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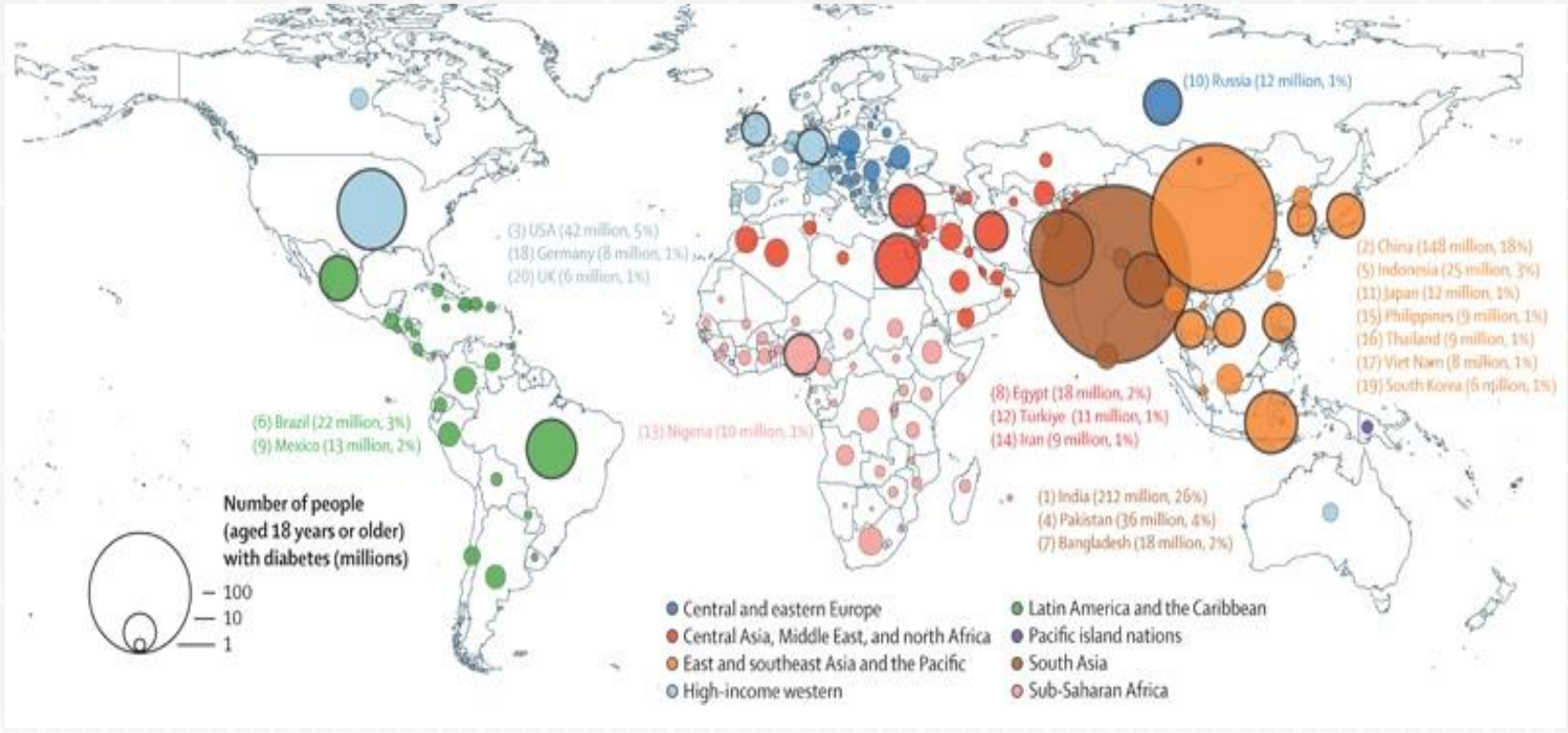
Leveraging bioavailability of Linagliptin and bioactive glucagon-like peptide-1 (GLP-1) through self-therapeutic nanostructured lipid carriers (NLC): An in vivo study

Kok-Hou Lok (School of Pharmacy)

Main Supervisor: A/P Dr. Alice Chuah Lay Hong

Co-Supervisor 1: Dr. How Chee Wun

Co-Supervisor 2: A/P Dr Rajesh Sreedharan Nair



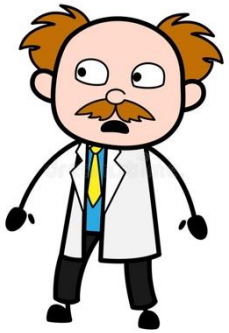
NCD Risk Factor Collaboration (2022) indicates that the number of adults living with diabetes has increased by more than 600 million to approximately 828 million since 1990 [1].

Lancet. 2024 Nov;404(10467):2077–2093.

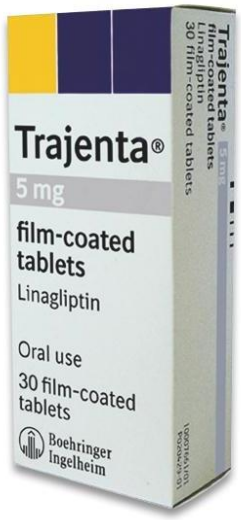
Pharmaceutical Wastage

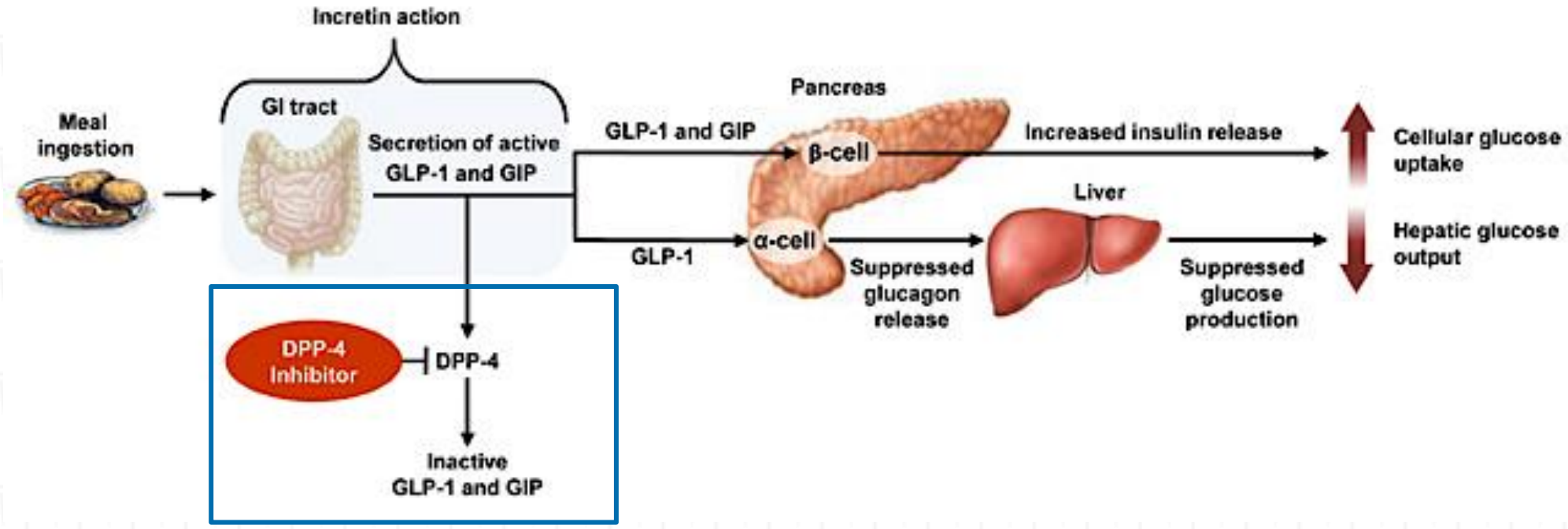
Patients
- Non-compliance
- Poor health literacy

HCP
- Ineffective counselling
- Do not provide enough support



Scientists
- <u>Obsolete technology</u>





- **Linagliptin (Trajenta®)**, is a highly selective orally taken **inhibitor of dipeptidyl peptidase-4 (DPP-4)**, an enzyme that is responsible for the degradation of enteroendocrine L-cells secreted **glucagon-like peptide-1 (GLP-1) hormone**.

