are not charged with approval of new excipients (Thompson 1997). In the U.S., the dossier on a new excipient must be filed by the excipient manufacturer as a drug master file (DMF)-Type 4. This data is then referenced when an investigational new drug application (IND), new drug application (NDA), or abbreviated new drug application (ANDA) is filed for a dosage form using the excipient. The existence of a DMF for a specific excipient, however, does not guarantee regulatory acceptance for the use of that excipient with a drug. The safety data for the excipient provided in the DMF needs to support the administration route, excipient dosing level and dosing frequency (Stella and Rajewski 1997). In addition, the regulatory document referencing the DMF will need to provide supporting safety data on the complexing agent/drug combination. Because of the additional problems associated with using a new excipient, when considering using the complexation technique in drug formulations, it is advisable to start the dialogue with the regulatory agents as early in the development process as possible so the expectations by the agents are clearly communicated.

Drugs Containing Cyclodextrins

It is worthwhile to note that various CDs themselves have been used for different therapeutic indications as shown in clinicaltrials.gov, such as intravenous HP-β-CD for Niemann-Pick Type C1 Disease, oral α-CD on Fecal Fat Excretion, and oral α-CD for Decreasing Serum Chloesterol. According to clinicaltrials.gov, there are 32 clinical studies involving CD or CD complexation, and among them 11 studies are still recruiting study subjects or active but not recruiting. An important player in the field of CD complexation, CyDex Pharmaceuticals, Inc. was acquired by Ligand in 2011 and operates as a wholly-owned subsidiary of Ligand (http://www.ligand.com/cydex). In addition to approved drug products, CyDex is supporting drug development efforts with more than 40 companies, including developing a Captisol®-enabled IV formulation of Carfilzomib for refractory multiple myeloma for Onyx Pharmaceuticals (acquired by Amgen in 2013).

Chordiya and Senthilkumaran have summarized marketed drug products according to different CD derivatives (α-CD, β-CD, HP-β-CD, RM-β-CD, SBE-β-CD and HP-γ-CD), and most of the approved drugs are marketed in Europe and Japan, only a few in USA (Chordiya and Senthilkumaran 2012). The drugs approved in the United States and around the world utilizing SBE-β-CD (Captisol) include but not limited to Vfend® (voriconazole) and Zeldox®/Geodon® (ziprasidone mesylate) by Pfizer, ABILIFY (aripiprazole) by Bristol-Myers Squibb (https://notendur.hi.is/thorstlo/cyclodextrin.pdf), and Nexterone (amiodarone hydrochloride) of Baxter. The drugs approved in the United States and around the world utilizing HP-β-CD include but not limited to Sporanox (itraconazole) by Janssen, Idocid (indomethacin) by Chauvin, and MitoExtra (mitomycin) by Novartis. For Itraconazole (Sporanox), a broad-spectrum antifungal agent, based on HP-β-CD, Janssen developed different both oral (capsule) and oral (solution) formulations.

Patent Issues

Applications of complexation agents especially modified CDs are heavily patented. The use of CD derivatives, for example, will typically involve certain royalty payment. However, this may also present opportunities for patent protection of new formulations containing complexes of new chemical entities (NCEs).

Cost-of-Goods Considerations

The cost-of-goods is an important factor to consider in the current drug development environment. When complexation technology is used in a drug formulation, the cost of the complexing agents and the potential royalty payment associated with the technology may make the formulated products less attractive in a very competitive market. Additionally, the development cost with complex-containing formulations may be higher because of additional toxicity studies required, for example.