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COMBATING CORONAVIRUS: KEY ROLE OF CYCLODEXTRINS IN TREATMENT AND PREVENTION

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DESCRIPTION

Roquette has recently identified that its **KLEPTOSE®** hydroxypropyl beta-cyclodextrins (HPβCD) product, a functional excipient and a specialty active pharmaceutical ingredient (API), may be effective to help the joint efforts of the scientific and pharmaceutical communities working on treating and preventing new emerging viruses such as the coronavirus.

HPβCD 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. **KLEPTOSE®** is a cyclodextrin, a group of structurally related natural products formed during bacterial digestion of cellulose. Cyclodextrins have indeed been shown to be effective as solubilizing and stabilizing agents in vaccines, monoclonal antibodies and oral formulations. Moreover, cyclodextrins can potentially be used for infection containment or as virucidal agents after structural modification. **The company's new position paper speaks to the potential role of cyclodextrins, such as HPβCD, in detail: "Combating Coronavirus: Key Role of Cyclodextrins in Treatment and Prevention."**

BACKGROUND

A new strain of coronavirus (SARS-CoV-2) 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 (COVID-19), 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 SARS-CoV-2 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.

Our KLEPTOSE® HPβCD may be part of a helpful solution to speed up the early stage development process and help rapidly scale-up vaccine candidate production.

Paul Smaltz, Head of the Global Pharmaceutical Business Unit

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 COVID-19. 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 fforts to accelerate the clinical development and implementation of life-saving COVID-19 drug treatments.

ANTIVIRALS

Combinations of antivirals have been repurposed to treat COVID-19 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 COVID-19. 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 COVID-19 and proposed cyclodextrins for formulation enhancement. *(*Available as a commercial product)*

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	HPβCD[5]
OSELTAMIVIR*	APPROVED ANTI-INFLUENZA DRUG	BITTER TASTE	βCD[6]

VACCINES

Accelerated measures are being taken by companies and institutions to develop vaccines against COVID-19 infection as there are currently no approved vaccines. Since the release of the SARS-CoV-2 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 Novavax[9] 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, HPβCD 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, HPβCD induces little Immunoglobulin E (IgE) production, which is a risk factor affecting the allergenic potential of vaccines.[12,13] HPβCD can act as a safe and efficient adjuvant in developing successful vaccines for COVID-19 prevention. Daiichi Sankyo is conducting a Phase I clinical trial in Japan for their HPβCD 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 (leronlimab),[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 HPβCD 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 HPβCD 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 (MβCD) 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 COVID-19 is spreading rapidly across the globe, and effective treatments are in urgent need. Companies are accelerating their drug development to combat COVID-19 infection; nevertheless, formulation development for any drug candidate is critical and challenging. HPβCD 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.

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