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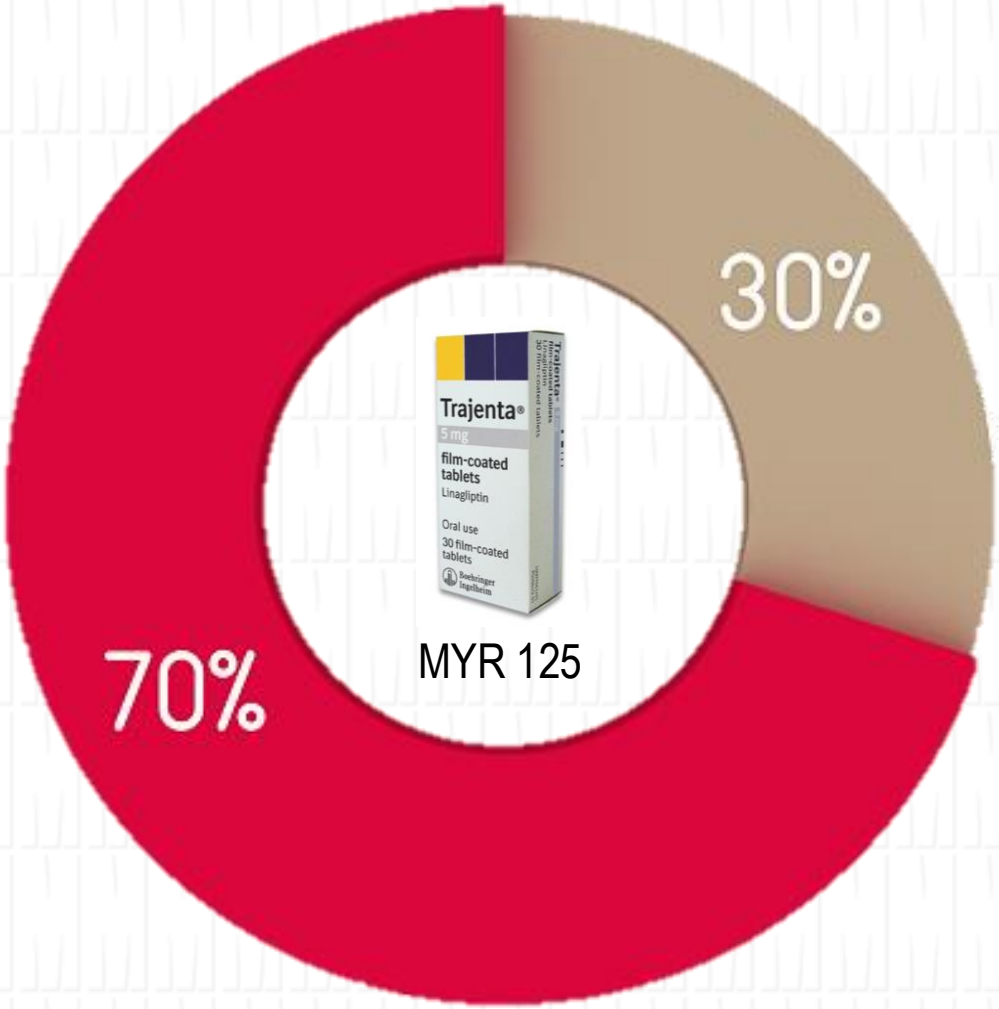
MYR88



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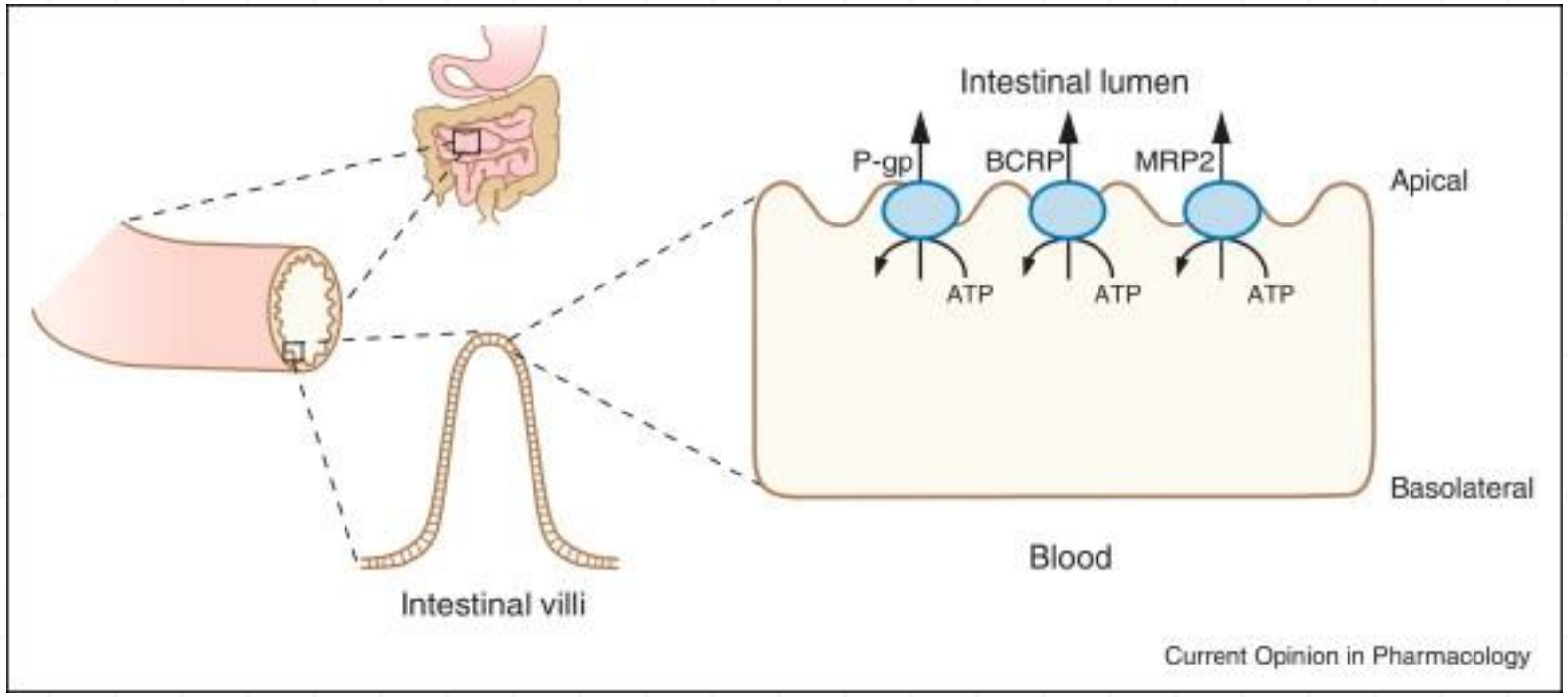
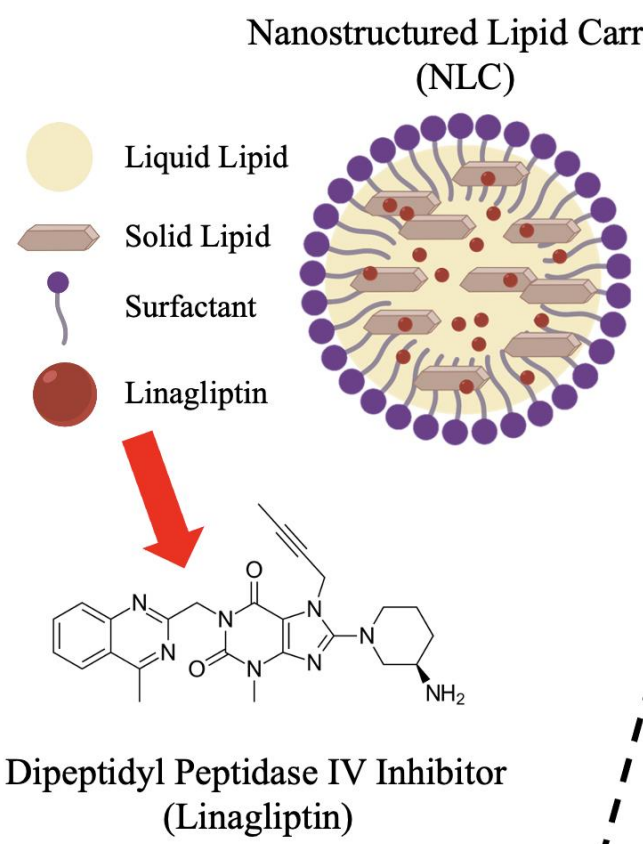
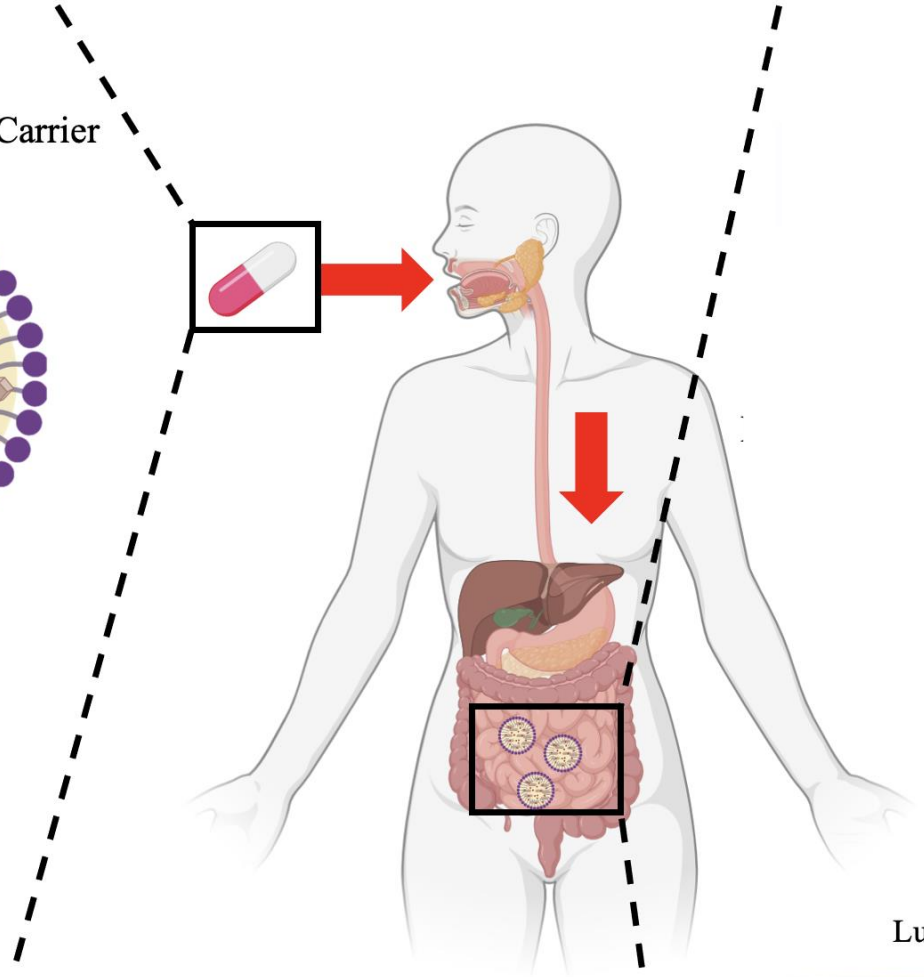
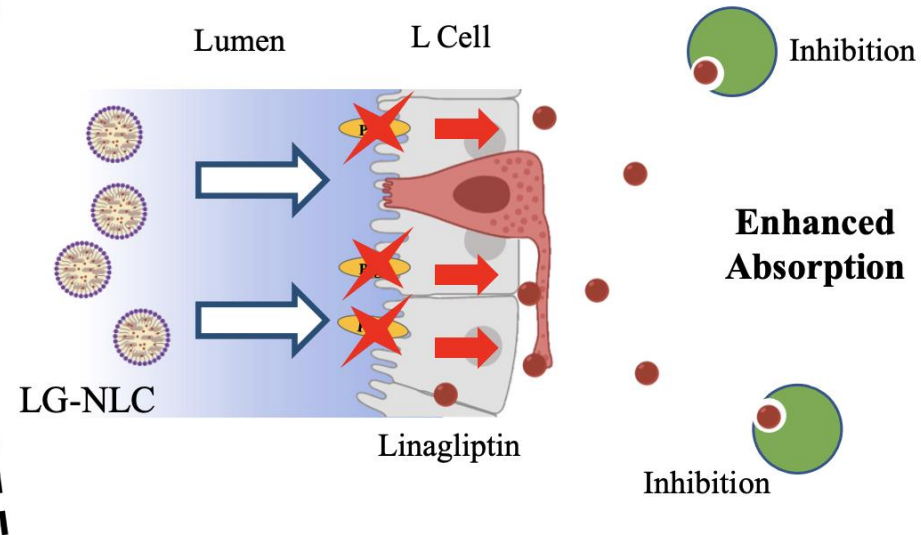
Linagliptin possesses a low bioavailability of only approximately 30% [3].



