GELUCIRE® 44/14 FOR TYPE-IV LIPID BASED FORMULATIONS AND THEIR IN VITRO IN VIVO PERFORMANCE EVALUATION

AGNIVESH SHRIVASTAVA1, KETKEE DESHMUKH1, RENUKA TIWARI1, SUNIL BAMBARKAR2, NABIL FARAH2, KAVITA SINGH3
1GATTFOSSE INDIA PVT. LTD., MUMBAI, INDIA; 2GATTFOSSE SAS, FRANCE; 3SPPSTPM, NMIMS, INDIA.

CONTACT INFORMATION: ashrivastava@gattefosse.in

PURPOSE
• Ticagrelor (TGR) is an oral antiplatelet agent, indicated use in thrombotic cardiovascular events.
• TGR belongs to BCS Class-IV drug attributing to its poor solubility and permeability with log P value 2.
• Gelucire® 44/14 (Lauroyl polyoxy-32 glycerides) is obtained by an alcoholysis reaction between coconut oil and polyethylene glycol-32 (PEG-32) under controlled conditions. It has HLB of 14 and CMC of 700.50 mg/mL, which helps as non-ionic emulsifying base, to improve the pseudo-solubility in GI medium of insoluble drugs.
• Purpose of the present work is to evaluate Gelucire® 44/14 as a solubilizer for enhancement of dissolution and in vivo performance of TGR.

OBJECTIVES
• To prepare capsules of lipid formulations of TGR with Gelucire® 44/14 in combination with auxiliary excipients to meet final the “Self-Emulsifying Systems” as SEDDS or SMEDDS, for enhancement of the pseudo-solubility and dissolution of TGR in GI medium.
• To evaluate performance of TGR formulations by in vitro lipolysis study and in vivo Pharmacokinetic study on rats.

METHODS
Solubility Study: Solubility of TGR was evaluated in water along with its dispersions with Gelucire® 44/14 in various ratios and other lipid excipients. The samples were stirred for 72h at 35±2°C and evaluated for drug content in supernatant after centrifugation.

Formation Development:

Step-1: Gelucire® 44/14 was melted at 65°C (+ 2°C above the melting point).
Step-2: TGR was added in the molten mass of Gelucire® 44/14 under constant stirring.
Step-3: The solution of TGR in Gelucire® 44/14 cooled at 40°C followed by addition of Transcutol® HP (Solutrans), Labrasol® ALF (Cosmaxent), Launiglycer® 90 (Cosmaxent) and PEG 400 (Cosmaxent). Two formulations were fabricated with different compositions and fill weights i.e. 300 mg (F-1) and 750 mg (F-2).
Step-4: The solution of Step 3 was filled into hard gelatin capsules and kept for cooling at room temperature. The capsule formulations were evaluated for in vitro dissolution tests. In vitro lipolysis test and in vivo Pharmacokinetic study on rat model.

RESULTS

Solubility Study in Different Excipients:
• The solubility of TGR depicted in the Fig. 1, Gelucire® 44/14 showed enhancement in the solubility in water.
• Water solubility of TGR was found to be 3.58 µg/mL, highest solubility was seen with Transcutol® HP, followed by PEG 400, Labrasol® ALF, Tween® 80, Propylene glycol and Capryol® 90.
• The excipients were selected for formulation based on their TGR solubility and miscibility with Gelucire® 44/14.
• TGR:Gelucire® 44/14 in the ratios of 1:5 and 1:6.6 were taken for further studies.

In vitro Dissolution:
• Dissolution of developed formulations and market reference was performed in HCl Buffer pH 1.2, 0.2% Polyoxy 80 HCl in water. Acetate buffer pH 4.5 and Phosphate buffer pH 6.8, 300 mL, using USP-II apparatus, 75 rpm at 37°C.
• The dissolution of the developed lipidic formulations was found to be significantly comparable to the market reference (Fig. 2).

In vitro Lipolysis Study:
• Apparatus: pH stat apparatus (Metrohm AG, Switzerland).
• Medium: Lipolysis medium pH 6.5 (fasted state): Tris Maleate 2mM, CaCl2 1.4 mM, NaCl 150 mM, NaClO3 3mM, Phospholipid choline 0.75 mM, M&K water Qs.
• Volume: 36 mL

Both Gelucire® 44/14 formulations demonstrated good solubilization capacity to maintain TGR in pseudosolution upon digestion (Table 1, Fig.3).

In vivo Pharmacokinetic Study:
• Animal Model: Male rats with weight of 200 to 250 g
• Dose: 10 mg of TGR per kg body weight by Oral gavage to 1.5 mL.
• No. of Groups: 2 groups for GSR formulations: 1 for Market reference
• Sampling: Blood samples were collected up to 24 h & analysed by HPLC.

CONCLUSIONS
• Gelucire® 44/14 was employed effectively to enhance the dissolution and in vivo performance of a BCS Class-IV drug i.e. TGR.
• In vitro lipolysis demonstrates good performance results of developed formulations (obtained during the in vitro dissolution test), to maintain stable pseudo-solubility of the drug in micelle upon digestion, and finally to predict a good in vivo in vitro correlation.
• The in vivo pharmacokinetic study on rat model showed significant improvement in the in vivo performance of formulations i.e. T_max, C_max and AUC, versus the market reference.
• The in vivo results obtained are in agreement with the results of in vitro lipolysis tests.
• Gelucire® 44/14 can be effectively applied as part of SEDDS or SMEDDS formulations, to enhance dissolution and bioavailability of BCS-Class IV drugs, from Super-Generic (505 b ii) and product lifecycle management perspectives.

REFERENCES:
• Vincent Jemin et al., Development of Self Emulsifying Lipid Formulations of BCS class II drugs with low to medium lipophilicity. Int. J. Pharmaceutics 490 (2015) 385-392
• www.gattefosse.com

ACKNOWLEDGEMENT:
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Table 1: In vitro Lipolysis:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F-1</th>
<th>F-2</th>
<th>Market reference</th>
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<tr>
<td>T_max (h)</td>
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<tr>
<td>C_max (mg/mL)</td>
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<td>AUC_C0 (mg/mL*h)</td>
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Fig. 1: Solubility of TGR in different excipients.

Fig. 2: In vitro dissolution of TGR formulations.

Fig. 3: % Solubility of TGR during lipolysis.

Fig. 4: In vivo pharmacokinetic study of TGR formulations.