

Combating Coronavirus: Key Role of Cyclodextrins in Treatment and Prevention

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Background

A new strain of coronavirus (2019-nCoV) started to emerge in late December 2019 from Wuhan, the capital of Hubei Province in central China, which is a city with a population of 11 million. The pneumonia-like illness, which has spread rapidly since first appearing in late December 2019, was declared a 'public health emergency' by the World Health Organization. As of 10 Feb 2020, the virus has infected over 40,000 people in China, over 300 in other countries, and killed more than 900 people.

According to the US CDC, "person-to-person spread is thought to occur mainly via respiratory droplets produced when an infected person coughs or sneezes, similar to how influenza and other respiratory pathogens spread. These droplets can land in the mouths or noses of people who are nearby or can possibly be inhaled into the lungs." At the molecular level, the sequence analysis and high sequence similarity of 2019-nCoV to that of SARS-CoV suggests that angiotensin-converting enzyme 2 (ACE2) is the receptor for entry into human cells.¹

Roquette is committed to helping patients in need. Roquette has extensive experience and a long history of supplying KLEPTOSE® hydroxypropyl beta-cyclodextrins (HPβCD) as a functional excipient and a specialty active pharmaceutical ingredient (API). It is approved for oral and parenteral administration in humans by the EU, US, and Chinese regulatory authorities. In this short communication, we will review treatment strategies and the potential role of cyclodextrins in combating the illness as an excipient, adjuvant and potentially an API.

Treatment Strategies

Several antiviral drugs targeting Ebola and HIV, for example, have been repurposed and have shown promising results in patients, however, there is no approved treatment specific to 2019-nCoV. Infected patients are treated to relieve typical symptoms. The crisis urges the development of novel medicines to save lives. Scientists, clinicians and governments across the world are focusing all efforts to accelerate the clinical development and implementation of life-saving 2019-nCoV drug treatments.

Antivirals

Combinations of antivirals have been repurposed to treat 2019-nCoV and have shown positive results. However, the development of antiviral drugs can be hampered by formulation challenges, most notably poor aqueous solubility of the active compound.² Adequate drug solubility is imperative to ensure bioavailability and consequently, the efficacy of oral antiviral treatments. In the case of parenteral therapy, which offers the benefit of rapid onset in critically-ill patients, drug solubility is even more critical, given that intravenous solutions must be particulate-free and buffered to physiological pH.

Table 1 shows antiviral drugs currently being tested or in development to treat 2019-nCoV. Cyclodextrin drug delivery systems can effectively overcome formulation challenges of antiviral drugs by offering improved solubility and bioavailability. HPβCD is cited in the FDA's list of Inactive Pharmaceutical

Ingredients, and is approved for use in oral and parenteral formulations due to its high aqueous solubility and excellent safety profile even at relatively high doses.³

Table 1. Current antiviral drugs tested or in development for treatment of 2019-nCoV and proposed cyclodextrins for formulation enhancement

API	Regulatory status	Formulation challenge	Proposed cyclodextrins
Remdesivir	Compassionate use/ clinical trials	Limited solubility	SBE-CD ⁴
Lopinavir + ritonavir*	Approved anti-HIV drug	Limited solubility	HP β CD ⁵
Oseltamivir*	Approved anti-influenza drug	Bitter taste	β CD ⁶

**Available as a commercial product*

Vaccines

Accelerated measures are being taken by companies and institutions to develop vaccines against 2019-nCoV infection as there are currently no approved vaccines. Since the release of the 2019-nCoV genetic sequence in early January 2020, scientists have been working around the clock to produce stable versions of the vaccines mainly based on non-living subunit vaccine and mRNA vaccine technologies. Companies including Johnson & Johnson,⁷ Clover Pharmaceuticals,⁸ and Novavax⁹ are developing virus subunit vaccines. Other companies like Moderna and CureVac are developing messenger RNA-based vaccines.^{10,11}

