

Pharmacokinetic delivery and metabolizing rate of nicardipine incorporated in hydrophilic and hydrophobic cyclodextrins using two-compartment model

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Abstract

➤The dispersion routes of cyclodextrin complexes with nicardipine (NC), such as hydrophilic hydroxypropyl- β -cyclodextrin (NC/HP β CD) and hydrophobic triacetyl- β -cyclodextrin (NC/TA β CD), through the body for controlled drug delivery and sustained release have been examined. The two-compartment pharmacokinetic model described the mechanisms how human body handles with ingestion of NC-cyclodextrin complexes in gastrointestinal tract (GI), distribution in the blood (Plasma), and their metabolism in the liver. The model showed that drug bioavailability was significantly improved after oral administration of cyclodextrin complexes. The mathematical significance of this study to predict nicardipine delivery using pharmacokinetic two-compartment mathematical model and linear ordinary differential equations approach represents a valuable tool to emphasize its effectiveness and diminish the side effects.

Methods

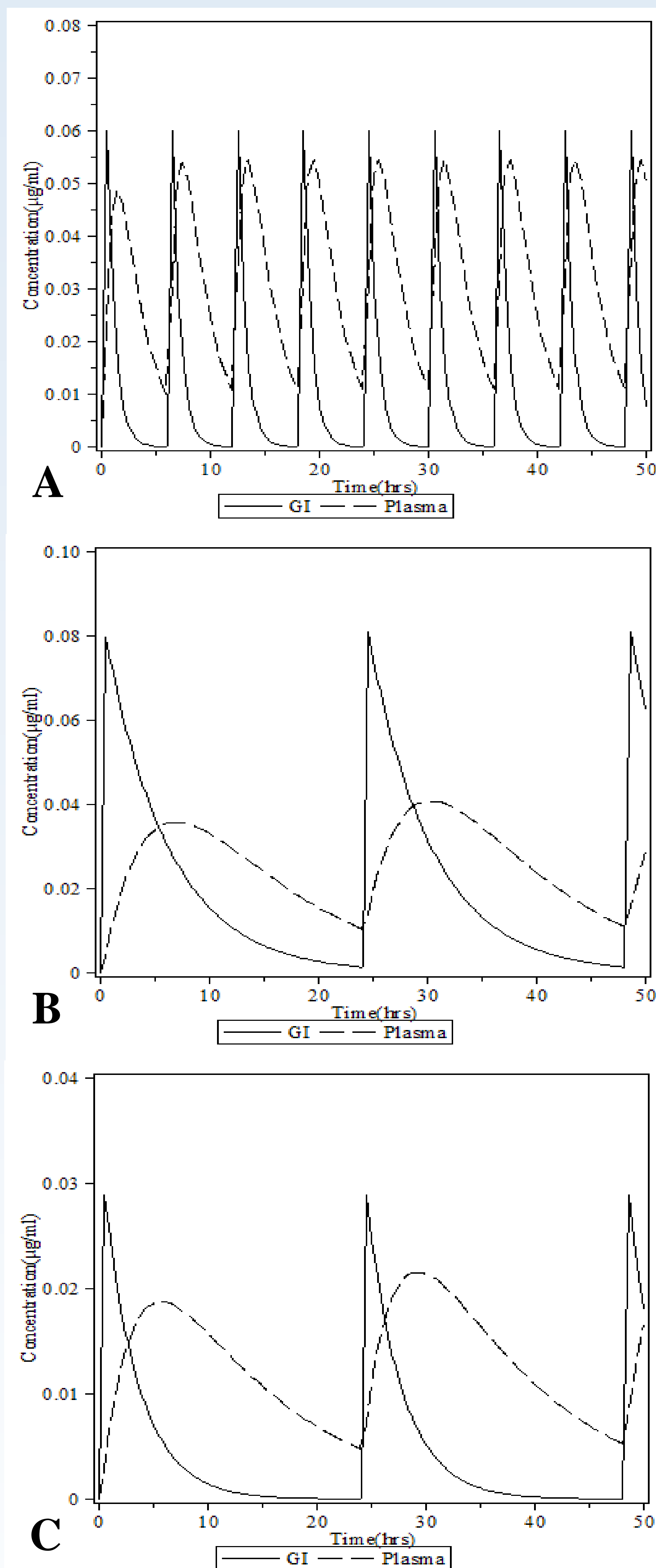
➤The experimental pharmacokinetic parameters, such as maximum plasma concentration (C_{max}), the time to reach C_{max} (T_{max}), and elimination half-life time ($t_{1/2}$) together with dissolution profiles were taken from *in vivo* study of Fernandes and coauthors. To simulate the NC dose-dependent release and its metabolic degradation we used computer linear algebra algorithms in the Maple 15 software (Maplesoft GmbH, Aachen, Germany). The pharmacokinetic two-compartment model included two different compartments: the first compartment ($x(t)$ or $\frac{dx}{dt}$) describes the drug concentration in the GI and second ($y(t)$ or $\frac{dy}{dt}$) describes its concentration in the plasma by following differential equations:

