

Neusilin®

Increased bioavailability and improved stability of
Dihydropyridine derivatives with Neusilin® US2 for hard capsules

Dihydropyridine derivatives, also known as calcium channel blockers, are slightly water-soluble drugs, and poorly absorbed in the digestive tract. In order to improve absorption, addition of an absorbefacient (agents that improve absorption), improvement of dosage form designs etc. are necessary. The general means to overcome poor absorption are: pulverization of crystals, addition of surfactants, emulsification, cyclodextrin inclusion, dissolution in polyethylene glycol, vegetable oil etc. However, these approaches may not guarantee sufficient absorption from digestive tract. Dihydropyridine derivatives are also unstable to light exposure and are prepared into light resistant preparations or stored in light-resistant containers.

In this newsletter, we refer to a patent published by the European patent office in 1991 (Publication no. 0448091A2) where the authors provide a solution to the above problem by formulating the dihydropyridine derivatives into a non-micelle composition by adding a fatty acid monoglyceride and/or a polyoxyethylenesorbitan fatty acid ester and absorbing further on to a porous inorganic carrier like **Neusilin®**.

Formulation summary

Component	Example 1	Example 2	Example 3
	Amount (g)	Amount (g)	Amount (g)
Dihydropyridine derivative	20.1	20.1	20.1
Unsaturated fatty acid monoglyceride, Excel O-95R (palmitoleic/oleic/linoleic/linolenic acid)	650	-	325
Polyoxyethylenesorbitan monooleate, TO-10M (non-ionic surfactant)	-	650	325
Neusilin® US2	370	370	370
Croscarmellose sodium, Type A	30	30	30
Purified water	250	250	250

Dihydropyridine derivatives were mixed with the fatty acid and non-ionic surfactant either alone or in the ratio 1:1 to prepare a non-micelle solution by stirring at 40°C. **Neusilin®** was added to this mixture in a stirring granulator. To this, croscarmellose sodium, Type A and purified water was added before preparing the granules. The granules were dried at 40°C for 17 hours with a forced air drier and passed through a sieve of 42-200 mesh to give fine granules for capsules.

Bioavailability studies

Bioavailability (BA) of the pharmaceutical composition was conducted as follows. A composition from examples was administered to beagle dogs weighing about 10 kg after fasting for 20 hours before administration at a dose of 3 mg/0.1 ml/kg. Blood samples were drawn at given time intervals up to 24 hours after the administration. The plasma of the blood sample was centrifuged, deproteinized with acetonitrile and determined by high performance liquid chromatography (HPLC). The BA% was estimated on the basis of blood concentration.

	Additives used	Absorption (BA%)
Example 1	Excel O-95R/ Neusilin ® (fatty acid/ Neusilin ®)	23.0
Example 3	Excel O-95R + TO-10M (1:1)/ Neusilin ® (Fatty acid+ non ionic surfactant/ Neusilin ®)	29.4
Control	No additive	0.3

Stability tests

The dihydropyridine preparations with **Neusilin**® were subjected to stability tests at 60°C for 4 weeks. The content of analogous substance and appearance was recorded.

Additives used	Stability (60°C, 4 weeks)	
	Content of analogous substance* (%)	Appearance
Excel O-95R/ Neusilin ®	2.9	Colored
TO-10M/ Neusilin ®	1.2	No change
Excel O-95R + TO-10M/ Neusilin ®	1.6	No change

*Dihydropyridine degradation products

Conclusions

Dihydropyridine derivatives prepared by adding a fatty acid monoglyceride and/or polyoxyethylenesorbitan fatty acid ester and absorbing on to **Neusilin**® markedly improved the bioavailability and stability of these pharmaceutical compositions. In addition, this preparation facilitated the production of hard capsules.

To obtain **Neusilin**® sample or to find your local distributor, please [contact us](#). For more technical information, please visit www.fujichemical.co.jp/english/neusilin.html

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