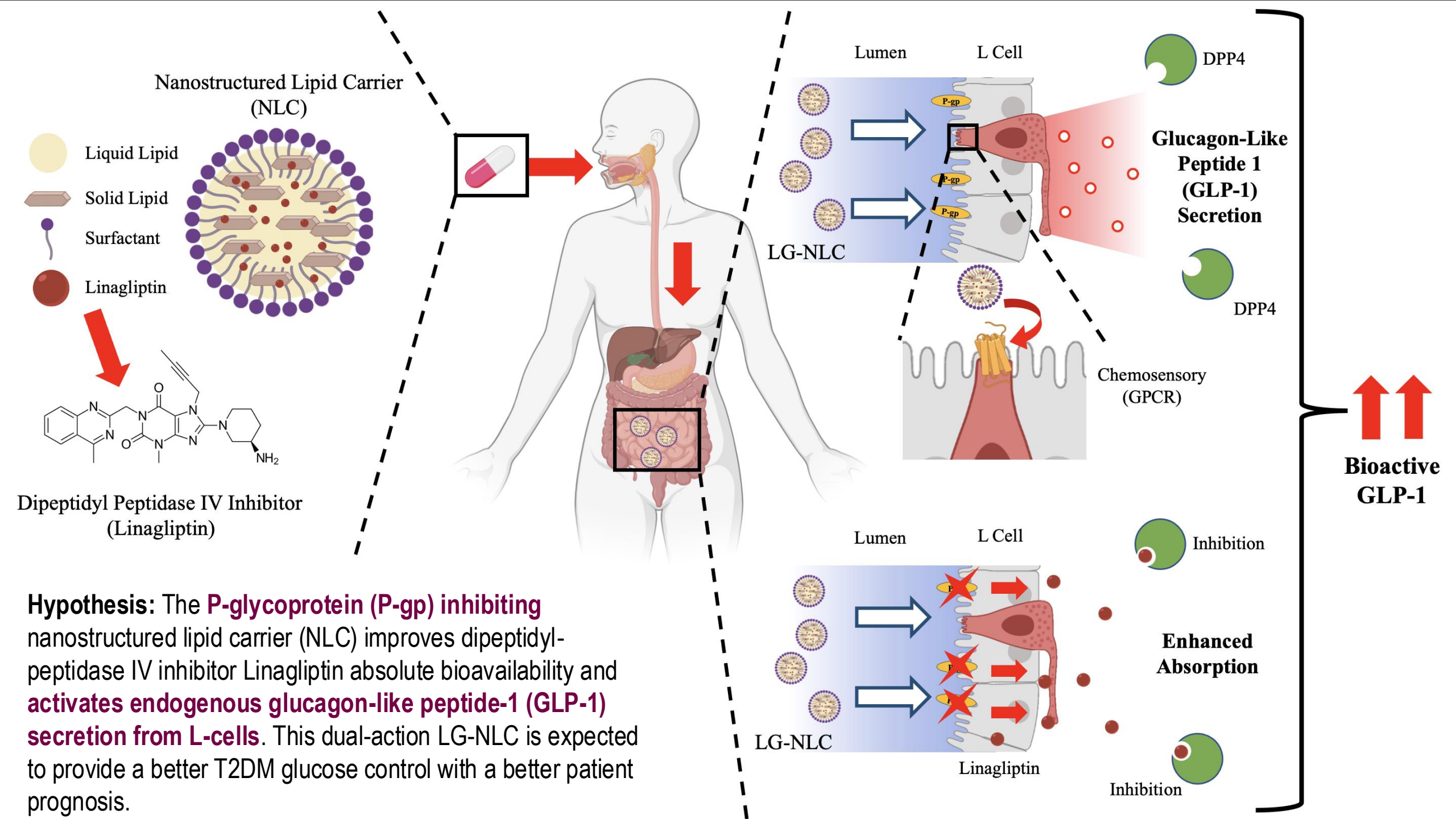
Poor permeability arising from P-glycoprotein (P-gp) efflux as oral absorption barriers [3].







Hypothesis: The **P-glycoprotein (P-gp) inhibiting** nanostructured lipid carrier (NLC) improves dipeptidyl-peptidase IV inhibitor Linagliptin absolute bioavailability and **activates endogenous glucagon-like peptide-1 (GLP-1) secretion from L-cells**. This dual-action LG-NLC is expected to provide a better T2DM glucose control with a better patient prognosis.



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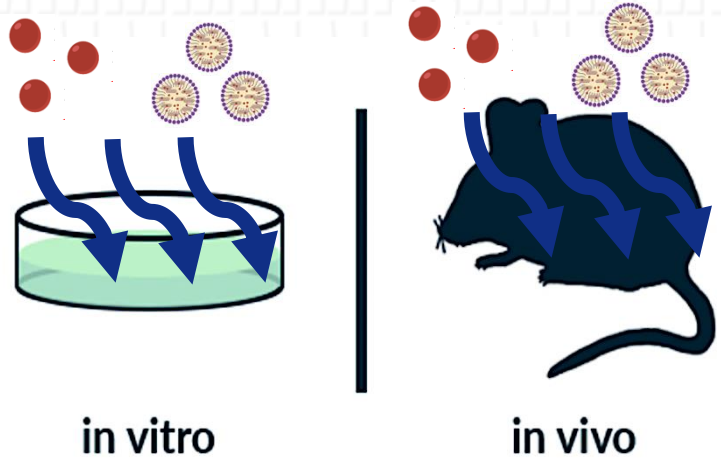
In Vivo Studies

Pharmacokinetics and Pharmacodynamics



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A) Pharmacokinetics (PK)

- Male non-specific pathogen-free Sprague-Dawley rats aged 8–9 weeks (183.5 ± 21.1 g) were obtained from the Monash University Malaysia Animal Research Platform.
- Project ID: 45141.
- Fasted for 13 h (from 17:00 to 06:00) with free access to water prior to oral gavage (5.5mg/kg).

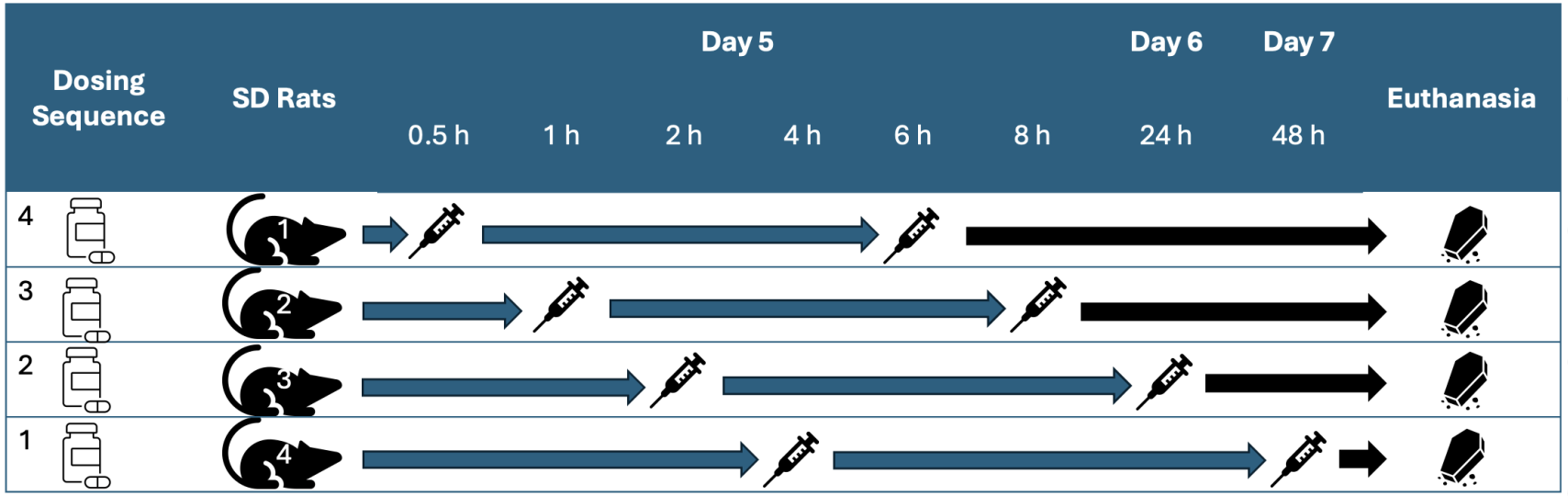

Figure 4: Experimental timeline for drug administration, blood sampling, and euthanasia in four rats treated with either Linagliptin solution or LG-NLC to obtain plasma concentration result.

