CYCLODEXTRIN-BASED SUPRAMOLECULAR DEEP EUTECTIC SOLVENT (CYCLODES): A NOVEL SYNERGIC APPROACH FOR POORLY SOLUBLE DRUG DELIVERY

Gennaro Balenzano[a], Giuseppe Francesco Racaniello[a], Ilaria Arduino[a], Angela Assunta Lopedota[a], Antonio Lopalco[a], Valentino Laquintana[a], Nunzio Denora[a,*]

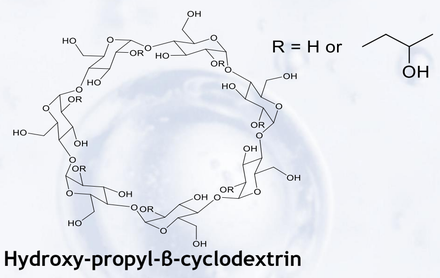
[a]Department of Pharmacy, Pharmaceutical Sciences, University of Bari "Aldo Moro", Via E. Orabona, 4, I-70125 Bari, Italy

mail: gennaro.balenzano@uniba.it

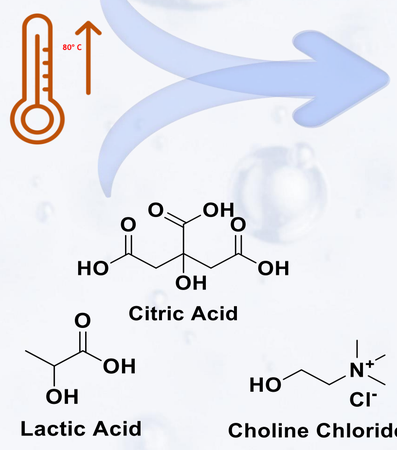
Deep Eutectic Solvent

Deep eutectic solvents (DES) represent a novel and green approach in chemistry being synthesized from readily available materials characterized by hydrogen bond acceptor and donor moieties.

These mixtures are prepared by heating and mixing two or more compounds, usually solids at room temperature (RT), at a specific molar ratio, resulting in a clear crystal liquid even at low temperatures [1]. All of these benefits and adaptable characteristics have helped to support the development of novel systems for potential new applications in a variety of fields over the past 20 years, including the potential use of DESs in the pharmaceutical industry as solvents for chemical reactions, liquids for extraction, or even as drug delivery systems (DDSs) [2].



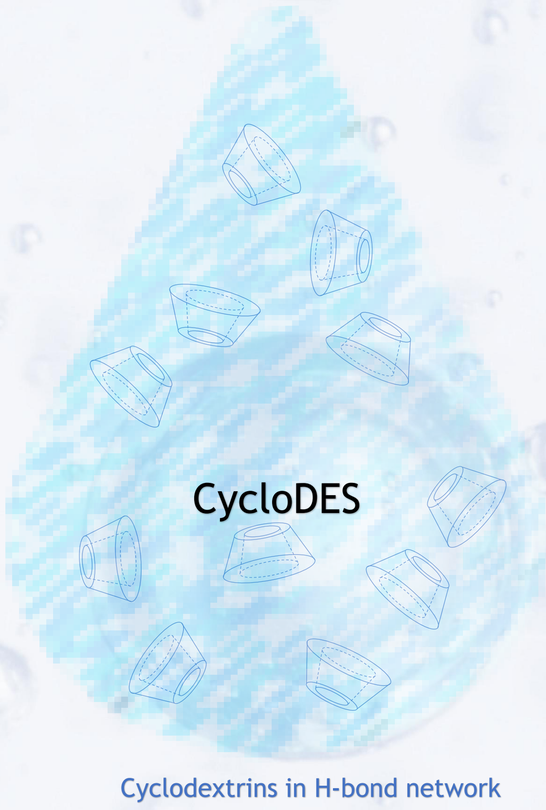
Hydroxy-propyl-ß-cyclodextrin



Citric Acid

Lactic Acid

Choline Chloride



Cyclodextrins in H-bond network

Aim of the Work

Herein, a new class of DES composed of a complexation agent, namely hydroxy-propyl-ß-cyclodextrin (HPßCD), was adopted as hydrogen bond donor to combine the two solubilization-enhancing approaches induced by supramolecular complexation and the DES generated using proper hydrogen bond acceptor.

For this purpose, cyclodextrin-based supramolecular DES (CycloDES) were physical-chemical characterized and loaded with three different BCS class II model drugs, specifically Cannabidiol (CBD), Indomethacin (IND), and Dexamethasone (DEX), evaluating the influence of different factors on the observed solubility and permeation compared with the only HPßCD/drug complexation.

