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Solubility Enhancement for Diethyldithiocarbamate-Zinc for Lung Cancer Treatment

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SUMMARY

Diethyldithiocarbamate zinc ($Zn(DDC)_2$), has shown promising antineoplastic effects against a wide variety of cancers. However, this application was hindered by its poor water solubility. Therefore, complexation with cyclodextrin was used to enhance the solubility. Five different concentrations of 2-hydroxyl beta-cyclodextrin (HP) and ether beta-cyclodextrin (SBE) were used. CD-$Zn(DDC)_2$ solutions were freeze-dried for further characterisation using DSC, TGA and FT-IR. The phase solubility study showed a significant water-solubility enchantment of $Zn(DDC)_2$, and the characterisation studies confirmed the formation of inclusion complexes CD-$Zn(DDC)_2$. Overall, CDs have improved $Zn(DDC)_2$ solubility significantly and showed a promising anticancer activity against lung cancer cells. Hence, CD-$Zn(DDC)_2$ complexes have a great potential for further studies against cancer.

INTRODUCTION

Diethyldithiocarbamate zinc $Zn(DDC)_2$ a disulfiram (anti-alcoholism drug) metabolite, has shown strong anti-cancer activity in vitro (Wiggins et al., 2015). Disulfiram activity is dependent on the availability divalent cations as Cu^{++} and Zn^{++} (Meraz-Torrers et al., 2020). Few reports studied the combination of Zinc and disulfiram for cancer treatment. However, this application was limited by low aqueous solubility and rapid metabolism for disulfiram (Wiggins et al., 2015).

Cyclodextrins (CDs) are cyclic oligosaccharides pharmaceutical excipients used to increase the solubility of drugs. CDs have a truncated shape with an external hydrophilic surface and internal hydrophobic cavity, that enable complexation with hydrophobic drugs (Suliman et al., 2021).

Therefore, development of stable solutions of $Zn(DDC)_2$ complex is required to permit further investigation exploring its anti-cancer activity. In this study complexes of CDs and $Zn(DDC)_2$ were prepared, characterised and invitro assessed for lung cancer treatment.

MATERIALS AND METHODS

Two types of CDs were used, 2-hydroxyl beta-cyclodextrin (HP) and sulfobutyl ether beta-cyclodextrin (SBE) to form inclusion complexes with $Zn(DDC)_2$. The complexes were prepared by mixing $Zn(DDC)_2$ with both types of CDs at room temperature using five different concentrations (1%, 5%, 10%, 15% and 20% w/w). UV spectrophotometer was used to detect CD-$Zn(DDC)_2$ concentrations at 260nm. Solutions were freeze-dried for further characterisation studies such as DSC, TGA and FT-

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IR. Cytotoxicity of CD-$Zn(DDC)_2$ on lung cancer cell lines A549 was evaluated using MTT assay (Suliman at el., 2021).

RESULTS AND DISCUSSION

The solubility of $Zn(DDC)_2$ increased significantly upon adding beta cyclodextrins. ($P<0.05$). Solubility reached 3.92 ± 0.07 and 4.46 ± 0.17 mg/ml for SBE-CD and HP-CD complexes respectively. No significant difference between the two types of CD ($P>0.05$). The phase solubility of $Zn(DDC)_2$ was Ap-type phase according to Higuchi and Connors model. This type of phase solubility deviates positively from linearity. The Ap profile for solubility study is isotherm, suggesting that CDs proportionally more effective at higher concentrations. Correspondingly, this phenomenon was also reported in phase solubility studies using CDs to solubilise $Cu(DDC)_2$ (Suliman et al., 2021).

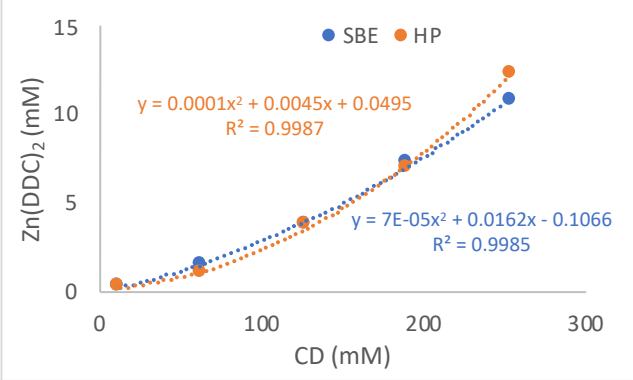

Fig. 1. *Phase solubility diagram of $Zn(DDC)_2$ in CDs.*

Table 1. *$Zn(DDC)_2$ solubility (mg/ml) in assorted CD solutions.*

SBECD	$Zn(DDC)_2$ Concentration (mg/ml)	HPCD	$Zn(DDC)_2$ Concentration (mg/ml)
1%	0.08 ± 0.04	1%	0.06 ± 0.1
5%	0.50 ± 0.01	5%	0.37 ± 0.01
10%	1.38 ± 0.04	10%	1.33 ± 0.04
15%	2.62 ± 0.03	15%	2.51 ± 0.01
20%	3.92 ± 0.04	20%	4.46 ± 0.04

Differential scanning calorimetry (DSC) results showed that free $Zn(DDC)_2$ had a sharp endothermic peak at 182°C, indicating the crystal status of the compound. While the two CDs showed an endothermic broad peak around 85°C due to the water loss. Freeze-dried formulations showed no endothermic peaks. Therefore, it is an indication for strong complexation of the amorphous drug in the CDs cavity

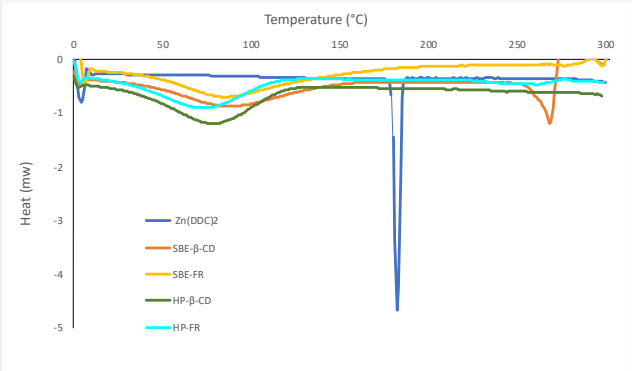

Fig. 2. *DSC Thermograph for CD-$Zn(DDC)_2$ complexes.*

MTT assay results has shown a strong cytotoxic effect against lung cancer cells, where the inclusion complexes of $Zn(DDC)_2$ were found to be more cytotoxic than the free drug due to the enhanced solubility of the formulations (data not shown).

CONCLUSIONS

The use of $Zn(DDC)_2$ as anticancer has always been challenged by its poor aqueous solubility. Inclusion complexes of $Zn(DDC)_2$ in CDs have overcome poor solubility issues to enable potential clinical application. The formulation of inclusion complexes was confirmed using thermal analysis. Results suggest that the developed formulations have a great potential for further studies for anticancer applications.

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