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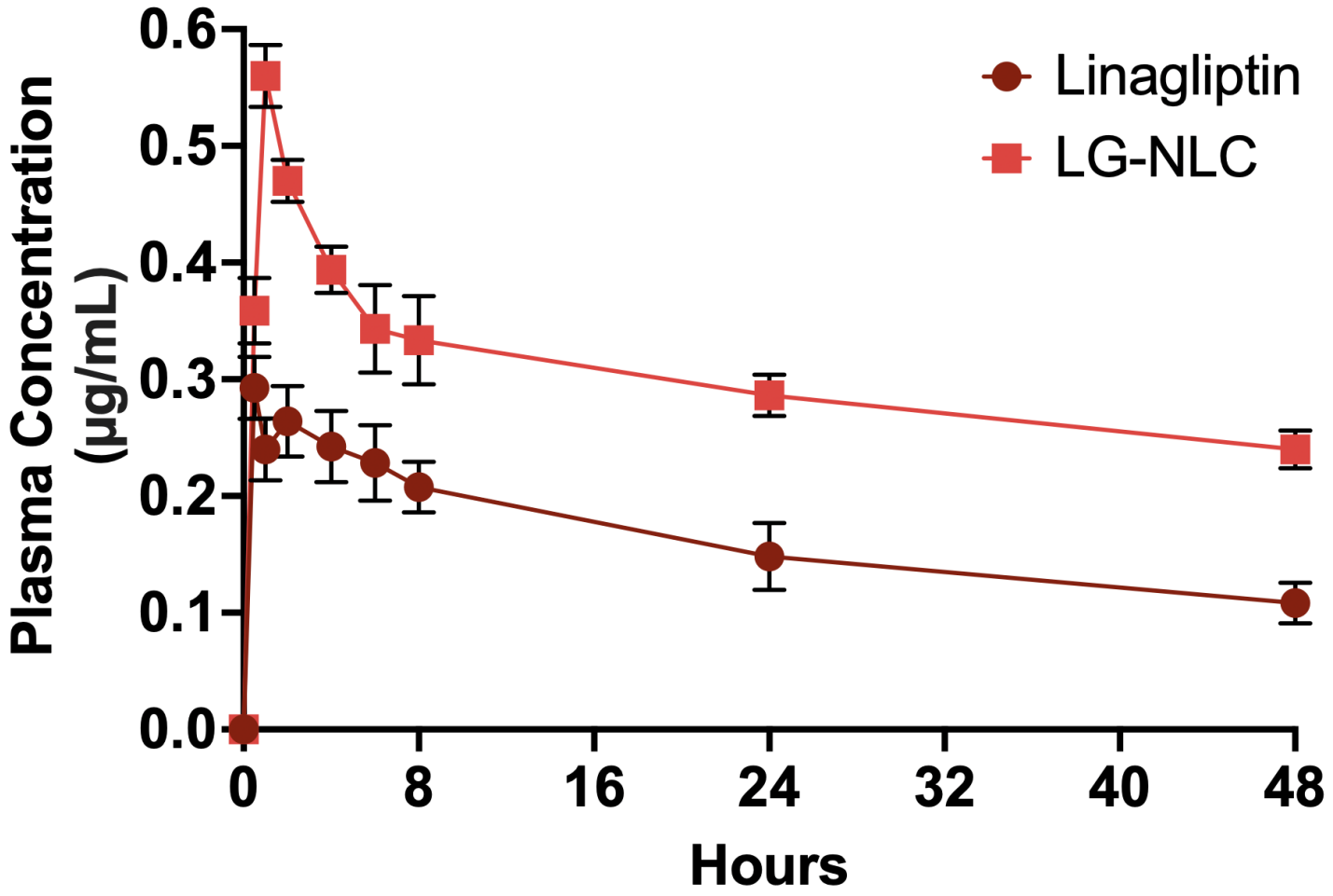


Figure 5: Mean plasma concentration–time profiles of Linagliptin solution and LG-NLC following single oral administration (5.5 mg/kg) in male Sprague–Dawley rats over a 48 h sampling period (n = 6).

A) Pharmacokinetics (PK)

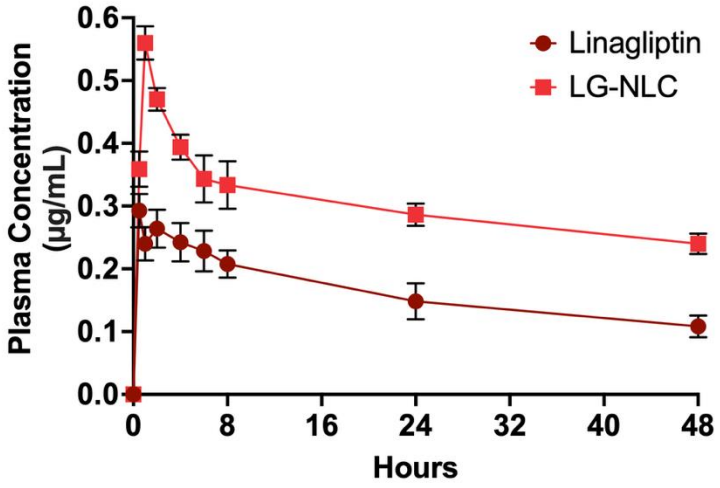


Table 3: Pharmacokinetic parameters of unformulated Linagliptin and LG-NLC.

Pharmacokinetic parameters	Linagliptin	LG-NLC
Peak plasma concentration, Cmax (µg/mL)	0.293 (± 0.027)	0.560 (± 0.027)
Time to reach peak plasma concentration, Tmax (h)	0.5	1
Elimination rate constant, k (h−1)	0.0162 (± 0.0028)	0.0082 (± 0.0016)
Elimination half-life $t_{1/2}$ (h)	43.917 (± 7.298)	87.289 (± 14.887)
Area under the curve from 0-48 h, AUC_{0-48^h} (µg·h/mL)	7.795 (± 0.718)	14.401 (± 0.473)
Extrapolated area under the curve, $AUC_{48^h-\infty}$ (µg·h/mL)	6.991 (± 2.127)	30.115 (± 4.777)
Total systemic exposure, $AUC_{0-\infty}$ (µg·h/mL)	14.786 (± 2.754)	44.516 (± 4.837)
Relative bioavailability (%)	-	301.07

B) Pharmacodynamics (PD)

Rats were treated with either vehicle control, Linagliptin solution, or LG-NLC:

1. **Body weight measurement (BWM)**
2. **Records food and water intake (RFWI)**
3. **Fasting blood glucose (FBG)**
4. **Glucagon-like peptide-1 (GLP-1)**
5. **Oral glucose tolerance test (OGTT)**

