



Neusilin®

Formulation of Sodium Valproate tablets with Neusilin

Sodium valproate has been widely used as an anti-epileptic agent to cure epilepsy and prevent epileptic stroke. Frequent administration of the tablet is often recommended to sustain blood plasma levels of sodium valproate. A slow and sustained release of the active ingredient will be beneficial to patients who need to maintain sustainable levels of sodium valproate in the blood plasma.

Due to its highly hygroscopic nature, sodium valproate formulations often poses problem during production and storage. In this newsletter, we refer to a patent published in Japan in 1987 (Shou 62-81309) where **Neusilin®** was successfully used to formulate sustained release sodium valproate tablets with excellent stability.

Method of preparation of sustained release sodium valproate tablets

Example: Sodium valproate (200 parts) dissolved in water was absorbed on to **Neusilin®** (97 parts) and dried in an oven to make a free flowing powder. This portion was mixed with ethyl cellulose (45 parts) and 1,2-dichloroethane (100 parts). The mixture was kneaded and homogenized before drying in an oven. Sodium valproate tablets (345 mg, Φ 10 mm) were manufactured by direct compression with a suitable lubricant (magnesium stearate, 3 parts). The tablets were then film coated using suitable film coating materials. For therapeutic use, the authors of the patent recommend 400-1,200 mg of sodium valproate orally once or twice a day depending on the age and body weight of the patient.

Dissolution rate of the tablets were calculated by determining the amount of valproic acid in dilute hydrochloric acid solution using gas chromatography.

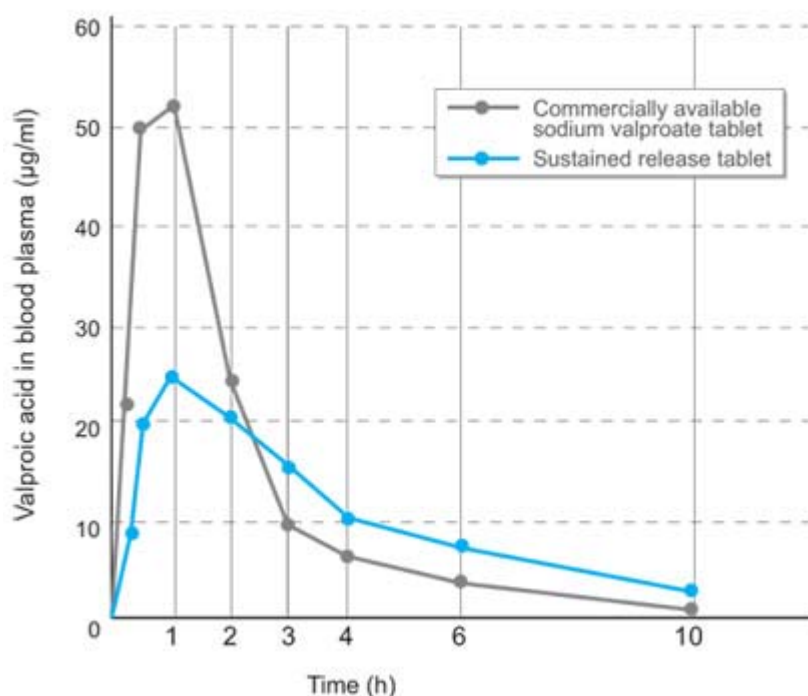
Table 1. Dissolution rate of sodium valproate tablets

Sample Tablets	Dissolution volume (n=6, Mean%) after					
	1h	2h	3h	4h	5h	6h
Sodium valporate - 100mg	45.2	63.4	72.1	84.6	91.3	95.0
Sodium valproate- 200mg	45.0	60.0	70.2	75.0	83.4	91.3
Sodium valproate-300mg	40.1	62.0	73.4	83.2	90.0	95.4
Marketed tablet -Sodium valproate -200mg	100.0	-	-	-	-	-

Pharmacological tests

Male Beagle dogs (body weight 11-14 kg) fasted overnight were orally administered 2 tablets each. Both control and experimental batch received commercially available sodium valproate tablets and sustained released tablets containing 200 mg sodium valproate respectively. Blood sampling was performed at 0.25, 0.5, 1, 2, 3, 4, 6 and 10 h after administration and the valproic acid levels in plasma were determined by gas chromatography.

Fig 1. Valproic acid levels in blood plasma of Beagle dogs after administering 2 tablets of 200 mg of sodium valproate



Stability tests

The sustained release tablets packed in Press Through Package (PTP) with polyvinyl chloride and aluminum foil were stored at 40°C, 75% RH for 3 months (accelerated stability tests). Appearance, hardness, content and dissolution tests were carried out to evaluate stability.

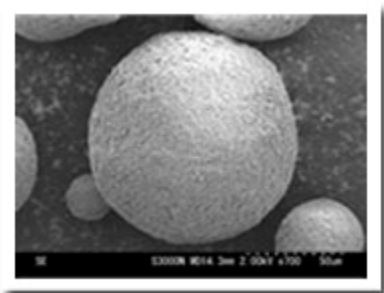
Table 2. Accelerated stability test data of sodium valproate tablets

Storage conditions	Appearance	Hardness (Kg/cm ²)	Content (%) (Valproic acid assay)	Dissolution test t ₅₀ (h)*
Onset	White film coated tablet	20	100	1.4
Room temperature (3 months)	No Change	21	100	1.5
40°C, 75% RH (3 months)	No change	18	99	1.4

*t₅₀; Hours needed for dissolving 50% of sodium valproate from the tablet

Conclusions

Neusilin® was successfully used in preparation of sustained release tablets of sodium valproate. The formulation overcame problems associated with stability of highly hygroscopic API like valproic acid as well as frequent administration to maintain sufficient levels of API in blood plasma. The success in this formulation can be attributed to the unique physical characteristics of **Neusilin®**. Large amounts of API can be loaded on to **Neusilin®** because of its highly porous nature and large surface area. **Neusilin®** is highly flowable, protects deliquescent drugs and enables the production of high quality tablets at lower compression forces.



Neusilin® US2 (X700)

Chemical formula: $\text{Al}_2\text{O}_3 \cdot \text{MgO} \cdot 1.7\text{SiO}_2 \cdot x\text{H}_2\text{O}$

Chemical Abstract Service (CAS) Number: 12511-31-8

U.S. Drug Master File (DMF) filed

Dosage and Safety

Neusilin® is extremely safe with no reports of adverse reactions and is an accepted ingredient by the US Pharmacopeia/ National Formulary and Japanese Pharmaceutical Codex. Please consult Fuji Technical sales team for your specifications.

Neusilin® is available in various grades to meet the diverse requirements of complex actives that can be converted to oral solid-dosage forms.

To obtain a sample or to find your local distributor, please contact us at pharma@fujichemical.co.jp. For more technical information, please visit www.fujichemical.co.jp/english/neusilin.html

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