Enhancing Solubility and Bioavailability of Adefovir Dipivoxil to Treat Viral Infections

Lindlelyn Tabula[1], Abhijit Date[2], Madhur Kulkarni[3]

[1]Department of Tropical Medicine, Medical Microbiology, and Pharmacology, John A Burns School of Medicine, University of Hawai'I Manoa, Honolulu, HI, USA
[2] The Daniel K. Inouye College of Pharmacy, University of Hawaii at Hilo, Hilo, HI, USA
[3] Indira College of Pharmacy, Pune, Maharashtra, India

INTRODUCTION

- Hepatitis B is a viral infection that impacts about 257 million individuals globally. It may be acquired through blood, semen, or other bodily fluids of those that are infected. If left untreated, this may lead to cirrhosis, hepatocellular carcinoma or even death.
- Although the infection can be prevented via immunizations, individuals who do become infected with the virus rely on different forms of medication to suppress viral activity.
- Adefovir dipivoxil (ADV) is a nucleotide analog of adenosine monophosphate, which inhibits hepatitis B virus (HBV) reverse transcriptase and further causes chain termination of the viral DNA preventing the integration into the host genome.
- Despite the benefits, only 59% of orally administered ADV is available for the therapeutic effect. This could be attributed to the limited solubility of ADV. Hence, there is a need to improve solubility and bioavailability of ADV, which will lead to reduction in the therapeutic dose and dose-related side effects.

AIM

- To develop and evaluate inclusion-complexes and solid dispersions of ADV to improve its solubility and hence, the bioavailability which could lead to reduction in therapeutic dose of ADV.

OBJECTIVE

To enhance solubility and oral bioavailability of ADV by developing:

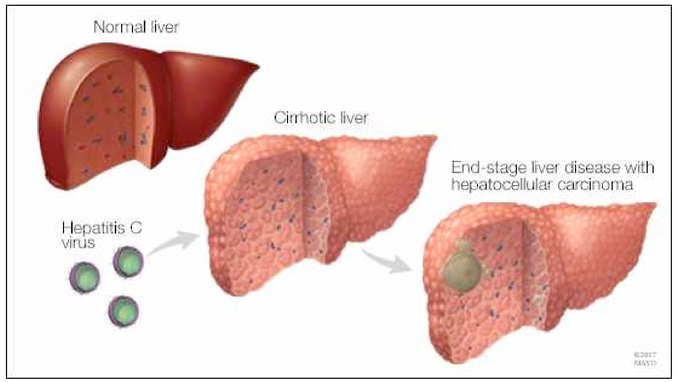
1. Inclusion-complexes of ADV and sulfobutyl ether-β-cyclodextrin: Cyclodextrins are cyclic oligosaccharides with a bucket shape structure. They have hydrophobic interior which allows for partial or complete shielding of hydrophobic drug and hydrophilic exterior which helps to solubilize the otherwise insoluble drug in the aqueous environment.
2. Solid dispersions of ADV: Solid dispersions are prepared by mixing the poorly soluble drug with hydrophilic carriers such as polymers or surfactants. They provide a hydrophilic environment for better wetting and dissolution of the drug.

APPROACH

1. Construction of standard plot of ADV using UV-Vis spectrophotometry: The standard plot was generated by graphing maximum absorbance vs concentration. The generated equation was used to calculate unknown concentrations of ADV in the future experiments.
2. Phase solubility studies of ADV in cyclodextrin (CD) solution: Concentrations of ADV vs. Cyclodextrin were graphed to determine association constant (how many molecules of cyclodextrin will interact with ADV) of the complex.
3. Preparation of the inclusion complex of ADV and CD involved various methods such as physical mixture, co-grinding, kneading, and co-evaporation using different solvents.
4. Preparation of solid dispersion of ADV and polymer (Polyethylene glycol 4000) or surfactact (Poloxamer 407) using melt fusion.
5. Characterization of inclusion-complexes and solid dispersions via *in vitro* dissolution.
6. Formulation of Tablets.

ACKNOWLEDGEMETS

Mahalo Nui Loa to Dr. Vivek R. Nerurkar, Dr. Angela Sy, Keeton Krause, and Indira College of Pharmacy students and faculty. This research was supported by the Minority Health International Research Training (MHIRT) Program at the University of Hawai'i through the NIMHD, National Institutes of Health (NIH) grant (T37MD008636-05). We acknowledge the support of UH Pacific Center for Emerging Infectious Diseases Research, COBRE funded through the NIGMS, NIH grant (P30GM114737).



"Hepatitis B medication complexed with solubility enhancer (Cyclodextrin) may decrease the effective dosage and reduce dose-related side effects"

QR CODE

ltabula@hawaii.edu

RESULTS

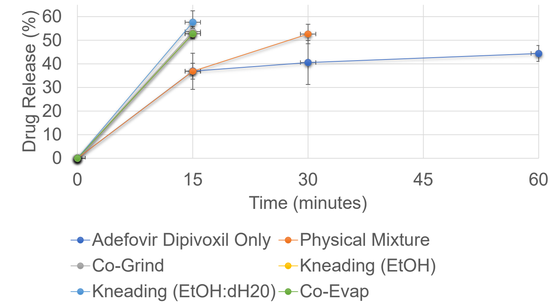


Figure 1: The method of preparation of ADV-CD complexes influenced the in vitro release of ADV (n=3 ± standard deviation)

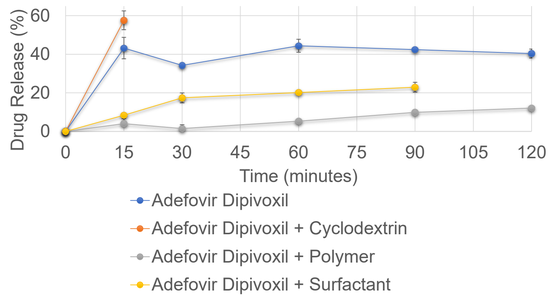


Figure 2: *In vitro* dissolution studies carried out in pH 7.2 phosphate buffer maintained at 37°C showed that ADV-CD inclusion complex showed highest and quickest drug release compared to ADV and ADV solid dispersions (n=3 ± standard deviation)

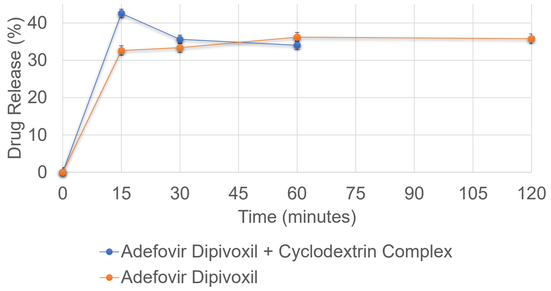


Figure 3: *In vitro* dissolution studies carried out in pH 7.2 phosphate buffer maintained at 37°C showed that ADV-CD inclusion complex containing tablet result in quicker release of ADV as compared to ADV tablet.

CONCLUSIONS

- Inclusion complexes of ADV and CD prepared by various methods such as physical mixing, co-grinding, co-evaporation and kneading showed significant enhancement in the rate and extent of drug dissolution. ADV-CD inclusion complex could be formulated as tablets to enhance the oral bioavailability of ADV for the treatment of HBV infection.

FUTURE DIRECTIONS

- Additional studies are warranted to establish the potential of the ADV-CD inclusion complex in enhancing the hydrolytic stability of ADV in the simulated gastrointestinal fluids which will further contribute towards the bioavailability enhancement.