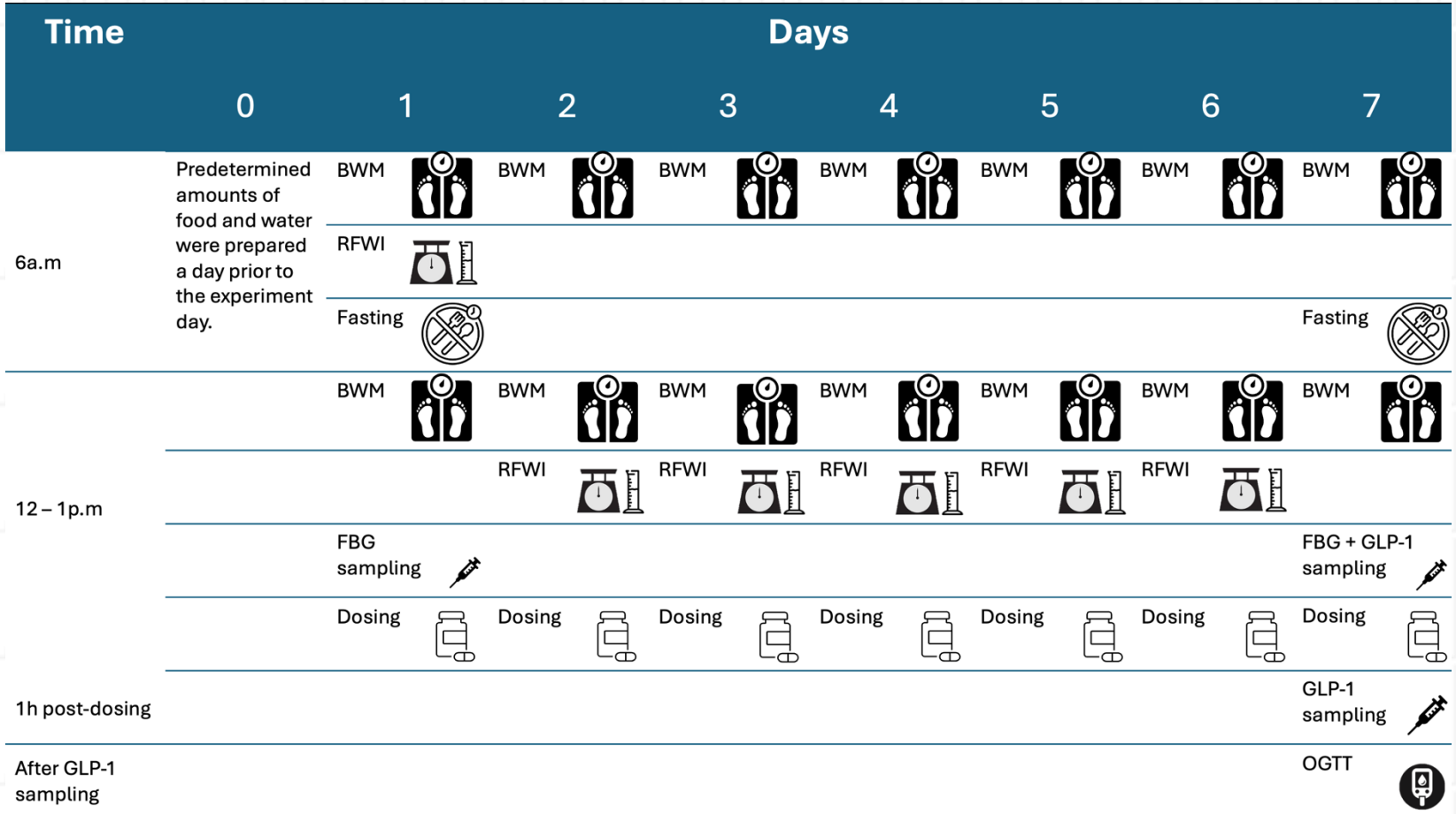
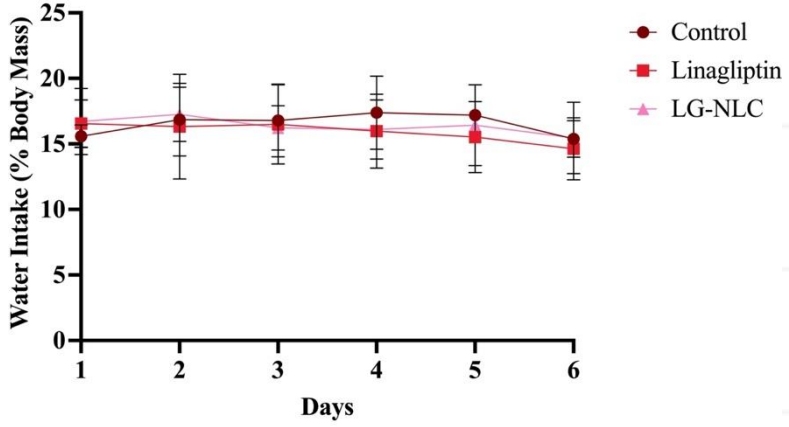
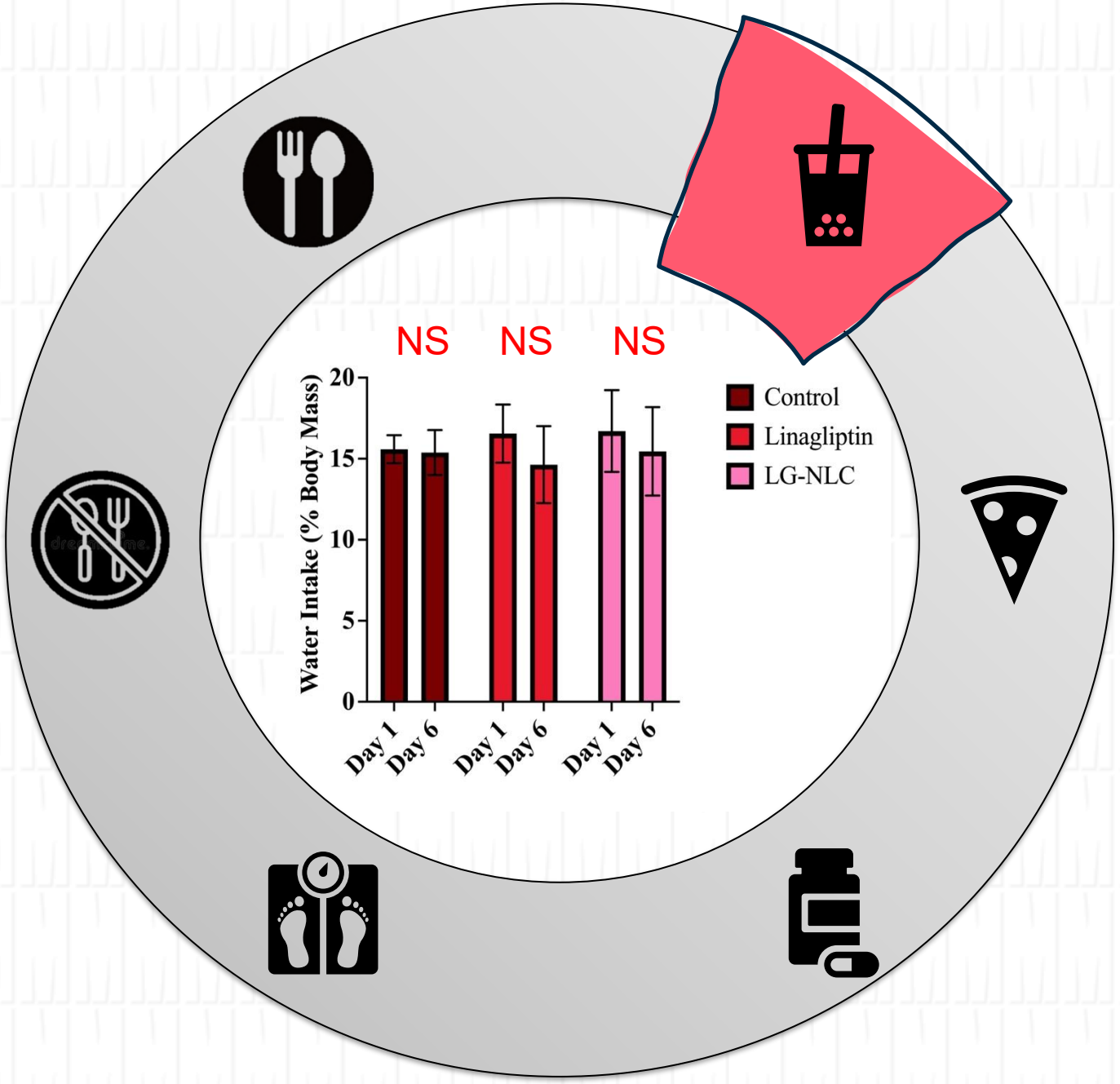


Figure 6: Experimental timeline for metabolic and pharmacodynamic assessments in male Sprague–Dawley rats treated with Linagliptin solution or LG-NLC (3 mg/kg Linagliptin equivalent), or vehicle control. (n = 5–6)

B) Pharmacodynamics (PD)
- Water Intake

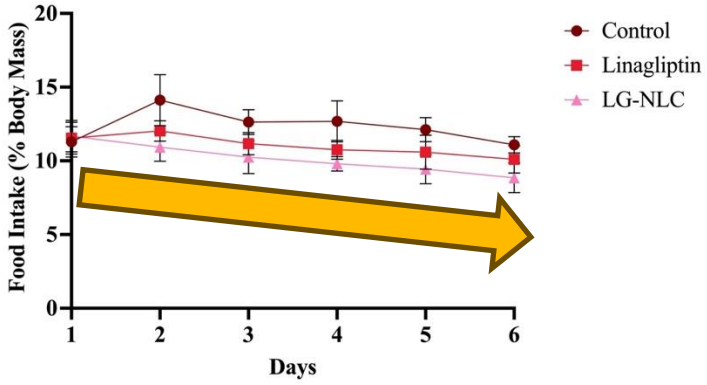
- Water intake remained unchanged across all groups
  - **Stable physiological hydration condition**

