EXTENDED ABSTRACT

DEVELOPMENT OF ORAL FORMULATIONS OF A BCS CLASS II DRUG – EZETIMIBE FOR IMPROVING ITS BIOAVAILABILITY AND THERAPEUTIC EFFICACY

Name of Student: **K. Mohan Raghava Srivalli** Roll No. **12621EN005**

Degree for which submitted: **Doctor of Philosophy in Pharmaceutics**

Name of Department/School: **Department of Pharmaceutics**

Signature of the Supervisor
(Dr. B. MISHRA)
Professor of Pharmaceutics
Department of Pharmaceutics
Indian Institute of Technology
(Banaras Hindu University)
Varanasi - 221005, India.

EXTENDED ABSTRACT

TITLE

Development of oral formulations of a BCS Class II drug – ezetimibe for improving its bioavailability and therapeutic efficacy.

BACKGROUND

Discovery of active pharmaceutical ingredients (APIs) by novel drug discovery technologies like high throughput screening and combinatorial chemistry has been producing clinically proven therapeutically active APIs. 70-90% of the clinically successful drug candidates, 40% of the APIs being marketed, and 80% of the drugs being marketed as tablets, are identified with low aqueous solubility.

Oral route is the most preferred route of administration and poor solubility is one of the main challenges to develop oral dosage forms with acceptable bioavailability. So, solubility improvement plays a crucial role in the development of oral pharmaceutical dosage forms. Numerous approaches, such as solubilization by cosolvents, complexation, solid dispersions, crystal engineering, cocrystals, salt formation, micronization, nanonization, etc. have been used to improve the solubility, dissolution and bioavailability of poorly soluble drugs.

The main purpose of any formulation research is to deliver the drug in its most bioavailable form. The basic requirement for such a formulation research is to consider the following three aspects in parallel: the physicochemical properties of the drug; selection of a suitable formulation; and the nature of excipients.

Drug:

The drug, ezetimibe (Eze), chosen in the present study, is a model BCS class II drug with low water solubility. Eze is chemically 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-

hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. It is the first of its kind hypocholesterolemic that serves as a cholesterol absorption inhibitor unlike other marketed lipid lowering agents that act by inhibiting the synthesis of cholesterol. Eze inhibits small intestinal absorption of cholesterol, but, being a P-glycoprotein (P-gp) substrate, the *in-vivo* absorption of Eze is lowered by P-gp efflux at the small intestinal brush border. The oral bioavailability of Eze is lowered to as low as 35% due to its low aqueous solubility and P-gp efflux.

Formulations:

The present investigation aimed to improve the oral bioavailability and therapeutic efficacy of Eze by employing three formulation approaches namely, cocrystallization, ternary cyclodextrin (CD) complexation, and nanonization.

Excipients:

The primary excipients employed in our study were nicotinic acid (NA) and nicotinamide (ND); hydroxypropyl-β-cyclodextrin (HPBCD); d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS); l-ascorbic acid-2-glucoside (AA2G).

NA, also known as niacin (vitamin B3), is a lipid lowering agent that acts by inhibiting lipolysis in adipose tissue. ND is an amide of niacin. It is safe and extensively used in humans and is highly hydrophilic in nature. HPBCD is the most commonly used water soluble CD derivative that has been employed in several marketed pharmaceutical products. TPGS is a novel lipid based highly water soluble non-ionic surfactant that has been approved as safe excipient by the United States Food and Drug Administration. It also exhibits P-gp inhibitory action and has been widely known to increase the solubility and bioavailability of water-insoluble drugs by many folds. AA2G is a facile hydrophilic excipient that has been approved as a food additive and is expected to be used as a

principle ingredient for solubilization in fat-soluble vitamin formulations and in other cosmetic products.

In the present study, Eze cocrystals (CoCs) were prepared using NA and ND as coformers; CD ternary complexes of Eze were prepared with HPBCD using TPGS/AA2G as ternary substance; and Eze NCs were prepared using TPGS and AA2G as stabilizers. Eze is a hypocholesterolemic, low water soluble, P-gp substrate. The excipients employed to formulate Eze were hydrophilic with or without additional potentials like P-gp inhibitory action or hypocholesterolemic action. We hypothesized that the selected formulations may serve to not only improve the solubility and dissolution properties of Eze *in-vitro* but also to enhance the *in-vivo* performance of Eze by either offering a synergistic hypocholesterolemic effect or improving its *in-vivo* absorption at the small intestinal brush border.

OBJECTIVES OF THE STUDY

The core objective of the present research work was therefore to improve the oral bioavailability and therapeutic efficacy of Eze by:

- Formulating Eze using following approaches - cocrystallization; CD ternary complexation; and nanonization.
- *In-vitro* and *in-vivo* characterization of each formulation approach.
- Comparing the optimized formulation from each formulation approach at *in-vitro* and *in-vivo* levels to propose the most suitable formulation approach to deliver Eze with highest bioavailability.

