact that the drug forms monotectic mixtures with PEG.

**Direct Compaction**

In this process polymer like hydroxypropyl methylcellulose and drug is dry-blended, compressed into slugs and then milled into a granular powder. The process results in enhanced dissolution rate of poorly water-soluble drugs without the use of solvent or heat addition to overcome the disadvantages of solid dispersion by these methods. This process is also cost effective and quicker. The compaction processes are believed to be particularly effective at enhancing the rate of drug dissolution because the drug particles are maintained in direct contact with the polymer particles during drug dissolution, in contrast with a physical mixture where the drug and polymer particles may rapidly disperse and be separated in the dissolution.
CYCLODEXTRIN COMPLEXATION

Cyclodextrins (CDs), homologous cyclic oligosaccharides have long been known to increase the apparent solubility of many lipophilic drugs through non-covalent inclusion complexation.[1,2] Cyclodextrins and their derivatives play an important role in the formulation development due to their effect on solubility, dissolution rate, chemical stability and absorption of a drug.[3,4] The α-, β- and γ-cyclodextrins are cyclic oligosaccharides consisting of six, seven and eight glucose units respectively. While it is thought that, due to steric factors, cyclodextrins having fewer than six glucopyranose units cannot exist. Chemical and physical properties of the four most common cyclodextrins are given in Table 1. The melting points of α-, β- and γ-cyclodextrins are between 240° and 265°C, consistent with their stable crystal lattice structure.[5]

Table-1: Some Characteristics of α-, β-, γ- and δ-Cyclodextrins

<table>
<thead>
<tr>
<th></th>
<th>α</th>
<th>β</th>
<th>γ</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of glucopyranose units</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>972</td>
<td>1135</td>
<td>1297</td>
<td>1459</td>
</tr>
<tr>
<td>Central cavity diameter (Å)</td>
<td>4.7-5.3</td>
<td>6.0-6.5</td>
<td>7.5-8.3</td>
<td>10.3-11.2</td>
</tr>
<tr>
<td>Water solubility at 25°C (g/100 ml)</td>
<td>14.5</td>
<td>1.85</td>
<td>23.2</td>
<td>8.19</td>
</tr>
</tbody>
</table>

They are enzymatic conversion products of starch. The enzyme cyclodextrin-glucosyltransferase produced by B. macerans acts on partially hydrolysed starch (a mixture of linear dextrins) and produces a mixture of cyclic and acyclic dextrins, from which pure cyclodextrins (CDs) are isolated.[6] The structure of the most important CD, β-cyclodextrin is shown in Fig. 1.

![Fig.1: The Structure of β-cyclodextrin](image-url)
The 'torus' shaped macro-ring is built of α-1,4-D-glucose units. As a consequence of conformation of glucopyranose units, all secondary OH- groups are located on one edge (wider edge) of the ‘torus’ like CD molecule while all primary OH-groups are on the other side (narrow side of torus). The lining of the internal cavity is formed by OH-atoms and glucosidic oxygen-bridge atoms, therefore, the inner surface is hydrophobic, but outer surface is hydrophilic.

**Pharmacokinetics of Cyclodextrins**\(^7\)
- The parent CDs are poorly absorbed from the g.i. tract
- Oral absorption studies have shown ≤ 2%, 0.1-0.3% and ≤ 0.1% absorption respectively with α-, β-, and γ - CDs.
- Intravenously administered CDs disappear rapidly from systemic circulation; excreted mainly through kidney. The t\(_{1/2}\) of β-CD 23.9 – 50.2 min in rat.
- The t\(_{1/2}\) of HP-β-CD is 24 min in rat, 48 min in dog and 72-108 min in human.
- α- and β-CDs are excreted almost completely in their intact form.
- Little or no distribution of most CDs into other tissues or storage compartments is observed.

**Safety of Cyclodextrins**
- Parent CDs are reported to be non-toxic and safe even at high oral doses.
- The LD\(_{50}\) in rats is reported to be greater than 12.5, 18.8 and 8.0 g /kg body weight for α, β-, and γ-CD respectively.
- α- and β-CDs produced no toxic effects when fed to rats for 30-90 days at 1%, of the diet or at 1 and 2 g /kg daily doses.