Non-living vaccine antigens, especially subunit vaccines, are poorly immunogenic and require additional adjuvant components to stimulate immunity. Finding an adjuvant to stimulate efficient, long-lasting and safe immune response is challenging. As an adjuvant, HP β CD induces Type 2 T-helper (Th2) cell response, enhances antigen (vaccine)-specific antibody titers, and maintains longer immune response. Moreover, unlike commonly used adjuvants in human vaccine, such as aluminum salt, HP β CD induces little Immunoglobulin E (IgE) production, which is a risk factor affecting the allergenic potential of vaccines.^{12,13} HP β CD can act as a safe and efficient adjuvant in developing successful vaccines for 2019-nCoV prevention. Daiichi Sankyo is conducting a Phase I clinical trial in Japan for their HP β CD adjuvanted influenza split vaccine.¹⁴

Monoclonal Antibodies

Monoclonal antibodies can specifically target the virus and render long-term effects. Given the successful treatments on other diseases, a few companies, like Regeneron (MERS-CoV antibodies),¹⁵ Wuxi Biologics (new development),¹⁶ CytoDyn (Ieronlimab),¹⁷ and Vir Biotechnology (CoV antibodies),¹⁸ have taken prompt actions to accelerate the development of their neutralizing antibodies. Proteins are inherently unstable, and selection of appropriate excipients for final formulation is critical to maintain antibody

stability during storage and shipment. Many case studies show that HP β CD is able to protect proteins from aggregation under various stress conditions.^{19,20} In addition, the validated safety profile in approved parenteral small molecule drugs, and the stability of HP β CD itself, suggest it as a versatile excipient in antibody formulation development.

Modified Cyclodextrin with Virucidal Activity

Modified beta-cyclodextrin can be rendered with antiviral activities. For example, to mimic heparin sulfates, which is a broad-spectrum antiviral agent but inefficient when diluted, β -cyclodextrin is modified with mercaptoundecane sulfonic acid. The new functional molecules are broad-spectrum, biocompatible, and virucidal at micromolar concentrations *in vitro* and *in vivo* (mouse model) against many viruses.²¹ Due to its safety, biocompatibility, and unique structure, cyclodextrins can be modified to provide nontoxic virucidal action.

Cyclodextrins for Infection Containment

Infection by enveloped viruses including coronavirus and influenza virus is mediated by viral binding to cellular receptors and fusion of the viral envelope with the host cell membrane. Evidence suggests that cholesterol present in microdomains in the viral envelope and cell membrane are required for successful entry of enveloped viruses into the host cell.

Cyclodextrins are able to sequester cholesterol from viral particles, thereby causing lipid raft disruption and consequent structural deformation of the viral envelope.²² Cyclodextrins can also deplete cholesterol from host cell membranes, rendering them less susceptible to viral infection. For example, methylated beta-cyclodextrin (M β CD) has been demonstrated to reduce coronavirus and influenza A viral infectivity via cholesterol depletion.^{23,24} This property of cyclodextrins can potentially be harnessed for the development of skin disinfectant solutions. Moreover, prophylactic nasal and throat sprays can be developed to prevent viral transmission via the respiratory route. Cyclodextrin formulations have the advantage of biocompatibility to skin and mucous membranes.

Conclusion

The 2019-nCoV is spreading rapidly across the globe and effective treatments are in urgent need. Companies are accelerating their drug development to combat 2019-nCoV infection; nevertheless, formulation development for any drug candidate is critical and challenging. HP β CD can effectively act as a safe, enabling excipient for solubility enhancement of antiviral drugs, stability improvement of therapeutic monoclonal antibodies, and as a vaccine adjuvant. Cyclodextrins can potentially be used for infection containment or as virucidal agents after structural modification.

For more information on how Roquette can share its expertise on HP β CD with your specific formulation, please contact WEN-CHIN.FOO@roquette.com.

References

1. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. *Journal of Virology*, Jan 2020, JVI.00127-20; DOI: 10.1128/JVI.00127-20.
2. *Antiviral drugs: from basic discovery through clinical trials*. John Wiley & Sons, 2011.
3. Cyclodextrins used as excipients (EMA/CHMP/495747/2013). European Medicines Agency, 2017.

