British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.1149

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the 13th APS International PharmSci 2022

Disulfiram Inclusion Complexes - A Nebulization Approach to Fight COVID-19

Ana Maria Pereira[a,b], Ayse Kaya[a], Dan Alves[a], Niusha Ansari-Fard[a] and Mohammad Najlah[a]*

[a] Pharmaceutical Research Group, School of Allied Health, Faculty of Health, Education, Medicine and Social Care, Anglia Ruskin University, Bishops Hall Lane, Chelmsford CM1 1SQ, UK. [b] GMPriority Pharma Ltd., Priors Way, Coggeshall, Colchester, CO6 1TW, UK

ARTICLE INFO

Received: 17/06/2022
Accepted: 07/07/2022
Published: 02/11/2022

*Corresponding author.
Tel.: +44 1245 684 682
Fax: +44 1245 684 682
E-mail:
mohammad.najlah@aru.ac.uk

KEYWORDS: disulfiram; β-cyclodextrin; SARS-CoV-19; nebulization

SUMMARY

Disulfiram (DS) has an excellent anti-viral activity; however, its low water-solubility and first-pass metabolism are limiting its clinical applications. Cyclodextrins (CDs) have been used as solubility enhancers and carriers of DS proposed for inhalation to treat SARS-CoV-19. Two types of CDs (hydroxypropyl β-cyclodextrin and sulfobutyl ether β-cyclodextrin) were used to form inclusion complexes with DS, and drug solubility was assessed using spectrophotometric analytical method. Formulations were freeze-dried and characterized using DSC, TGA and FTIR. Nebulization technique was used to assess the potential for generating aerosols. Both CDs improved DS solubility and demonstrated a strong DS-CD interaction. All inclusion complexes were proved to be suitable for inhalation, therefore, potentially effective therapy for further investigation against SARS-CoV-19 is shown.

INTRODUCTION

Despite the vaccinations are already available for COVID-19, the cases incidence is still of concern and long-term immunization hasn't been acquired. Disulfiram (DS), an anti-alcoholism drug, has a potent anti-viral activity (Ou et al. 2021). However, it is poorly soluble in water, rapidly metabolised, and highly instable in acidic gastric environments (Ou et al. 2021). Cyclodextrins (CDs), in particular, hydroxypropyl β-cyclodextrin (HP-β-CD) and sulfobutyl ether β-cyclodextrin (SBE- β-CD), are chemically and physically stable biocompatible carriers that are widely used to improve the solubility of drugs (Suliman et al. 2021). The aim of this study is to enhance the water-solubility of DS by HP and SBE β-CDs and assess the nebulization properties of resulting inclusion complexes.

MATERIALS AND METHODS

Solubility studies were carried as reported before by Suliman et al. (2021), and analysed by UV spectrophotometry at 262 nm (DS 296.51 g/mol, was purchased from Acros Organics, USA; HP 1555 g/mol, and SBE 2242.05 g/mol, from Glentham Life Sciences, UK; HPLC grade-water and ethanol 70%, from Fisher Scientific, UK). Samples of the previously prepared HP20% and SBE20% formulations were then left for 2h at -20°C, 24h at -80°C, and freeze-dried for 3 days using Lyotrap LTE freeze dryer. Powders were characterized using DSC, TGA and FTIR. Lastly, nebulization analysis was performed using Malvern's Spraytec laser diffraction size analyser and Pari LC Sprint air-jet nebulizer.

https://doi.org/10.5920/bjpharm.1149

RESULTS AND DISCUSSION

For both CDs, the higher the CD concentration, the higher the DS final concentration (Figure 1). Hence, both CDs significantly enhanced the drug solubility. DS had a polynomial relationship with the increase of HP-β-CD (N_A type phase solubility), and a linear function with the increase of SBE- β-CD (A_L type phase solubility) (Nicol, Matubayasi, and Shimizu 2016).

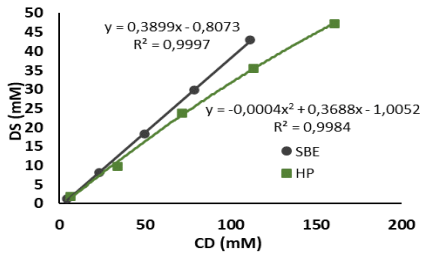

Fig. 1. *Phase solubility diagrams of DS and CD.*

Characterization of freeze-dried CD-DS inclusion complexes using differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and Fourier transform infrared spectroscopy (FTIR), reported an amorphous state of DS included in both CDs. This indicated the formation of stable CD-DS inclusion complexes. All loaded CDs demonstrated a relatively high aerosol output (Figure 2), and mean droplet sizes suitable for inhalation (Table 1).

