

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 lyophilization 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 lyophilization 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
AUC₀₋₂₄	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
°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 pharmaceuticals
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	Elimination 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
r²	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
T_g	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
Λ_z	Terminal elimination rate constant

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