I

PLASMA AND BRAIN PHARMACOKINETICS OF DICLOFENAC, IBUPROFEN AND THEIR HYDROXYETHYL ESTERS

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This Thesis Was Submitted in Partial Fulfillment of the Requirements for the Master's Degree in pharmaceutical sciences

Faculty of Graduate Studies

Isra University, Amman, Jordan

May,2018

II

COMMITTEE DECISION

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I, Rawan Radi AL-abadleh, authorize Israh University to supply hard and electronic copies of my thesis to libraries, establishments, or bodies and institutions concerned with research and scientific studies upon request, according to the university regulations.

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DEDICATION

This thesis is dedicated to my parents Radi & Najah

who have always loved me unconditionally and

whose good examples have taught me to work hard for the things that I aspire to achieve.

This work is also dedicated to my brother, Mohammad and

to my sisters, Reham, Ruba, Baraa, Esraa, Anwar & Jomana.

The greatest dedication is to my dear uncle Faisal Jaafreh.

ACKNOWLEGEMENT

Thank God who helped me to accomplish this work

First and foremost, I have to thank my parents for their love and support throughout my life. Thank you both for giving me strength to reach for the stars and chase my dreams. My only brother and six sisters deserve my wholehearted thanks as well.

There have been many people who have walked an alongside me during the last 3years. They have guided me, placed opportunities in front of me and showed me the doors that might be useful to open. I would like to thank each and every one of them

I would especially to thank Dr. Jamal Al.jilani & Dr. Ahmad A.Talhouni.

Dr.Jamal Al.jilani thank for your guidance, encouragement and contagious positive attitude. I am extremely grateful for everything you have taught me, you have been awesome. Thanks also to my supervisor Dr. Ahmad A.Talhouni for good advice during the final writing process.

Especially thanks to Research Laboratory Supervisor Mousa Siam for all guidance and thanks for every one worked in the faculty of pharmacy.

To all my friends, thank you for your understanding and encouragement in many, many moments of crisis. Your friendship makes my life a wonderful experience . I cannot list all the names here, but you are always on my mind.

This thesis is only a beginning of my journey.

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List of abbreviation & symbols

Abbreviation or Symbols	Definition
%ID/g	Percentage of injected dose that is delivered per gram brain

AA	Ascorbic Acid
AchE	Acetylcholinesterase
AD	Alzheimer's Disease
AJ	Adherens Junction
AMT	Adsorptive-Mediated Transcytosis
APP	Amyloid β Protein Precursor
AUC $_{0-t}$	Area under the concentration up to the last measurable
Aβ	Amyloid Beta
BBB	Blood-Brain Barrier
BchE	Butyryl cholinesterase
BCSFB	Blood-Cerebrospinal Fluid Barrier
CDS	Chemical Delivery System
C_{max}	Maximum Concentration
CMT	Carrier-Mediated Transport
CNS	Central Nervous System
COX	Cyclooxygenase
CP	Choroid Plexus
CSF	Cerebrospinal Fluid
CVOs	Circumventricular Organ
Da	Dalton
DAKG	Diacetyl Ketoprofen Glyceride
DHAA	Dehydro-Ascorbic Acid
DHP	Dihydropyridine/Pyridinium
ECF	Extracellular fluid
EP	Eppendorf tube
GIT	Gastrointestinal Tract
GLUT1	Glucose-Transporter 1
HED	Hydroxyethyl Diclofenac
HEI	Hydroxyethyl Ibuprofen
HPLC	High Performace Liquid Chromatography
IP	Intraperitoneal

ISF	Interstitial Fluid
K	Lipid- water partition coefficient
K01	The rate of absorption
K10	The rate of elimination
K_{disapp}	First-order rate constant
Km	Equililbrium distribution constant
L	Membrane thickness
LAT1	L-type Amino acid Transporter 1
L-DOPA	L-dihydroxyphenyl Alanine
Log P	Logarithm of the n-octanol-water partition coefficient
MW	Molecular Weight
NSAIDs	Non-steroidal anti-inflammatory drugs
pAUC	Plasma area under the curve
PG	Prostaglandin
P-gp	P-glycoprotein
Pka	Dissociation constant
Pm	Permeability
PS	Permeability-surface area
RMT	Receptor-Mediated Transport
SVCT2	Sodium-Dependent Vitamin C Transporter 2
$T_{1/2}$	Half-live
TJ	Tight Junction
T_{max}	Time at which the maximum concentration

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ABSTRACT

Many compounds have a limited ability to penetrate into the central nervous system (CNS) due to the existence of the blood-brain barrier (BBB). The CNS distribution of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and diclofenac is of interest because is an effective therapeutic agent for the treatment of neurodegenerative disease in which the long-term use of NSAIDs may reduce the risk, or delay the onset of Alzheimer's disease (AD). The aim of this study was to evaluate the brain-targeting efficiency of two prodrugs of NSAIDs, hydroxyethyl ibuprofen (HEI) and hydroxyethyl diclofenac (HED) after intraperitoneal (IP) administration to rats using the pharmacokinetic analysis in plasma and brain. In vitro stabilities of the two prodrugs were evaluated to determine both their stability in the aqueous medium, and their feasibility to undergo enzymatic cleavage by esterases in biosample, also in vivo study was performed on rats for pharmacokinetic studies. The concentration of the compounds in biosamples including plasma and brain were measured using High performance liquid chromatography (HPLC). The mobile phase that used for diclofenac and HED was consisted of80% methanol, 20% water, to each litre, 2ml acetic acid was added. While the mobile phase for ibuprofen and HEI composed of 20mMphosphate buffer solution(pH2.5) and acetonitrile in volume ratios of 55:45 and 56:54 for plasma and brain sample respectively the pH for the entire mobile phase was 5. The result

showed that the AUC_{brain}/AUC_{plasma} ratio was 0.16, 0.16, 1.234, 0.027 for ibuprofen, HEI, HED, and diclofenac respectively. The HED exhibited enhancement of brain targeting as prodrug where its ratio is 45 fold than diclofenac. The ratio for HEI and ibuprofen is the highest but at the same time it is equal to each other, despite that the AUC_{plasma} of ibuprofen is twice more than for HEI, whereas the ibuprofen level in brain and plasma are highly correlated to each other, this is may be explained that the rate of absorption of ibuprofen resulted from IP administration of HEI to the brain is more than the other and the T_{max} is very shorter 2.472. In conclusion, the hydroxyethyl-related structure may play an important role in transport across the BBB.