Formulation of Injectable Controlled Release Valproic Acid in Castor Oil Base

By
Rawand Mohammed Salah Doghmosh

Supervisor
Dr. Samer Hasan Hussein-Al-Ali

Co-Supervisor
Prof. Dr. JabarFaraj Al-Wakeel.

This Thesis was submitted in Partial Fulfillment of the Requirements for the Master’s Degree of Pharmaceutical Sciences.

Faculty of Graduate Studies
Isra University
جامعة الإسراء

نموذج تفويض

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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 5°C ± 3°C, 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 5°C ± 3°C, 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.
In the Name of Allah, the Most Merciful and the Most Compassionate.

First and foremost, my acknowledgment and limitless thanks goes to Allah who made this work become truth.

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I would like to express my sincere gratitude deepest thanks to my Supervisor Dr. Samer Al-Ali, for his scientific guidance and support. Wishing him continuous progress.

I would like to express my sincere gratitude deepest thanks and appreciation to my Co-Supervisor Dr. JabarFaraj Al-Wakeel, who gave me the project idea, who shows me the right way to take throw the whole experiment period, I really appreciate his precious time that he gave to make this work possible and I wouldn’t forget the tremendous scientific support for me. He was a professor, a teacher, and a father. I would like to dedicate this work, my words, thanks and my appreciation to him, because without him this would be hard to accomplish.

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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>KH$_2$PO$_4$</td>
<td>potassium di hydrogen phosphate</td>
</tr>
<tr>
<td>NaOH</td>
<td>Sodium hydroxide</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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