Results and Discussion

Preparation and Characterization

CycloDES preparation

CycloDES were prepared with different components at a specific molar ratio through vigorous stirring and heating at 80°C for 24 hours.

A crystal-clear aspect confirmed the generation of the eutectic mixture.

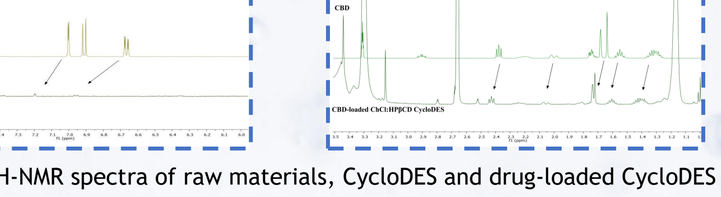


Figure 1. CycloDES preparation

^{1}H-NMR analysis

The values of chemical shifts indicated the interaction among the components with greater chemical shift values, evidence of hydrogen bonding formation, as seen in the figure. The spectra for the loaded samples showed that the drug structure was preserved during the incorporation process, and the chemical shift displayed the same displacement as that observed for the component, but to a smaller degree, implying the drug's inclusion in CycloDES but not their involvement in the mixture's structure.

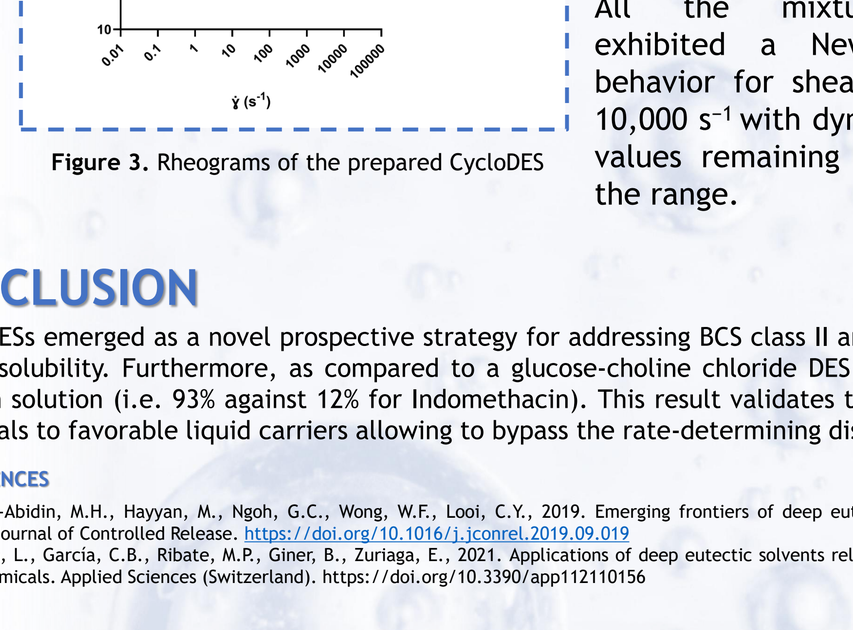


Figure 2. ^{1}H-NMR spectra of raw materials, CycloDES and drug-loaded CycloDES

Rheology of CycloDES

Figure 3. Rheograms of the prepared CycloDES

Rheological measurements were crucial for ensuring the development of systems suitable for various applications.

All the mixtures studied exhibited a Newtonian fluid behavior for shear rates below 10,000 s^{-1} with dynamic viscosity values remaining stable for all the range.

Solubility Enhancing Effect Evaluation

Although DEX solubility was already considerably enhanced by HPßCD alone, the binary system of LA and the ternary system of CA and LA demonstrated comparable results in terms of 158 and 230-time fold improvements over water solubility, respectively. All of the studied IND-containing CycloDES had higher solubility values than the control sample, which was a solution of drug and HPßCD solution. Finally, because of its previously proven instability in acidic environments, ChCl: HPßCD was the only appropriate CycloDES for CBD solubilization. As a result, CBD was loaded with a 45-fold and 175-fold improvement in terms of solubility when compared to HPßCD water solution and water, respectively.