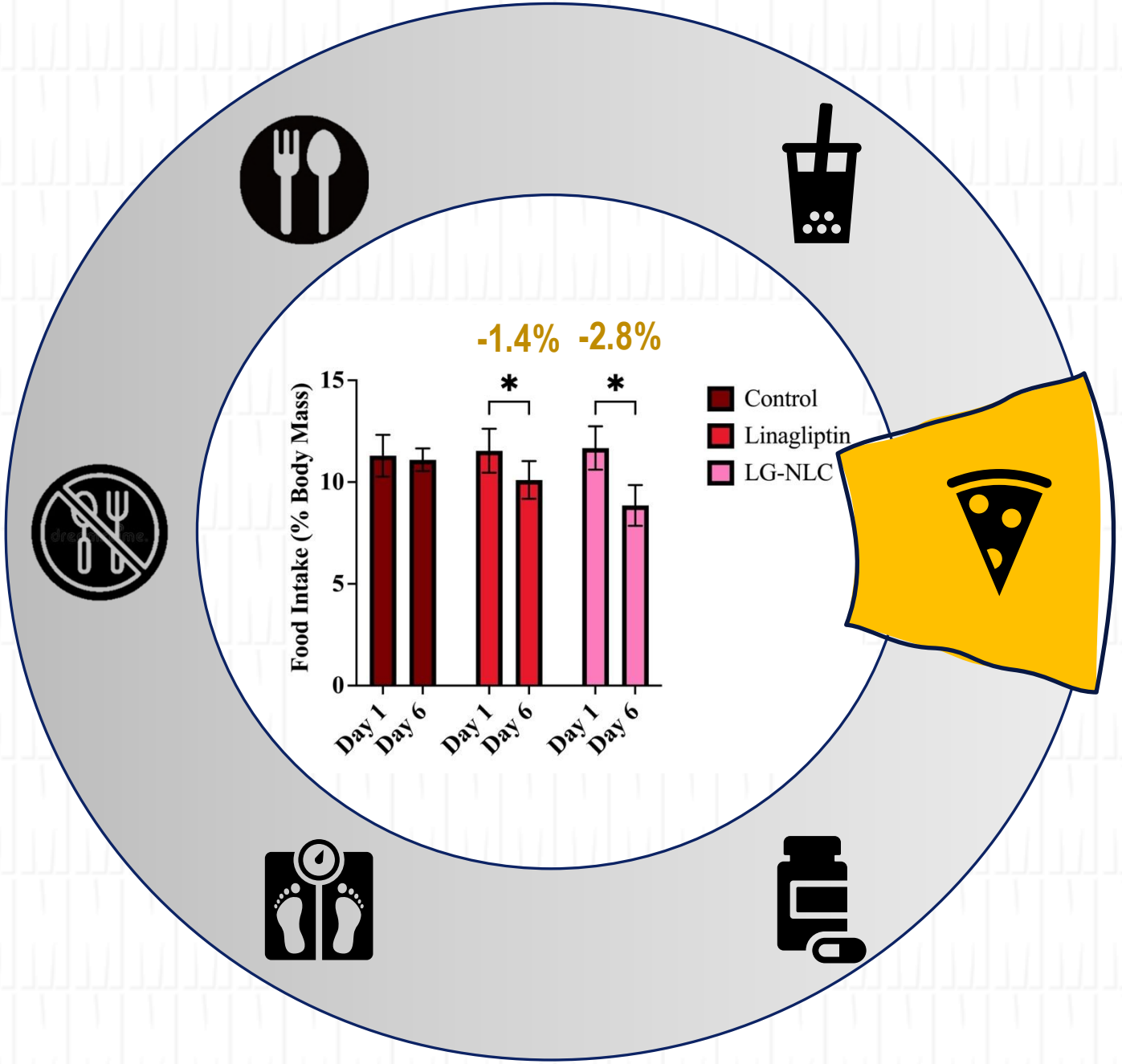




B) Pharmacodynamics (PD) - Food Intake

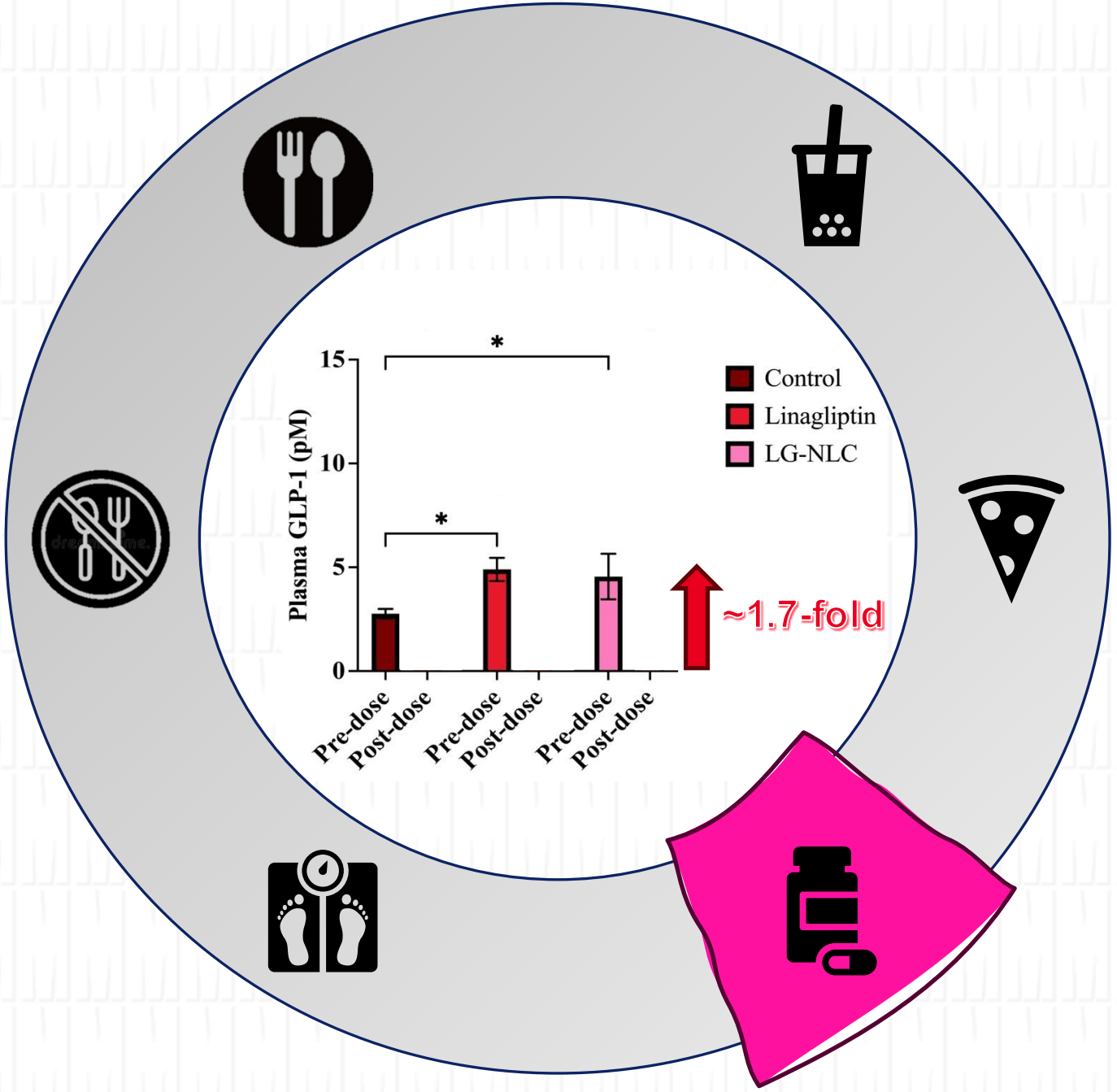
- Food intakes declined progressively over six days to **1.4% and 2.8%** below baseline in Linagliptin and LG-NLC-treated groups.
- GLP-1 has been implicated in delaying gastric emptying and attenuating appetite [4].





B) Pharmacodynamics (PD)
- GLP-1 Secretion

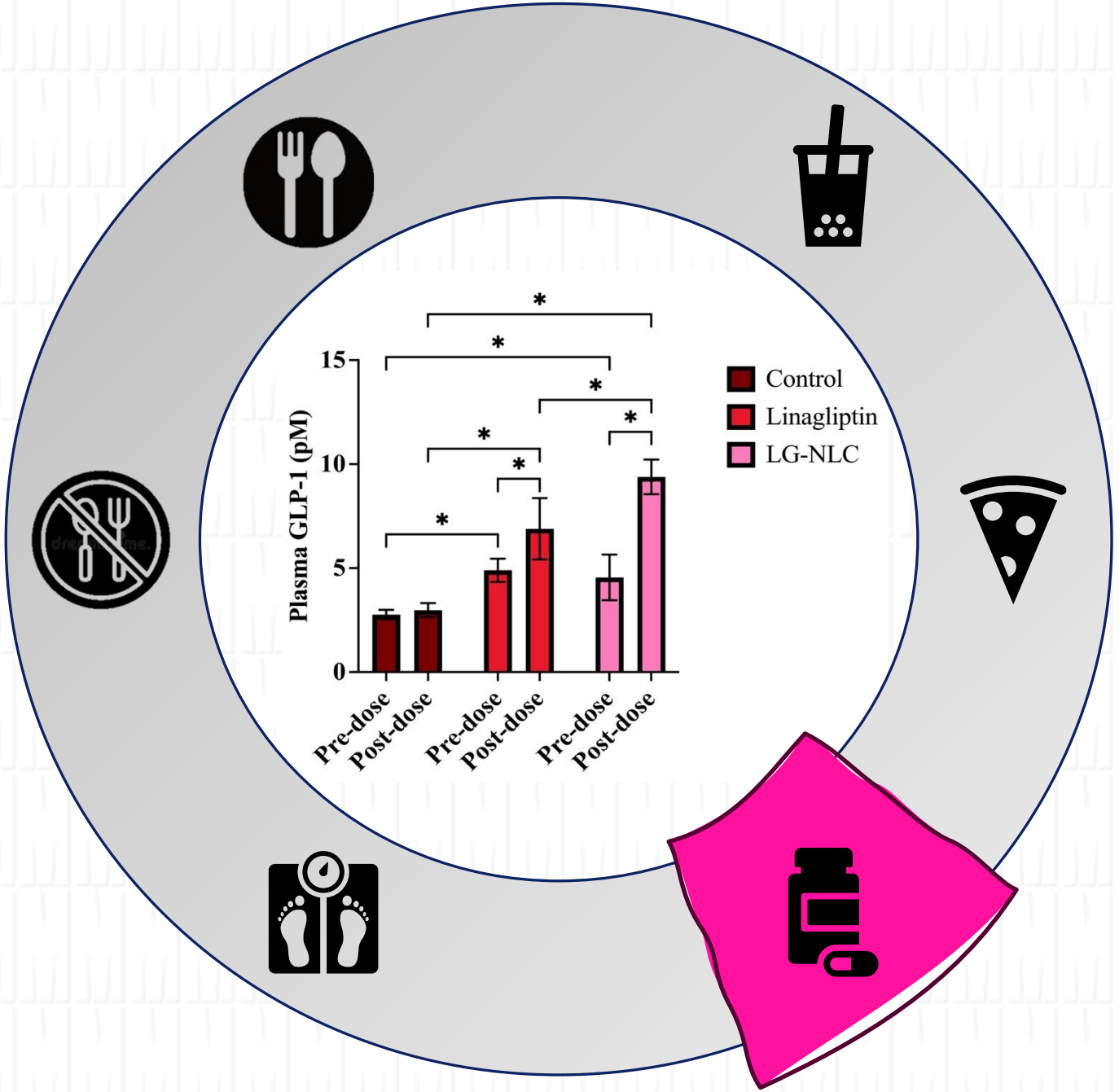
- **Elevated basal GLP-1 levels** [4]