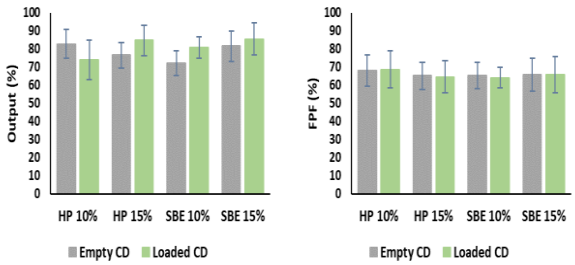

Fig. 2. *Aerosol output and Fine particle Fraction (FPF) of each empty and loaded CD.*

A small size distribution (span) is required to prevent droplet deposition on the upper respiratory tract. Table 1 shows that all loaded CDs had a smaller span than the empty CDs, hence being delivered to the lower respiratory tract. Additionally, all formulations had high FPF (Figure 2), indicating that the constitution of the formulations does not influence liquid breakdown, due to nebulization high conductivity (Lehmann et al. 2021).

Table 1. *VMD, Span and %≤5.4 μm of the empty and loaded CDs.*

Parameter	Formulation	Empty CD	Loaded CD
VMD (μm)	HP 10%	1.8 ± 1.0	2.5 ± 0.6
	HP 15%	1.5 ± 0.7	3.4 ± 0.8
	SBE 10%	1.7 ± 1.2	3.0 ± 1.0
	SBE 15%	1.6 ± 1.0	3.0 ± 0.8
Span	HP 10%	5.0 ± 3.6	1.4 ± 0.2
	HP 15%	5.3 ± 2.9	2.1 ± 0.2
	SBE 10%	3.7 ± 0.5	2.3 ± 0.4
	SBE 15%	6.5 ± 4.2	2.5 ± 0.3
%≤ 5.4 μm	HP 10%	82.2 ± 2.2	93.0 ± 8.0
	HP 15%	84.1 ± 2.2	76.3 ± 10.9
	SBE 10%	90.2 ± 1.0	79.4 ± 8.0
	SBE 15%	80.5 ± 6.4	77.0 ± 10.6

CONCLUSIONS

Both inclusion complexes successfully enhanced the solubility of DS, showing a strong interaction between DS and both CDs. In addition, the high output and FPF of both inclusion complexes, as well as the small droplet sizes and low polydispersity, suggest that all formulations might have a great potential for pulmonary delivery by nebulization.

REFERENCES

Lehmann, Jennifer, Michael R. Agel, Konrad H. Engelhardt, Shashank R. Pinnapireddy, Sabine Agel, Lili Duse, Eduard Preis, Matthias Wojcik, and Udo Bakowsky. 2021. "Improvement of Pulmonary Photodynamic Therapy: Nebulisation of Curcumin-Loaded Tetraether Liposomes." Pharmaceutics 13 (8).

Nicol, Thomas W.J., Nobuyuki Matubayasi, and Seishi Shimizu. 2016. "Origin of Non-Linearity in Phase Solubility: Solubilisation by Cyclodextrin beyond Stoichiometric Complexation." Physical Chemistry Chemical Physics 18 (22): 15205–17.

Ou, An te, Jia xin Zhang, Yue fei Fang, Rong Wang, Xue ping Tang, Peng fei Zhao, Meng Zhang, and Yong zhuo Huang. 2021. "Disulfiram-Loaded Lactoferrin Nanoparticles for Treating Inflammatory Diseases." Acta Pharmacologica Sinica 42 (11): 1913–20.

Suliman, Ammar Said, Mouhamad Khoder, Ibrahim Tolaymat, Matt Webster, Weiguang Wang, Abdelbary Elhissi, and Mohammad Najlah. 2021. "Cyclodextrin Diethyldithiocarbamate Copper Ii Inclusion Complexes: A Promising Chemotherapeutic Delivery System against Chemoresistant Triple Negative Breast Cancer Cell Lines." Pharmaceutics 13 (1): 1–12.