STUDY DESIGN

The present research work was carried out in four parts:

Part I: Preparation and characterization of Eze CoCs.

Part II: Preparation and characterization of ternary CD complexes of Eze.

Part III: Preparation and characterization of Eze drug NCs.

Part IV: Evaluating the effect of each formulation approach on the *in-vitro* and *in-vivo* performance of Eze.

WORK DONE AND OUTCOME OF THE STUDY

Part I: Preparation and characterization of Eze CoCs.

Cocrystallization is one of the approaches to enhance the physicochemical properties of poorly water soluble drugs. The aim of this part of research was to prepare and characterize two new CoCs of Eze, using NA and ND. The ratio of drug:coformer in each CoC was optimized by solution state phase solubility and Job's plot studies. The Eze-NA CoC and Eze-ND CoC were crystallized with solvents, ethanol and acetone, respectively. The characterization studies covered the following: FTIR, DSC, powder XRD, SEM, aqueous solubility, dissolution, bioavailability and antihypercholesterolemic activity. FTIR, DSC and powder XRD confirmed the formation of CoCs. SEM pictures showed the distinguished morphology of CoCs compared to the respective parent components. Cocrystallization improved the solubility, dissolution, bioavailability and antihypercholesterolemic properties of Eze. The improvement in *in-vitro* and *in-vivo* properties may be attributed to distinguished CoC formation by differential hydrogen bonding of Eze with NA/ND and altered crystal packing style of each CoC.

Part II: Preparation and characterization of ternary CD complexes of Eze.

The purpose of this part of study was to improve the aqueous solubility, dissolution, pharmacokinetic and pharmacodynamic properties of a BCS class II drug, Eze by preparing ternary CD complex systems. The potential synergistic effect of two novel hydrophilic auxiliary substances, TPGS and AA2G on HPBCD solubilization of poorly water soluble hypocholesterolemic drug, Eze was investigated. In solution state, the compositions of the binary and ternary systems were optimized by phase solubility and Job's plot studies. The solid complexes prepared by freeze-drying were characterized by FTIR, DSC, powder XRD, NMR and SEM. The analytical techniques confirmed the formation of inclusion complexes in the binary and ternary systems. HPBCD complexation improved the solubility and dissolution properties of Eze and the addition of ternary component resulted in further improvement in the properties even compared to the binary system. Both the ternary systems remarkably enhanced the bioavailability and hypocholesterolemic properties of Eze.

Part III: Preparation and characterization of Eze drug NCs.

NCs have been widely accepted as potent formulations to overcome poor solubility, dissolution and bioavailability problems of hydrophobic drugs. NCs of Eze, a model BCS class II and hypocholesterolemic drug were developed using bottom up precipitation methods. TPGS and AA2G were the two stabilizers whose potential in developing Eze NCs was investigated. The formulations were systematically optimized by applying suitable experimental designs. Particle size and zeta potential portrayed the potential of both the stabilizers in producing Eze NCs. The optimized NC formulations were evaluated for *in-vitro* solubility and dissolution, solid state characters and *in-vivo* bioavailability and antihypercholesterolemic activity. The PXRD and DSC studies

confirmed the retention of crystallinity and the SEM images indicated lack of aggregation in dried NCs. Both AA2G and TPGS were identified as suitable stabilizers in nanonizing Eze and the NCs improved the *in-vitro* solubility and dissolution properties and enhanced the *in-vivo* bioavailability and hypocholesterolemic performance of Eze.

Part IV: Evaluating the effect of each formulation approach on the *in-vitro* and *in-vivo* performance of Eze.

Eze cocrystals were prepared using NA and ND as coformers; Ternary CD complexes of Eze were prepared with HPBCD using TPGS/AA2G as ternary substance; and Eze NCs were prepared using TPGS and AA2G as stabilizers. Two different formulations were prepared using each formulation approach and one optimized formulation was arrived at. The optimized formulation obtained employing each of the above approaches was compared at *in-vitro* and *in-vivo* levels and also with a marketed tablet formulation. TPGS based NCs were identified as the most suitable formulation as they produced the maximum enhancement in solubility, dissolution, bioavailability and pharmacodynamics of Eze. The dose reduction efficiency was also studied and reported for each of the optimized formulation.

CONCLUSION

The primary objective of a formulation development process is to deliver a particular drug with highest possible bioavailability by designing a most suitable formulation which involves use of minimum number of excipients and easiest possible technology so as to keep the cost of development as low as possible.

The present study aimed to improve the oral bioavailability and therapeutic efficacy of Eze by employing three formulation approaches namely, cocrystallization, ternary CD complexation and nanonization.

The study successfully identified:

1. NA and ND as novel coformers to generate Eze CoCs.
2. AA2G and TPGS as beneficial ternary components to Eze-CD systems.
3. AA2G and TPGS as suitable NC stabilizers for Eze.

NCs formulation was identified as the most suitable formulation approach and TPGS based NCs was identified as rational, simplest, economic, and most promising oral formulation for improving the *in-vitro* and *in-vivo* performance of Eze.