B) Pharmacodynamics (PD) - GLP-1 Secretion

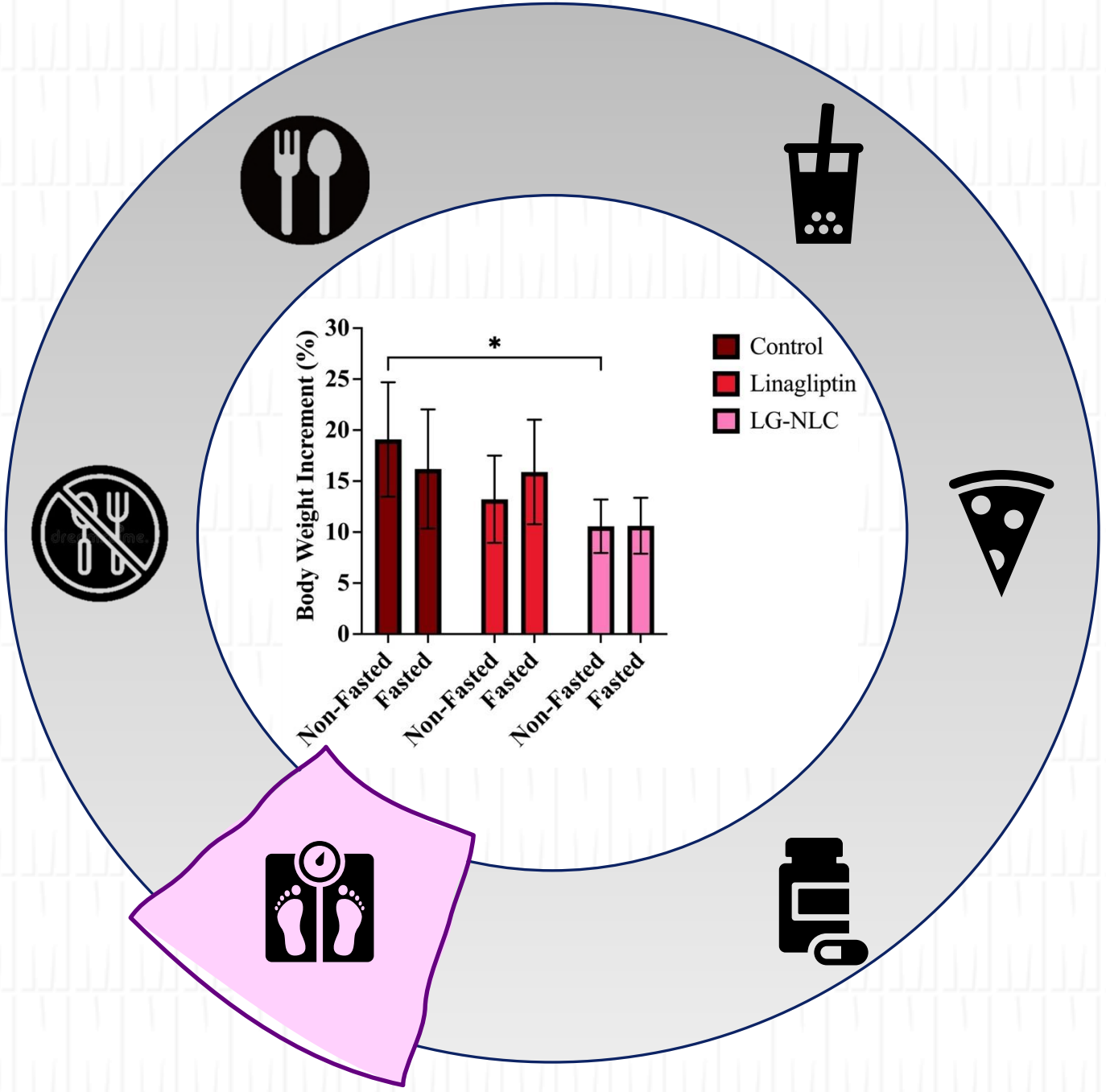
- **Elevated basal GLP-1 levels** [4]

- Elevated GLP-1 levels 1 h post-dosing LG-NLC:
  - **~3-fold higher than vehicle treated group.**
  - **~1.5-fold higher than linagliptin treated group.**



B) Pharmacodynamics (PD) - Body Weight

- Rats treated with LG-NLC showed **significantly lower cumulative body weight gain when not fasted**, but **no such effect was observed under fasting conditions**.
  - Transient differences in gastrointestinal content.



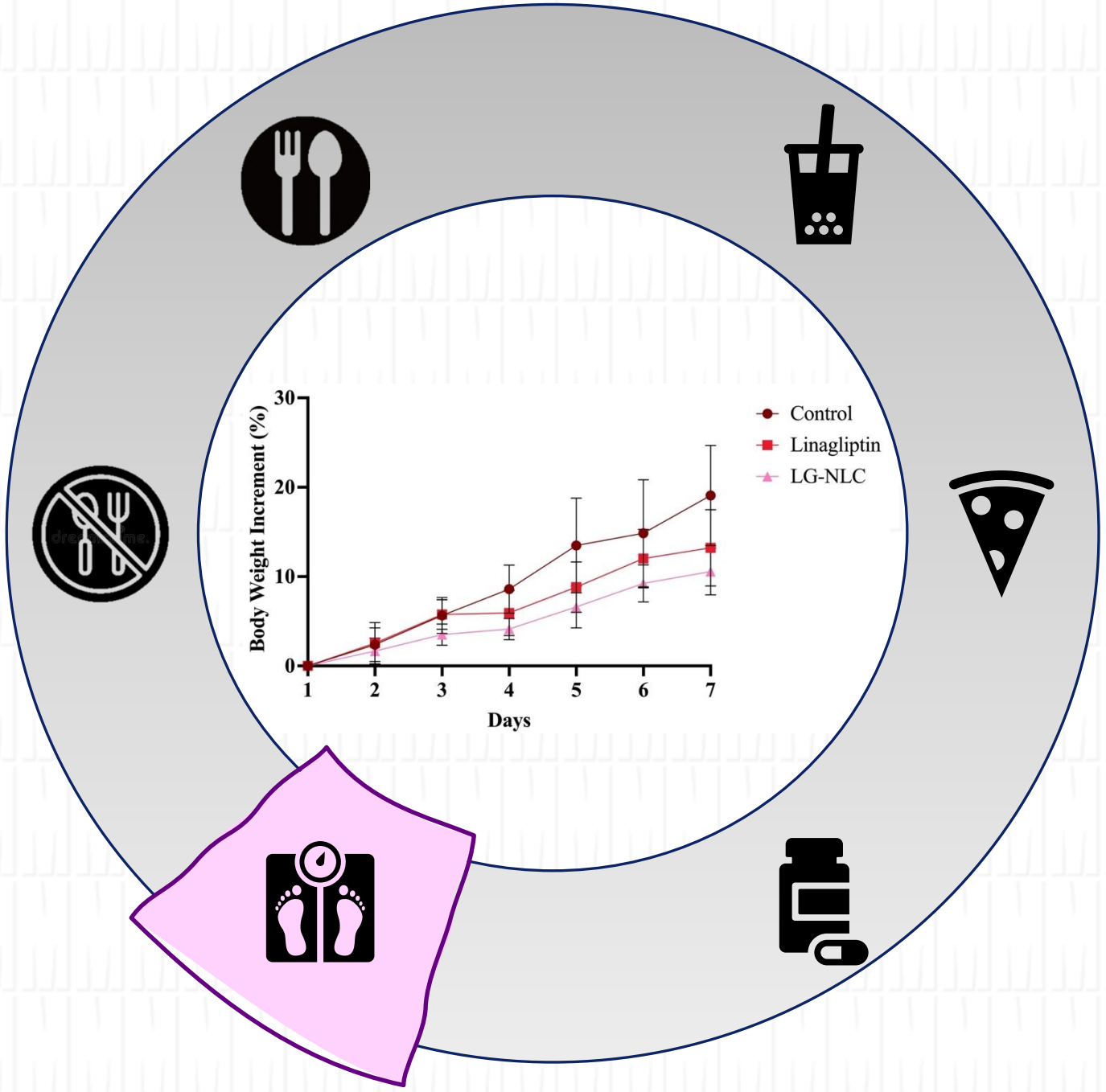
B) Pharmacodynamics (PD) - Body Weight

- Body weight increased steadily across all groups, with no reduction exceeding 10% of baseline weight.

Highlights

- We use body weight loss (BWL) as an objective measurement to refine short-term regulatory toxicology studies (up to 1 week).
- We shared data from 151 studies (in rat, dog & NHPs), including BWL, clinical signs and expected pharmacology.
- We have devised a decision tree for each species to show when the maximum tolerated dose has been exceeded.
- To recommend a maximum 10% BWL (in one week) for rat and dog, and 6% BWL for NHPs in short term regulatory toxicology studies.
- BWL above these limits rarely occurs in the clinical signs.

