Bioavailability Enhancing and Incretin Inducing Nanostructured Lipid Carrier for Diabetes: An In Vivo Evaluation

Kok-Hou Lok[1], Chee Wun How[1], Rajesh Sreedharan Nair[2], Lay-Hong Chuah[1]

1. School of Pharmacy, Monash University Malaysia, Bandar Sunway, 47500 Subang Jaya, Selangor, Malaysia.
2. School of Pharmacy, Faculty of Science, University of Nottingham Malaysia Campus, Semenyih, Selangor, Malaysia.

BACKGROUND AND INTRODUCTION

Did You Know ?

Diabetes patients taking Linagliptin (Trajenta®) continue to **pay an extra 70%**, only to obtain a **smaller improvement in blood glucose control** relative to newer drugs.

- The majority of incretin-based therapies act via glucagon-like peptide-1 (GLP-1) receptor agonism or dipeptidyl peptidase-4 (DPP-4) inhibition [1].
- Linagliptin, a DPP-4 inhibitor, has 30% bioavailability due to P-gp efflux and induces a modest 2-fold increase in GLP-1 compared with >10-fold elevations achieved by GLP-1 receptor agonism [2-3].

Aim: To evaluate the preclinical *in vivo* pharmacokinetic profiles and glucose-lowering efficacy of dual-action Linagliptin-loaded nanostructured lipid carriers (LG-NLC), designed to enhance oral bioavailability via P-gp inhibition and stimulate endogenous GLP-1 secretion from enteroendocrine L-cells in the GI tract.

METHODS

Male SD rats aged 8-9 weeks were obtained from Monash.

1) Pharmacokinetics:

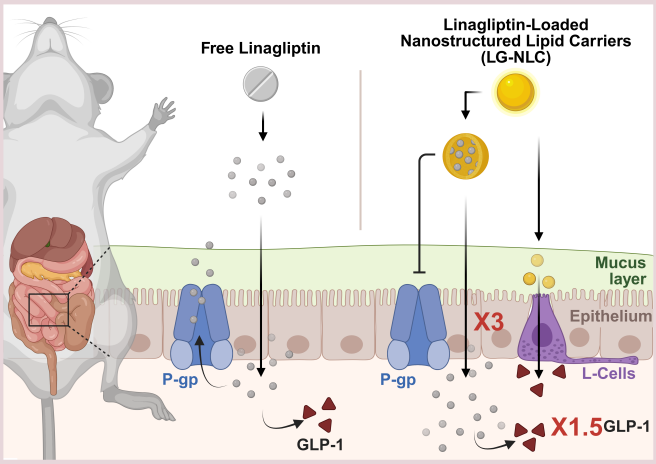
- Rats received either Linagliptin solution or LG-NLC following 13h of fasting.
- Tail vein blood samples were subsequently collected at 0.5, 1, 2, 4, 6, 8, 24, 48h post-dose.

2) Pharmacodynamics:

- Rats received either vehicle control, Linagliptin solution or LG-NLC for 7 days and the following metabolic parameters were assessed:
  - Body weight measurement (BWM)
  - Recording food and water intake (RWFI)
  - Fasting blood glucose (FBG)
  - Plasma active glucagon-like peptide-1 (GLP-1)
  - Oral glucose tolerance test (OGTT)

Table 1: Experimental timeline for pharmacodynamic assessments.

Time	Days							
	0	1	2	3	4	5	6	7
6a.m	Predetermined amounts of food and water were prepared a day prior to the experiment day.	BWM	BWM	BWM	BWM	BWM	BWM	BWM
		RFWI						
		Fasting						Fasting
12 – 1p.m		BWM	BWM	BWM	BWM	BWM	BWM	BWM
			RFWI	RFWI	RFWI	RFWI	RFWI	
		FBG sampling						FBG + GLP-1 sampling
		Dosing	Dosing	Dosing	Dosing	Dosing	Dosing	Dosing
1h post-dosing								GLP-1 sampling
After GLP-1 sampling								OGTT



We engineered a self-therapeutic nanocarrier that **increases Linagliptin bioavailability by 3X** and **induces endogenous GLP-1 secretion by 1.5X**.

RESULTS AND DISCUSSIONS

1) Pharmacokinetics:

- Oral administration of LG-NLC significantly enhanced Linagliptin systemic exposure compared to the free Linagliptin solution by ~3-fold increase in $AUC_{0-\infty}$ and a 2-fold increase in C_{max}.
- This enhanced exposure was underpinned by an altered disposition profile, characterised by a 2-fold prolongation of T_{max} and $t_{1/2}$.

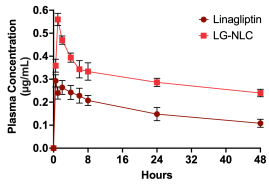


Figure 1: Mean plasma concentration–time profiles of Linagliptin solution and LG-NLC following single oral administration in male SD rats over 48h. (n = 6)

2) Pharmacodynamics:

- LG-NLC treatment did not alter water intake but reduced food intake by 2.8% in parallel with increased plasma GLP-1, suggesting enhanced satiety.
- However, BWM increased steadily over 7d, indicating good tolerability without clinical weight-loss effects.
- LG-NLC induced greatest post-dose GLP-1 elevation, but returned to baseline, similar to Linagliptin.
- This translated into the greatest glucose suppression during OGTT without affecting FBG.

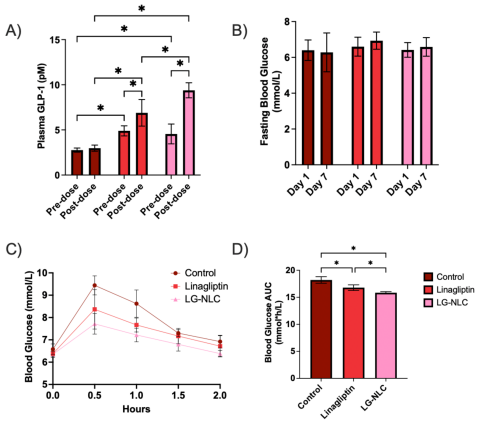


Figure 2: Comparative metabolic effects of vehicle control, Linagliptin, and LG-NLC on: (A) plasma active GLP-1 concentration, (B) FBG level, (C) blood glucose profile over 120 min in response to 2g/kg D-glucose, and (D) AUC of the blood glucose during OGTT. (n = 5-6)

CONCLUSION

The present study confirmed that the dual-action LG-NLC resulted in an approximately 3-fold increase in Linagliptin oral bioavailability and improved glycaemic control in vivo, suggesting that LG-NLC can offer better type 2 diabetes mellitus prognosis at a lower dose and treatment cost.

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