**Regulatory Status of Cyclodextrins**
- Accepted as new pharmaceutical excipients by USFDA
- A monograph on β CD in USP 23/NF 18, 1995 and European Pharmacopoeia 3\(^{rd}\) Ed., 1997

**Formation of Complexes**
One of the most important characteristics of CDs are their ability to form inclusion complexes. Inclusion complexation involves entrapment of a guest molecule totally or
partially in the cavity of host molecule without formation of any covalent bonds. CDs are typical host molecules and can entrap a wide variety of drug molecules resulting in the formation of monomolecular inclusion complexes.\cite{8,9} Usually 1 : 1 complexes are formed, but when a guest molecule is too long to find complete accommodation in one cavity, its other end is also amenable to complex formation leading to 2 : 1 (CD : drug) or sometimes 3 : 1 or 4 : 1 complexes. It may also be possible to form 1 : 2 and 1 : 3 (CD : drug) complexes. The central cavity of the cyclodextrin molecule is linked with skeletal carbons and ethereal oxygens of the glucose residues. It is therefore lipophilic, the polarity of the cavity has been estimated to be similar to that of aqueous ethanolic solution. It provides a lipophilic microenvironment into which suitably sized drug molecules may enter and be included. No covalent bonds are formed or broken during drug-cyclodextrin complex formation, and in aqueous solutions, the complexes are readily dissociated. Free drug molecules are in equilibrium with the molecules bound within the cyclodextrin cavity. Measurements of stability or equilibrium constants (Kc) of the drug-cyclodextrin complexes are important properties of a compound upon inclusion.

**Methods of Preparation of CD Complexes**

Many techniques are known to form complexes with cyclodextrins.

1. **Physical blending /Grinding method**\cite{10}
2. **Kneading method**\cite{11-14}
3. **Co-precipitation**\cite{15}
4. **Solid dispersion / Co- evaporated dispersion**\cite{10}
5. **Neutralization method**\cite{16}
6. **Spray drying**\cite{17}
7. **Lyophilization/ Freeze drying technique**\cite{18,19}
8. **Melting**\cite{20}
9. **Microwaveirradiation method**\cite{21}
10. **Supercritical antisolvent technique**\cite{23-29}

**Applications of Cyclodextrins**

Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favorably affected.\cite{30-41}
Recent Research Work on CD Complexation

Several studies reported the cyclodextrin complexation of a variety of drugs for various purposes. A summary of recent research on cyclodextrin complexation for enhancing the solubility, dissolution rate and bioavailability is given in Table 2.

Table 2: Summary of Recent Research on Cyclodextrin Complexation[^42-77]