4. Gilead uses SBECD-enabled remdesivir (GS-5734) for treating the first case of the 2019 novel coronavirus in the United States. Cyclodextrin News, 2020.
5. Complexation approach for fixed dose tablet formulation of lopinavir and ritonavir: an anomalous relationship between stability constant, dissolution rate and saturation solubility. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 2012, 73: 75-85.
6. Novel inclusion complexes of Oseltamivir Phosphate with beta cyclodextrin: Physico-chemical characterization. Journal of Pharmaceutical Sciences and Research, 2010, 2: 583-589.
7. Johnson & Johnson's response to the 2019-nCoV crisis. <https://www.jnj.com/coronavirus>
8. Clover successfully produced 2019-nCoV subunit vaccine candidate and detected cross-reacting antibodies from sera of multiple infected patients. <http://www.cloverbiopharma.com/index.php?m=content&c=index&a=show&catid=11&id=41>
9. NovaVax working very hard on coronavirus vaccine, R&D president says. <https://www.bloomberg.com/news/videos/2020-01-30/novavax-working-very-hard-on-coronavirus-vaccine-r-d-president-says-video>
10. Moderna president hopes to develop coronavirus vaccine in record setting time. <https://www.bloomberg.com/news/videos/2020-01-29/moderna-president-hopes-to-develop-coronavirus-vaccine-in-record-setting-time-video>
11. CureVac bids to develop first mRNA Coronavirus Vaccine. <https://www.labiotech.eu/medical/curevac-coronavirus-outbreak-cepi/>
12. Intranasal HP β CD-adjuvanted influenza vaccine protects against sub-heterologous virus infection, Vaccine, 2016, 34: 3191-3198.
13. HP β CD spikes local inflammation that induces Th2 cell and T follicular helper cell responses to the coadministered antigen. The Journal of Immunology, 2015, 194: 2673-2682.
14. A phase 1 study of HP β CD-adjuvanted influenza split vaccine. Available online: https://rctportal.niph.go.jp/en/detail?trial_id=UMIN000028530 (accessed on 10 Feb 2020)
15. Regeneron announces expanded collaboration with HHS to develop antibody treatments for new coronavirus. <https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-announces-expanded-collaboration-hhs-develop-antibody>
16. WuXi Biologics enables development of multiple neutralizing antibodies for novel coronavirus. <https://www.pharmaadvancement.com/manufacturing/wuxi-biologics-enables-development-of-multiple-neutralizing-antibodies-for-novel-coronavirus/>
17. Leronlimab under evaluation for potential treatment of coronavirus. <https://www.cytodyn.com/newsroom/press-releases/detail/379/leronlimab-under-evaluation-for-potential-treatment-of>
18. Vir biotechnology CEO on finding a coronavirus antibody. <https://www.bloomberg.com/news/videos/2020-01-29/vir-biotechnology-ceo-confident-coronavirus-vaccine-will-be-found-video>
19. Inhibition of agitation-induced aggregation of an IgG-antibody by hydroxypropyl- β -cyclodextrin. Journal of Pharmaceutical Science, 2010, 99: 1193-1206.
20. Effects of hydrophilic cyclodextrins on aggregation of recombinant human growth hormone. Pharmaceutical Research, 2004, 21: 2369-2376.
21. Modified cyclodextrins as broad-spectrum antivirals. Science Advances, 2020, 6: eaax9318.
22. Lipid raft disruption by cholesterol depletion enhances influenza A virus budding from MDCK cells. Journal of Virology, 2007, 81: 12169-12178.
23. Role of the lipid rafts in the life cycle of canine coronavirus. Journal of General Virology, 2015, 96: 331-337.

24. Lipid rafts are involved in SARS-CoV entry into Vero E6 cells. Biochemical and Biophysical Research Communications, 2008, 369: 344-349.

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