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Hybrid Lipid-Polymeric Nanoparticles for Enhanced Bioavailability of Vardenafil in Hepatic Encephalopathy Prevention: A Drug Repurposing Approach

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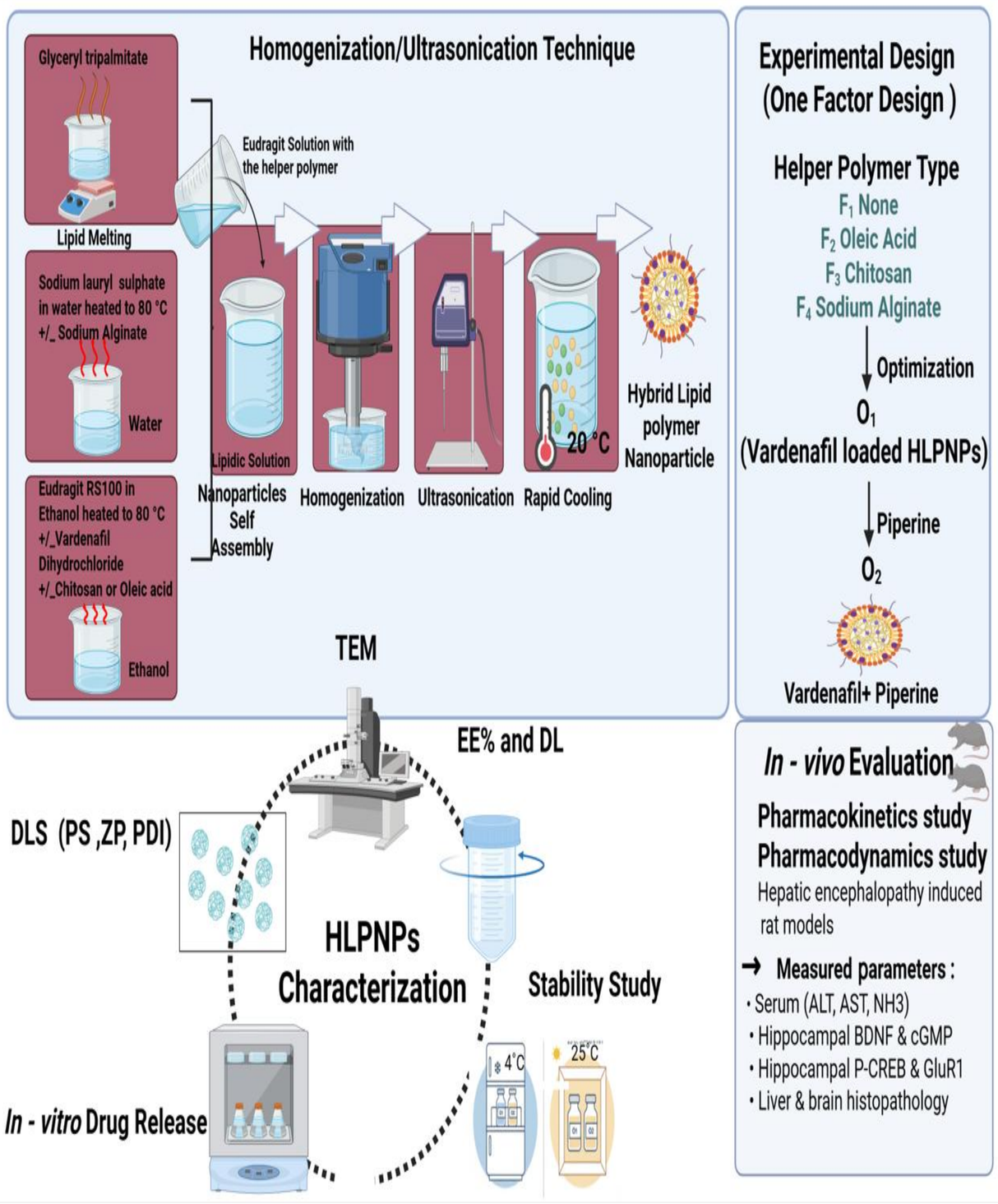
INTRODUCTION & AIM