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Drug</th>
<th>Cyclodextrin used</th>
<th>Purpose/Result</th>
<th>Ref.No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Analgesic, Antipyretic, Anti-inflammatory Drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Nimesulide</td>
<td>βCD, HP βCD, ME- βCD</td>
<td>Improved solubility and oral bioavailability</td>
<td>[42]</td>
</tr>
<tr>
<td>2</td>
<td>Aceclofenac</td>
<td>βCD, HP βCD</td>
<td>Improve solubility and dissolution rate</td>
<td>[43]</td>
</tr>
<tr>
<td>3</td>
<td>Diclofenac sodium</td>
<td>γCD, 2-HPγCD</td>
<td>Investigated aggregation of complexes through semi-permeable membranes and transmission electron microscopy</td>
<td>[44]</td>
</tr>
<tr>
<td>4</td>
<td>Indomethacin</td>
<td>Cationic βCD, CP βCD</td>
<td>Drug loading capacities of CP βCD were studied and complexes were confirmed by 1H NMR and DSC</td>
<td>[45]</td>
</tr>
<tr>
<td>5</td>
<td>Capsaicin</td>
<td>HPβCD</td>
<td>Improved percutaneous absorption</td>
<td>[46]</td>
</tr>
<tr>
<td>6</td>
<td>Etoricoxib</td>
<td>βCD, HP βCD, Poloxamer 407, PVP K30</td>
<td>Enhancement in solubility and dissolution rate</td>
<td>[47]</td>
</tr>
<tr>
<td>7</td>
<td>Ketrolac</td>
<td>HPβCD</td>
<td>Higher Transdermal Transport</td>
<td>[48]</td>
</tr>
<tr>
<td>8</td>
<td>Paracetamol</td>
<td>α, β and γ cyclodextrin</td>
<td>γ complexes are most stable than β complexes which are more stable than α complex</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td>Antimicrobial, Antifungal, Antiviral, Antibiotic Drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Acyclovir</td>
<td>Fluorinated amphiphilicα cyclodextrins hexakis</td>
<td>To prepare aqueous suspensions of nanoparticles</td>
<td>[50]</td>
</tr>
<tr>
<td>10</td>
<td>Rifampin Novabiocin Vancomycin</td>
<td>βCD</td>
<td>Affinity based antibiotic delivery mechanisms were developed</td>
<td>[51]</td>
</tr>
<tr>
<td>11</td>
<td>Sulfamethoxazole</td>
<td>Hydroxypropyl-β-cyclodextrin</td>
<td>Increased solubility</td>
<td>[52]</td>
</tr>
<tr>
<td>12</td>
<td>Trimethoprim Sulfamethoxazole</td>
<td>cyclodextrins (α-, β-, and γ-CDs)</td>
<td>The solubility enhancement of trimethoprim is much higher than that of sulfamethoxazole in the presence of SDS micelles</td>
<td>[53]</td>
</tr>
<tr>
<td>13</td>
<td>Vancomycin</td>
<td>β-cyclodextrin</td>
<td>modified release with improved</td>
<td>[54]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Quercetin</td>
<td>β-cyclodextrin</td>
<td>Enhanced drug release [55]</td>
<td></td>
</tr>
<tr>
<td><strong>III</strong> Anti hypertensive, Antianginal, Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Irbesartan</td>
<td>βCD, PEG 4000, PVP K90</td>
<td>Improved aqueous solubility, dissolution rate and Characterization of inclusion complexes by XRD, DSC, FTIR and SEM [56]</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Carvedilol</td>
<td>βCD, Citric acid</td>
<td>Improved aqueous solubility, dissolution rate and Characterization of inclusion complexes by XRD, DSC, FTIR and SEM [57]</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Felodipine</td>
<td>Cyclodextrins</td>
<td>FTIR, DSC and XRPD showed the confirmation of complexation of cyclodextrin with felodipine [58]</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Statins (Lovastatin, Simvastatin)</td>
<td>RMβCD</td>
<td>Improved solubility [59]</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Valsartan</td>
<td>βCD, HP βCD, PVP K30</td>
<td>Enhancement in solubility and dissolution rate [60]</td>
<td></td>
</tr>
<tr>
<td><strong>IV</strong> Sedatives, Antidepressant, Anti anxiety, Anti convulsant Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Lorzepam</td>
<td>HPβCD</td>
<td>Improved aqueous solubility and dissolution rate [61]</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Lamotrigine</td>
<td>βCD</td>
<td>Improved solubility and bioavailability [62]</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Doxepin</td>
<td>βCD</td>
<td>Characterization of inclusion complexes by NMR spectroscopy [63]</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Promethazine</td>
<td>monochlorotriazinyl-β-cyclodextrin</td>
<td>Alkaline medium is more favourable for producing the complex [64]</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Olanzapine</td>
<td>methyl-β-CD</td>
<td>Higher dissolution efficiency and stability [65]</td>
<td></td>
</tr>
<tr>
<td><strong>V</strong> Anti cancer Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Tacrolimus</td>
<td>Dimethyl-β-cyclodextrin</td>
<td>Improved delivery efficiency [66]</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Diferuloylmethane</td>
<td>hydroxypropyl-β-cyclodextrin</td>
<td>Improved the physical properties and antitumor activity [67]</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Betulin</td>
<td>γ-Cyclodextrin</td>
<td>Improved solubility both in vitro and in vivo [68]</td>
<td></td>
</tr>
<tr>
<td><strong>VI</strong> Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Omeprazole (Anti Ulcer)</td>
<td>βCD, MEβCD, L-arginine</td>
<td>Improved buccal permeation [69]</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Noscapine (Anti Tussive)</td>
<td>βCD</td>
<td>Improved aqueous solubility and pharmacokinetics [70]</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Bupivacaine HCl (Local Anaesthetic)</td>
<td>α-CD, β-CD, epichlorohydrin</td>
<td>Improved buccal delivery and Characterization of inclusion complexes by XRPD, DSC, FTIR [71]</td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSION

Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, micro emulsion and self-emulsifying systems have been successfully developed for formulation development of BCS class II drugs. Though several studies are reported in this area, more intense research is needed to evolve new and novel formulation techniques for BCS class II drugs.

REFERENCES


64. Octavian Popescu and Aurelia Grigoriu: Cellulose Chemistry and Technology., 2012; 46(5-6): 295-300.