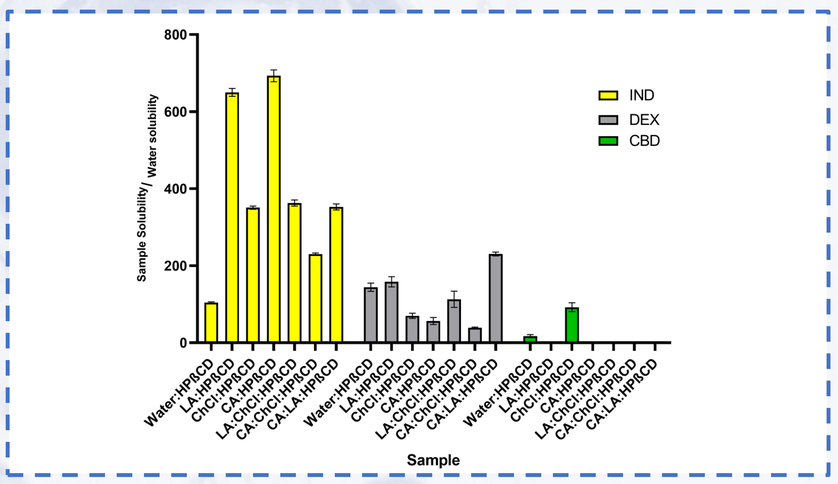


Figure 4. Drug solubility improvement in CycloDES against water solubility

After Dilution Stability

Glucose:ChCl DES was chosen as a benchmark for the structural analogy with ChCl:HPßCD DES and to investigate the impact of the synergy between HPßCD and DES. CycloDES revealed an enhanced capacity to keep a relatively high percentage of the drug in solution after the dilution. Following this observed synergy, it is significant to remark that the presence of HPßCD might solve one of the key DES-related difficulties when dilution is taken into account. On the other hand, by using CycloDES, it may be feasible to deliver poorly soluble medications while keeping them in solution after administration, enhancing their adsorption once at the target site.

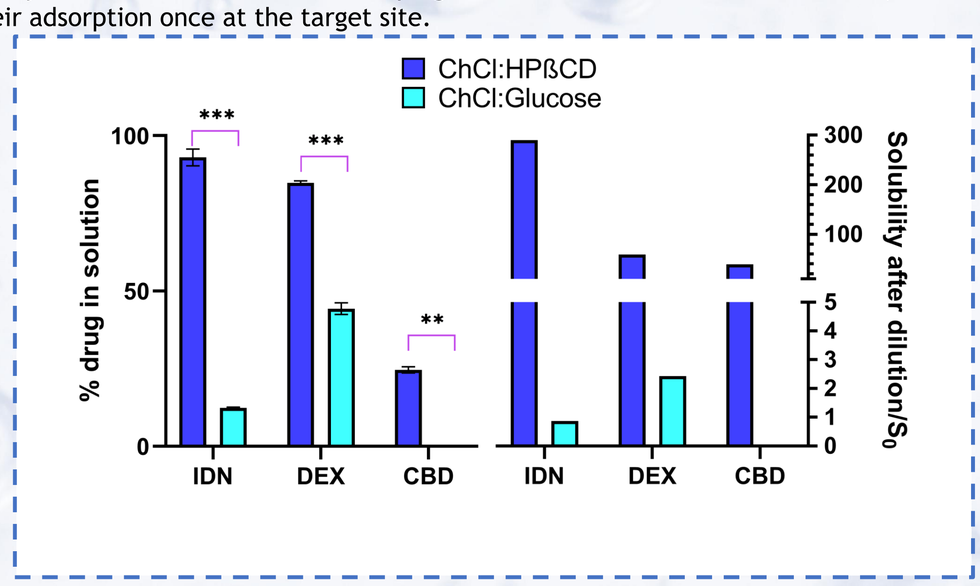


Figure 5. Drug solubility improvement in CycloDES against water solubility

Conclusion

CycloDESs emerged as a novel prospective strategy for addressing BCS class II and IV solubility issues, displaying at least a 100-fold improvement in the tested drug solubilities if compared to their water solubility. Furthermore, as compared to a glucose-choline chloride DES employed as a reference, CycloDESs demonstrated enhanced resistance to dilution, keeping a high proportion of drug in solution (i.e. 93% against 12% for Indomethacin). This result validates the solubility-enhancing effect, which is important for delivering BCS class II and IV drugs, passing from solid source materials to favorable liquid carriers allowing to bypass the rate-determining dissolving phase.

References

[1] Zainal-Abidin, M.H., Hayyan, M., Ngoh, G.C., Wong, W.F., Looi, C.Y., 2019. Emerging frontiers of deep eutectic solvents in drug discovery and drug delivery systems. Journal of Controlled Release. https://doi.org/10.1016/j.jconrel.2019.09.019

[2] Lomba, L., García, C.B., Ribate, M.P., Giner, B., Zuriaga, E., 2021. Applications of deep eutectic solvents related to health, synthesis, and extraction of natural based chemicals. Applied Sciences (Switzerland). https://doi.org/10.3390/app112110156