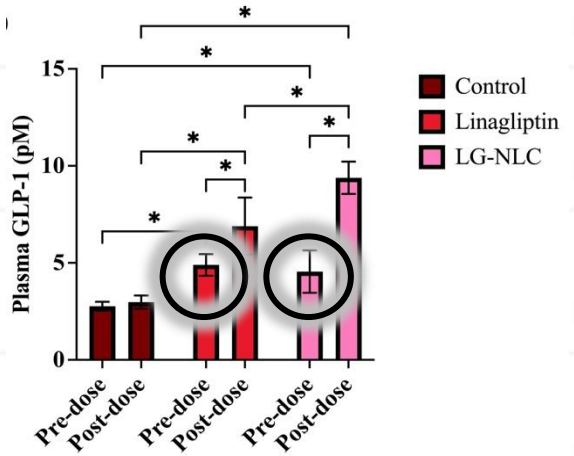
NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research



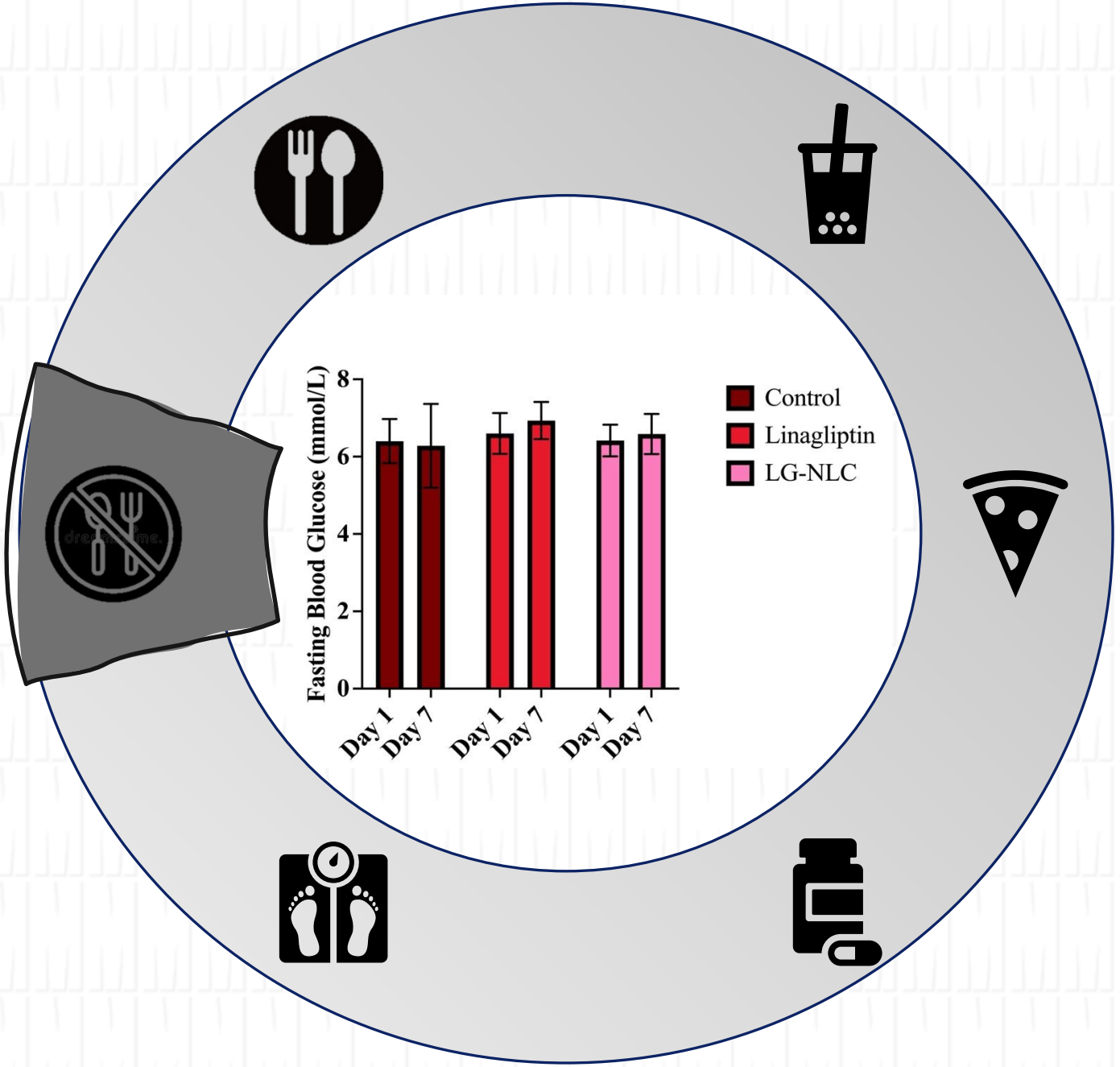
- LG-NLC was well tolerated and did not produce observable acute toxicity [6].

B) Pharmacodynamics (PD)
- Fasting Blood Glucose

- FBG levels did not differ significantly between treatment groups.
- Elevated GLP-1 level did not cause blood glucose reduction [4,7-8].

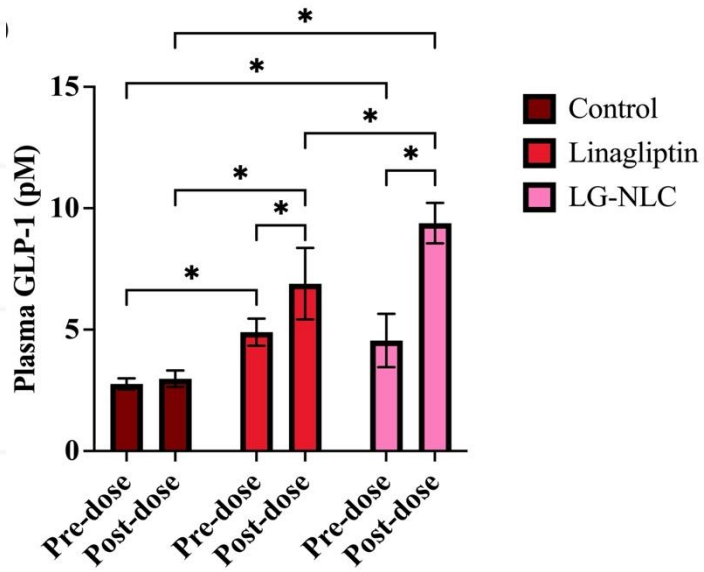


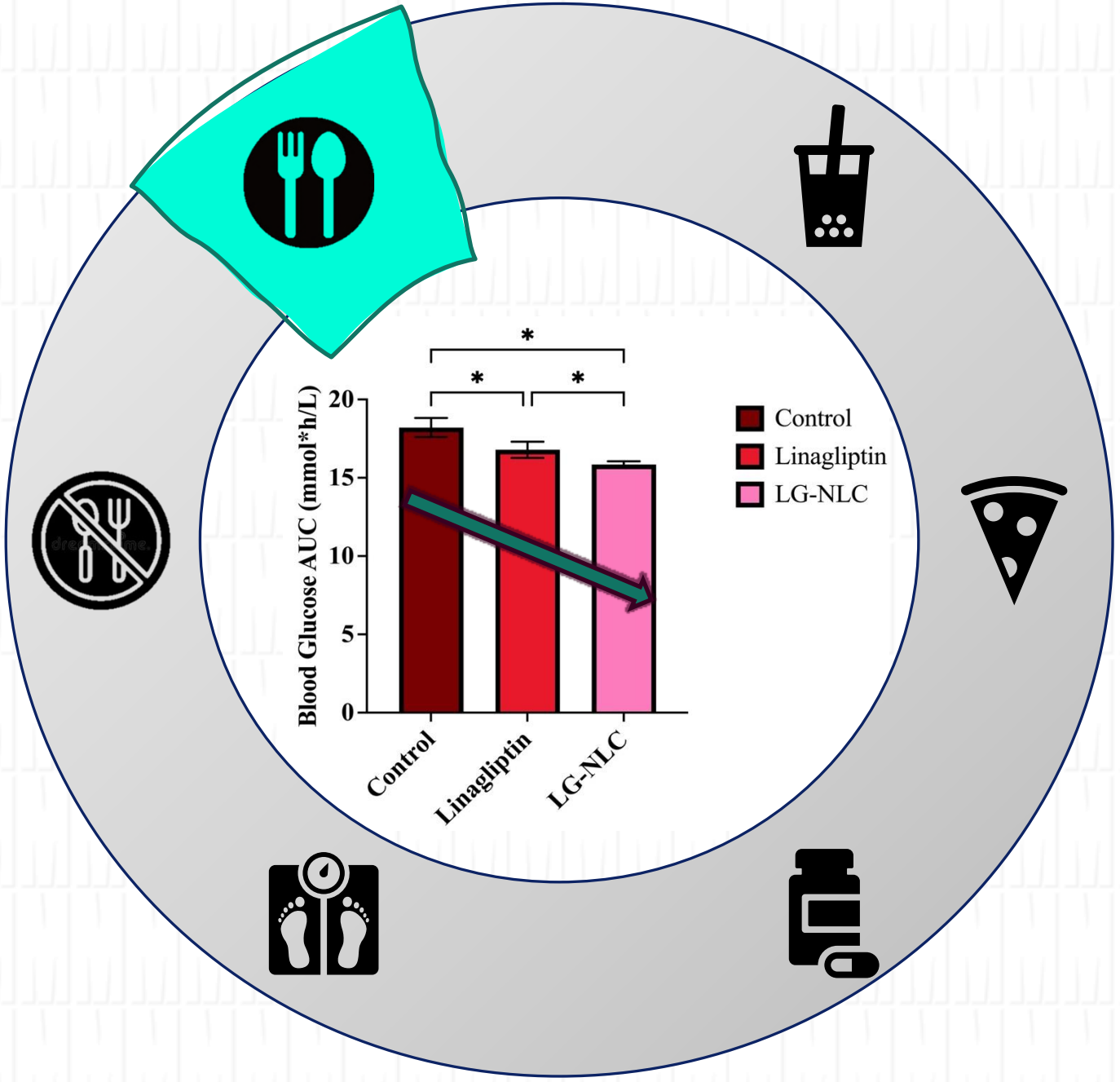
- Underscores the glucose-dependent insulinotropic action of GLP-1
  - **No hypoglycaemia side effect and is safe for elderly patients**



B) Pharmacodynamics (PD)
- Oral Glucose Tolerance

- Blood glucose AUC values:
  - **Control > Linagliptin > LG-NLC**
- Consistent with its greater GLP-1 elevation at 1 hour post dose.





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Conclusion

Dual Action LG-NLC:

- LG-NLC successfully enhanced the oral bioavailability of Linagliptin and improved its pharmacodynamic response in vivo compared to free Linagliptin
  - In Vitro: ↑ drug permeation and ↑ GLP-1 secretion
  - In Vivo: ↑ bioavailability, ↑ GLP-1 plasma level

Clinical Aspects:

- Dose: ↓ dose
- Metabolic parameters: ↑ oral glucose tolerance

Acknowledgement

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Resources:

Travel Grant:

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Thank you

lok.kokhou@monash.edu

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