Hepatic encephalopathy (HE) is a reversible neurocognitive disorder secondary to advanced liver failure, characterized by impaired cognition, altered behavior, and reduced quality of life. Its pathogenesis is primarily linked to the accumulation of ammonia and other neurotoxins resulting from hepatic dysfunction. The cyclic guanosine monophosphate (cGMP) signaling pathway; which plays a crucial role in neuroimmune regulation, has been implicated in the progression of HE. Vardenafil dihydrochloride (VD), a potent phosphodiesterase type 5 (PDE-5) inhibitor, enhances intracellular cGMP levels and may offer therapeutic potential for HE. However, its poor solubility and limited oral bioavailability hinder its clinical application. To overcome these challenges, hybrid lipid–polymeric nanoparticles (HLPNPs) are proposed as an advanced delivery system for VD. The incorporation of piperine, a known bioenhancer, within these nanoparticles may further improve VD's bioavailability and therapeutic efficacy. Therefore, this study aims to develop and optimize VD-loaded HLPNPs containing piperine as a bioavailability enhancer for potential prophylactic use against hepatic encephalopathy.

METHOD



RESULTS & DISCUSSION

Table 1 : Experimental design formulation, composition and response results

Formula code	Helper Polymer	PS (nm)	PDI	ZP (mV)	EE (%)
F_1	None	172.6 ±0.9	0.261 ± 0.03	-31.8 ±1.6	88.78 ±3.7
F_2	Oleic acid	126.8 ±0.3	0.177 ± 0.04	-32.3 ± 0.9	91.27 ±2.9
F_3	Chitosan	127.1 ±0.6	0.180 ± 0.05	-15.8 ± 1.9	93.81 ±1.8
F_4	Sodium alginate	171.7 ±0.2	0.224 ±0.03	-34.6 ±1.7	92.37 ± 1.7
F_5	None	173.0 ±0.8	0.270 ± 0.10	-30.3 ±2.0	87.67 ± 2.6
F_6	Oleic acid	124.7 ±0.3	0.160 ±0.03	-34.6 ±0.7	90.99 ±1.9
F_7	Chitosan	128.0 ±0.4	0.179 ± 0.04	-18.5 ± 0.4	94.00 ±2.8
F_8	Sodium alginate	174.2 ±0.1	0.250 ± 0.20	-33.8± 0.6	92.00 ± 1.9

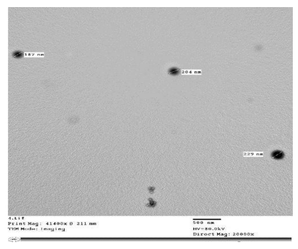


Figure 2: Transmission electron micrograph of O_1

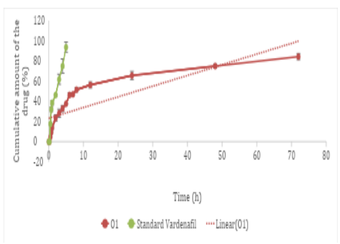


Figure *3: In-vitro* release profile of VD

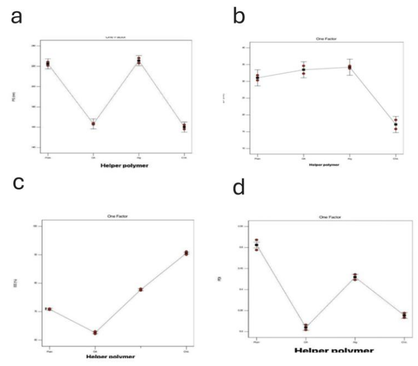


Figure 1: One-factor plot for (a) PS, (b) PDI, (c) ZP and (d) EE%

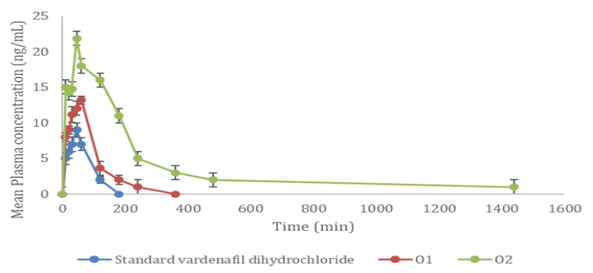


Figure 4: Mean plasma concentration-time curve of VD after oral administration.

