Formulation of Injectable Controlled Release Valproic Acid in Castor Oil Base

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Valproic acid (VA) is a known Antiepileptic medication, is given orally in a form of solutions or tablets and intravenously. Due to, oscillations of its plasma levels from these dosage forms, the serious adverse side effects on various systems especially liver toxicity and liver damage, and the unpleasant bitter taste of the oral solutions, there is a need to formulate VA in a way to minimize plasma oscillation and the unwanted toxic side effects this can be achieved by controlling the release of the drug,

VA was prepared as an intramuscular oil injectable solution, where VA is physically entrapped in castor oil vehicle. This injectable solution was prepared by using an ordinary mixing method, according to the US patent 9833459. By mixing ethyl alcohol, benzyl benzoate, valproic acid, α-tocopherol, polysorbate 80 (tween® 80) and castor oil. A homogenous, pale yellow clear oily injectable solution was obtained. Three formulas with different concentrations of VA were prepared using this method (4 g, 5 g, and 6 g). These injectable solutions were analyzed for clarity, stability at different temperatures at 5ºC ± 3ºC, 25˚C ± 2°C/60% RH ± 5% RH, and 40˚C ± 2°C/75% RH ± 5% RH for the three formulas, quantify the drug content, viscosity determination, injectability testing

and characterization of the in vitro release profile for the finished products. The three formulas had shown a great clarity against white back gowned and under a strong light, stability at different temperatures 5ºC ± 3ºC, 25˚C ± 2°C/60% RH ± 5% RH, and 40˚C ± 2°C/75% RH ± 5% RH were checked visually and using HPLC method, they show a great stability under these conditions, drug content for F1 was 107.7%, F2 was 98.4% and F3 was 93%, even the viscosity of the three formulas doesn't change by using different speed rates 25, 50 and 100 rpm, the viscosity for F1 was 20mPa˙s, for F2 was 35.5mPa˙s and for F3 was 52mPa˙s, and the manual injectability testing for F1 performed by 20 different individuals gave a good timing profile approximately 15.73 sec. In addition the in vitro release for the three formulas in buffer solution PH 7.4, showed that the release started after 24hrs and lasts for 16 days and the % release reaches to 99.8% in F1, 99.40% in F2 and 97.8% in F3.

COMMITTEE DECISION

This Thesis/Dissertation (Formulation of Injectable Controlled Release Valproic Acid in Castor Oil Base) was successfully Defended and Approved on …….

Examination Committee Signature

Dr. Samer Hasan Hussein-Al-Ali (Supervisor).

Dr. JabarFaraj Al-Wakeel (Co-supervisor).

Dr. Jamal Al- Karad (Internal Member).

Dr. Fatima Ali Tawfiq (External examiner).

Dedication

This thesis is dedicated to:

The sake of Allah, my Creator and my Master,

My great teacher and messenger, Mohammed (May Allah bless

and grant him), who taught us the purpose of life,

My great parents, who never stop giving of themselves in countless

ways,

My dearest husband, who supported me a lot,

My beloved brothers and sisters.
My beloved kids: Rayan, and Jad.

To all my family, the symbol of love and giving,

My friends who encourage and support me particularly, my best friend RawanHijawi

All the people in my life who touch my heart,

I dedicate this research.

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LIST OF ABBREVIATIONS OR SYMBOLS

MRDDS	Modified release drug delivery system
Cp	Plasma drug concentration
MEC	Minimum effect concentration
MTC	Minimum toxic drug concentration
VA	Valproic acid
CO	Castor oil
IM	Intramuscular
HDACs	Histone deacetylases
HIV	human immunodeficiency virus
CSF	Cerebrospinal fluid
NA	Not available
DDS	Drug delivery system
PCDDS	Parenteral controlled Drug delivery system
UDP-glucuronosyltransferase	Uridine 5'-diphospho-glucuronosyltransferase
IV	Intravenous
MCT	Medium chain triglycerides
BSS	British Standard Specification
USP	United States Pharmacopoeia
BP	British pharmacopoeia
RA	Ricinoleic acid
PLGA	Poly lactic-co-glycolic acid
GnRH	Gonadotropin-releasing hormone

LIST OF ABBR`EVIATIONS OR SYMBOLS

HPLC	High Performance Liquid Chromatography
AUC	Area Under the Curve
KH_2PO_4	potassium di hydrogen phosphate
NaOH	Sodium hydroxide
ICH	International Conference on Harmonization