



Cyclodextrins: Going from Supporting Role to Leading Actor

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Editorial

Cyclodextrins (CDs) are a family of cyclic oligosaccharides composed of 5 or more α -(1,4)-linked glucopyranose subunits among which α -, β -, and γ -cyclodextrin (consisting of six, seven, and eight glucopyranose subunits in a ring, respectively) are the three major types. After more than a hundred years of research since first discovered, cyclodextrins have been structurally and chemically characterized and widely applied in food, pharmaceutical and others playing supporting roles (e.g. as a delivery system of foods or drugs).

Interestingly, cyclodextrins are gradually going from supporting role to leading actor since in recent years it was found that cyclodextrins per se could be recruited as effective drugs for several diseases. The specific structural property of cyclodextrins (i.e. hydrophobic inside and hydrophilic outside) helps not only to host food/drug molecules as a delivery system but also to extract lipids (particularly cholesterol) from diseased tissues/cells as a potential drug.

Well characterized are the effects of hydroxypropyl-beta-cyclodextrin (HP β CD), a derivative of β -CD, on Niemann-Pick type C (NPC) disease and an autosomal recessive disorder characterized by intracellular cholesterol accumulation, gliosis and neuronal loss in selected brain regions. Accumulating evidence proved that HP β CD can prevent neurodegenerative changes in NPC1^{-/-} mice [1-4]. HP β CD has received orphan drug designation for the treatment of NPC disease. It was also showed that HP β CD has neuroprotective effects on Alzheimer disease which shares neuropathological features with NPC [5]. Methy-beta-cyclodextrin (M β CD), another derivative of β -CD, also has been reported to have antitumor effects via cholesterol depletion from lipid rafts in the plasma membrane of tumor cells [6-8].

Most recently, the potentially anti-atherosclerotic effects of cyclodextrins were evaluated. Zimmer et al. [9] reported that HP β CD could mediate regression of atherosclerotic plaques *in vivo* potentially by solubilizing extracellular and intracellular cholesterol crystals and increasing cholesterol efflux from macrophages *in vitro*. Our *in vivo* experimental data also shows that HP β CD can inhibit the progression of atherosclerosis (unpublished data). On the other hand, we revealed that cyclodextrins including α -CD, γ -CD, HP β CD and M β CD could alter the structures of low-density lipoprotein (LDL) and high-density lipoproteins (HDL; unpublished data) and inhibit LDL/HDL oxidation [10]. We also found that M β CD could inhibit the adhesion of monocytes onto endothelial cells by down-regulating adhesion molecules and caveolae [11]. Therefore, it seems that cyclodextrins could inhibit or even reverse the progression of atherosclerosis potentially via multiple mechanisms correlating with different key steps during atherogenesis including LDL/HDL oxidation, monocyte-endothelium adhesion, solubilization of cholesterol crystals, cholesterol efflux, among others.

Cyclodextrins are produced from starch via enzymatic conversion and have already been recognized as safe by the FDA. Therefore, the role switching of cyclodextrins from a drug delivery system to a commercial drug may be relatively easier and smoother than the development of a traditional new drug. For inclusion complexes of cyclodextrins with other drugs, cyclodextrins could be regarded as not only a drug carrier but a combination drug for combination therapy. For example, the cyclodextrin inclusion compounds of an antitumor drug may be used to treat cancer and atherosclerosis simultaneously. In the future, more attention should be placed on developing drug efficacy of cyclodextrins while applying their drug-delivery capability.

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