$$\frac{dx}{dt} = D(t) - \frac{Dx}{Dt} - xt_{1/2}$$

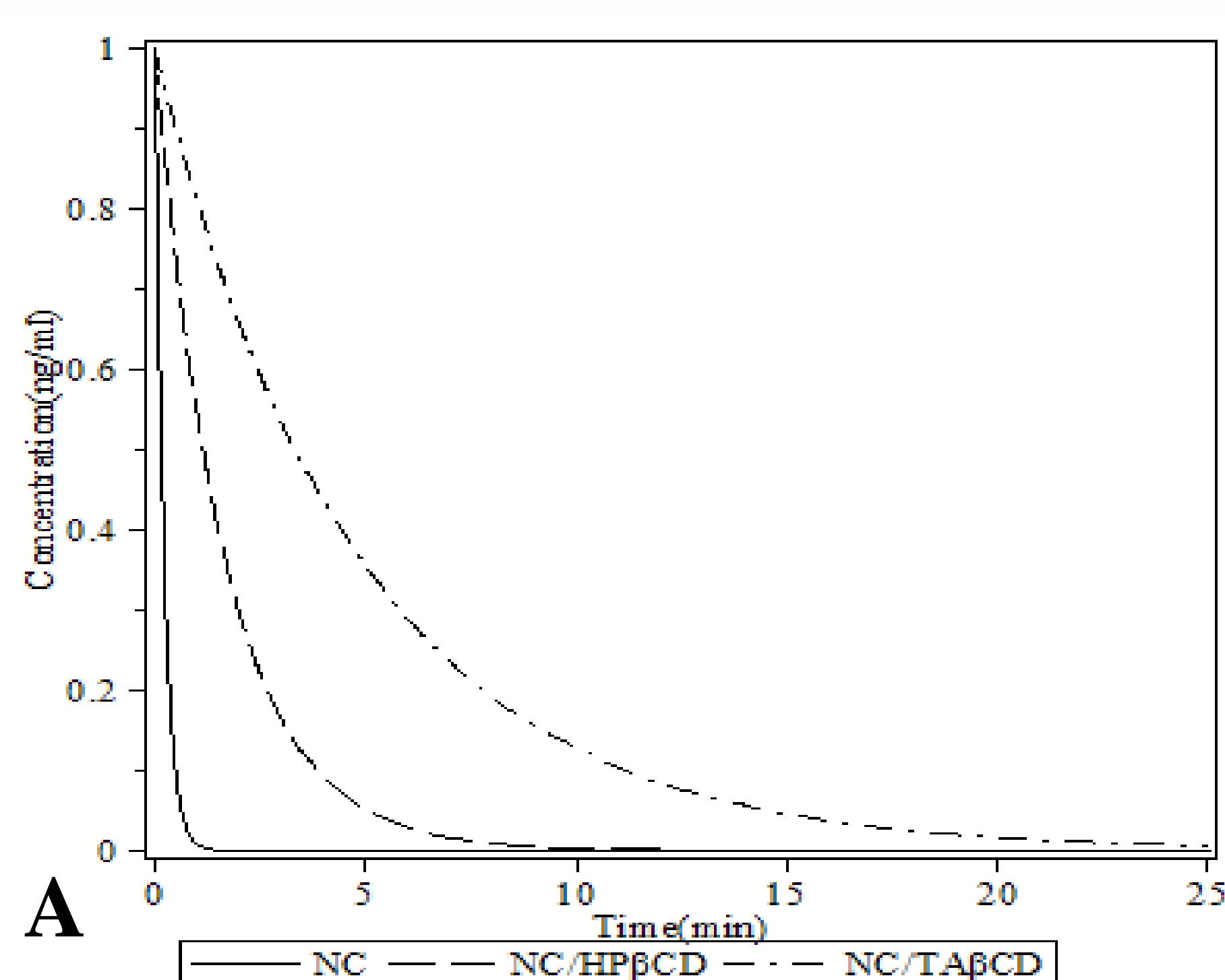
$$\frac{dy}{dt} = xt_{1/2} - yt_{1/2}$$

where $D(t)$ is the drug dosage in mg/ml, $\frac{Dx}{Dt}$ is the dissolution rate of NC in the GI, and $t_{1/2}$ value is the half-life parameter either for the GI or plasma.