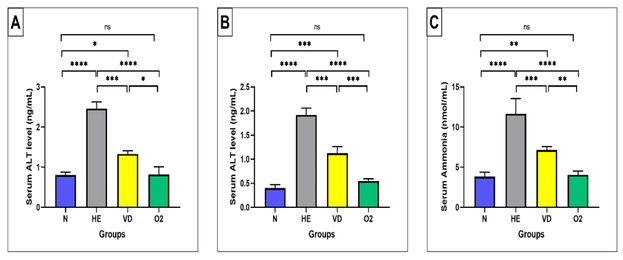


Figure 5:The effect of the different treatments on serum levels of: (A) Alanine aminotransferase (ALT),(B) Aspartate aminotransferase (AST), (C) ammonia

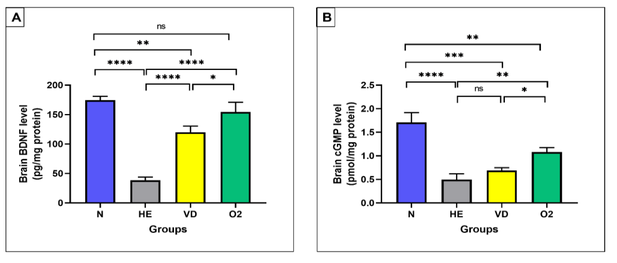


Figure 6: The effect of the different treatments on the hippocampal levels of: (A) Brain-derived neurotrophic factor (BDNF),(B) Cyclic guanosine monophosphate (cGMP)

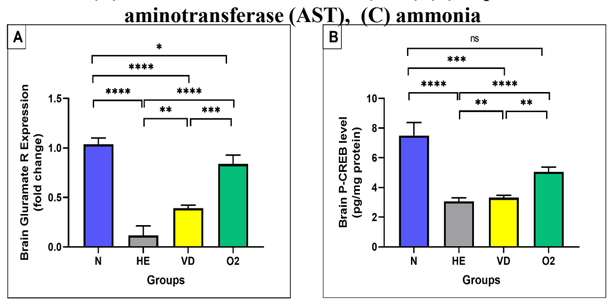


Figure 8: The effect of the different treatments on the hippocampal levels of: (A) Glutamate R1 expression (GluR1),(B) cAMP-responsive element binding protein (P-CREB)

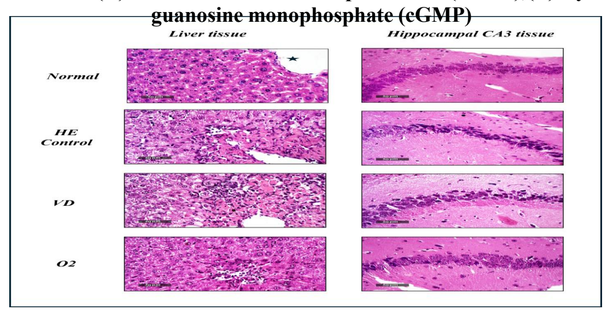


Figure 7: Histopathological examination of liver and hippocampus CA3 tissue of the different groups.

CONCLUSION

This study developed a novel vardenafil dihydrochloride (VD) formulation encapsulated in hybrid lipid–polymeric nanoparticles (HLPNPs) with piperine as a bioavailability enhancer. Oleic acid was identified as the optimal helper lipid, producing nanoparticles of 127 nm with a PDI of 0.18, zeta potential of −31.92 mV, and an encapsulation efficiency of 93%. The optimized formulation showed good stability at 4 °C and sustained drug release. Pharmacokinetic studies revealed that HLPNP-VD doubled VD bioavailability compared to the pure drug, and the addition of piperine resulted in a tenfold increase. In a hepatic encephalopathy (HE) rat model, a pharmacodynamics study showed significant improvement in liver function markers (ALT, AST, and ammonia) and restoration of hippocampal neurochemical balance BDNF, cGMP, GluR1, and P-CREB levels compared to standard VD treatment. Overall, these findings highlight HLPNPs as a promising delivery system for enhancing VD bioavailability, reducing dosage requirements, and improving therapeutic outcomes.

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