Enhancement the Bioavailability of Fenofibrate using Self emulsifying Microspheres and Dry emulsion

A thesis submitted

By

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Abstract

Oral administration of fenofibrate (FF) is considered a practical route of administration for enhancing the bioavailability of the drug. However poor solubility of the drug as well as poor absorption is some of the major limitations which should be overcome when considering this route. Self emulsifying microspheres (SEM) by virtue of forming the drug in a molecular form as solid dispersion and small particle size can greatly enhance the drug absorption. Incorporation of the drug in lyophilized dry emulsion provides higher dissolution and better bioavailability. The objective of this study was to prepare FF loaded self emulsifying microspheres and lyophilized dry emulsion for the oral route to improve the drug bioavailability and provide high blood levels of fenofibric acid which is the active metabolite of fenofibrate.

FF loaded self emulsifying microspheres were successfully prepared using quasi solvent diffusion method to form the drug in a molecular form and FF loaded lyophilized dry emulsion was successfully prepared by lypholization to enhance the dissolution and the bioavailability of the drug. A full factorial design was constructed for the self emulsifying microspheres to study the influence of four independent variables namely; the type of the polymer, the amount of Aerosil, the amount of talc and the type of the oil. The dependent variable was the entrapment efficiency percentage (EE %). Bioavailability and pharmacokinetic study of fenofibrate self-emulsifying microspheres and dry emulsion in human volunteers was performed for the selected FF self emulsifying microspheres and dry emulsion formulations. FF loaded dry emulsion showed smaller particle size and higher entrapment efficiency (EE %) compared to their alternative self emulsifying microspheres. Also they had higher dissolution pattern than alternative self emulsifying microspheres. Both self emulsifying microspheres and dry emulsion showed good stability up to six months. FF loaded self emulsifying microspheres and dry emulsion which showed reasonable entrapment efficiency (63% and 74%) were selected for further comparative studies. FF loaded self emulsifying microspheres (F6) were

prepared by quasi solvent diffusion method using drug loaded in castor oil (0.8 gm containing 0.667 gm drug), Polymer: HPMC AS LF (0.1 gm), Aerosil 200:0.4 g, Talc:0.5 g, while dry emulsion (E6) was prepared by the same components using lypholization technique. Both self emulsifying microspheres and dry emulsion had high values of yield, high drug loading, small angle of repose, small particle size and high values of entrapment. It should be mentioned that dry emulsion has higher values of yield, higher drug loading, smaller angle of repose, smaller particle size and higher values of entrapment. Both self emulsifying microspheres and dry emulsion are capable of formation of microemulsion upon contact with the intestinal fluid. The microemulsion formed by the microspheres and dry emulsion was characterized for spontaneity of self-emulsification, droplet size and polydispersity index analysis, viscosity, zeta potential, Count rate, Conductivity and %Transmittance. DSC studies of the microspheres and dry emulsion showed low crystallinity indicating the presence of drug in amorphous form. The pharmacokinetics in human plasma showed that the relative bioavailability of self emulsifying microspheres and dry emulsion was enhanced compared to that of the market product (Lipanthyl ®) with values of 265.52% and 243%, respectively. It is worthy to note that the method of preparation had a significant effect on the bioavailability of fenofibrate, as evidenced by the significantly shorter (T_{max}) of lyophilized dry emulsion (E6) compared to self emulsifying microspheres (F6), with values of 2.00 and 2.50 hr, respectively.

Therefore, this study revealed that enhanced absorption of fenofibrate formulated in the form of self emulsifying microspheres and dry emulsion following its oral administration is due to enhancement of the dissolution of the drug.

Keywords: Oral drug delivery; Self emulsifying microspheres; Dry emulsion; Fenofibrate; Bioavailability.

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List of Abbreviations

Adv Advanced

AHA American Heart Association

Alex Alexandria

ANOVA Analysis of variance

apoA-I Apolipoprotein A-I

apoA-II Apolipoprotein A-II

APOB Apolipoprotein B

AUC_{0-24} Area under the plasma concentration-time curve

BCS Biopharmaceutical classification system

BS Bile salt

C Carbon

CHL Cholesterol

C.V Coefficient of variance

C/L Coconut/labrasol

CE Collision energy

C_{max} Peak plasma concentrations

^{o}C Celsius

Co Company

cp Centipoise

CXP Collision exit potential

CYP450 Cytochrome P450

D Drugs

DE Dry emulsion

df Degree of freedom

DP Declustering potential

DSC Differential scanning calorimetry

EE % Entrapment efficiency percent

EP Entrance potential

FDA Food and drug administration

FF Fenofibrate

GI Gastro intestinal

GIT Gastro intestinal tract

HCHOLA3 Hypercholesterolemia autosomal dominant, 3

HDL High density lipoprotein

HLB Hydrophilic lipophilic balance

HMG-CoA 3-hydroxy-3-methylglutaryl-coenzyme A

HPMC Hydroxy propyl methyl cellulose

HPMC AS Hydroxypropyl methylcellulose acetate succinate

HPMC AS LF Hydroxy propyl methyl cellulose acetate succinate fine form

HPMC AS LG Hydroxypropyl methylcellulose acetate succinate granular form

IDL Intermediate density lipoprotein

Int. J.Pharm International journal of pharmaceutics

IS Internal standard

LC-MS/MS Liquid chromatography mass spectrometry

LCT Long chain triglycerides

LDL Low density lipoprotein

LDL Low density lipoprotein

LDLRAP1 Low density lipoprotein receptor adaptor protein

Lz Elimnation rate constant

M Molar

M/N Maisine /nigella

m/z Mass/charge ratio

MCT Medium chain triglycerides

MRM Multiple reaction monitoring

MRT Mean residence time

nm Nanometer

O/W Oil in water

P Probability

PCSK9 Proprotein convertase subtilisin/kexin type 9

PDI Polydispersity index

PEG Poly ethylene glycol

P-gp P-glycoprotein

PL Phospholipids

PPARs Peroxisome proliferator-activated receptors

PPARα Peroxisome proliferator-activated receptor α

psi, Pound per square inch

r^2 Coefficient of determination

SCT Short chain triglycerides

SD Standard deviation

SE Self-emulsifying

SEDDS Self emulsifying drug delivery system

SEM Self emulsifying microspheres

SES Self-emulsifying systems

SLN Solid lipid nanoparticles

SLS Sodium lauryl sulphate

SMEDDS Self-micro emulsifying drug delivery systems

SNEDDS Self-nano emulsifying drug delivery system

S-SEDDS Solid self emulsifying drug delivery system

T% Transmittance Percentage

TEM Transmission electron microscope

TG Triglyceride

Tg glass transition temperature

T_{max} Time needed to reach maximum concentration of active metabolite

TPGS Tocopheryl polyethylene glycol 1000 succinate

VLDL Very low density lipoprotein

wt/wt Weight per weight

ZS Zeta sizer

λ_{max}. Lambda of maximum absorption

Λz Terminal elimination rate constant

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