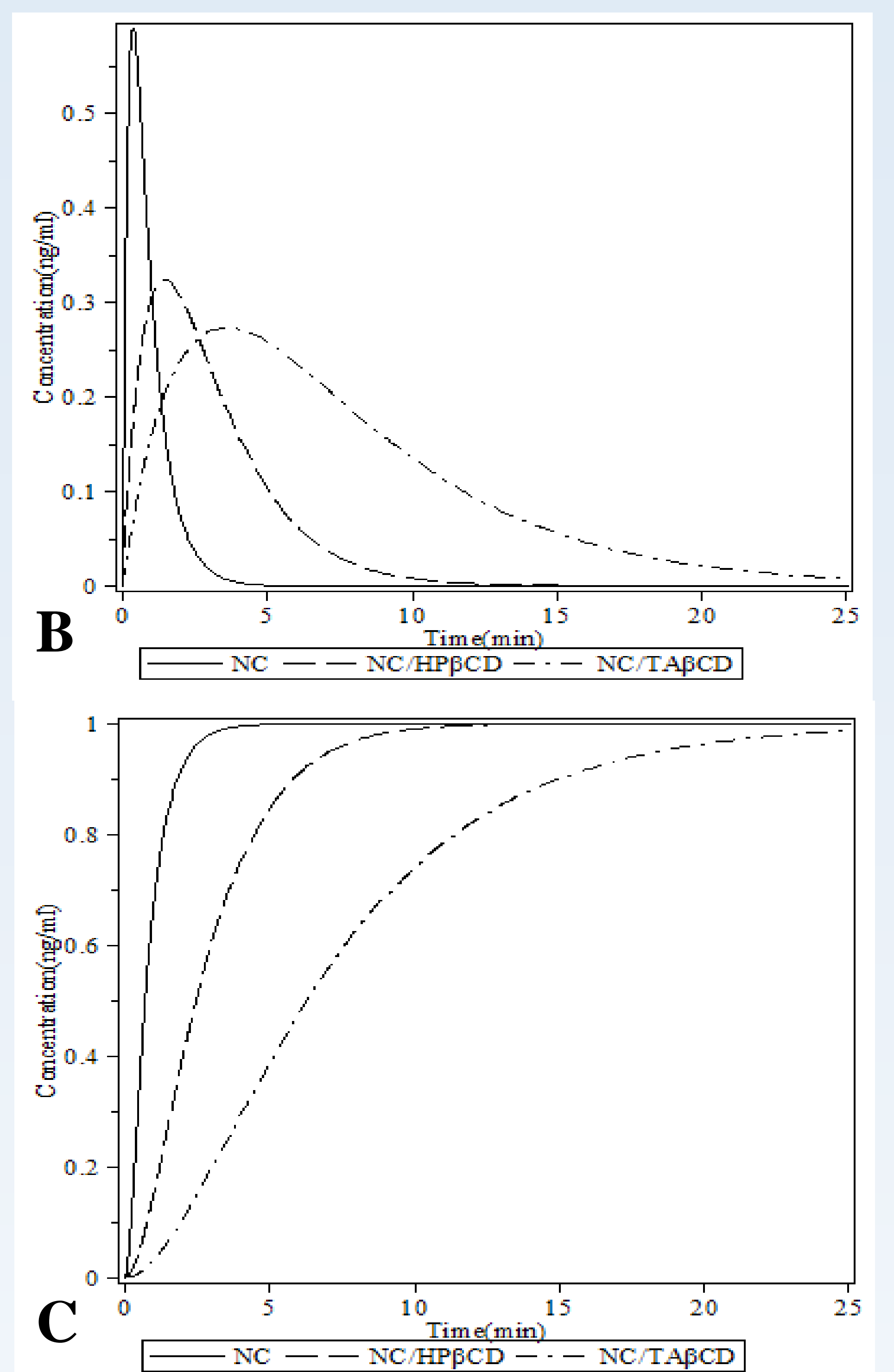
Results



➤Fig.1: Loading of long-range GI and plasma concentration-time profiles from a dosage regime ($D(t)$) for NC (A), NC/HP β CD (B), and NC/TA β CD (C) chemical compounds after oral administration as functions of time.



Results



➤Fig. 2: Short-range GI (A) and plasma (B) concentration profiles (ng/ml) for NC, NC/HP β CD, and NC/TA β CD and their metabolizing rates (C) as functions of time.

Conclusion

➤The NC release rate is the $t_{1/2}$ -dependent process and, therefore, can be adjusted to prolong and optimize 'time release' mechanism by controlling the formulation ratio of its hydrophilic (NC/HP β CD) or hydrophobic (NC/TA β CD) complexes. Because $y(t)$ is dose- and $x(t)$ -dependent as the level of the drug in the circulatory system, it should last long enough for a drug to be effective. With subsequent equal dose levels for specified chemical compounds, which are taken orally, the periodic plasma concentrations were significantly prolonged for the NC formulations, especially for hydrophilic one, and maintained thereafter.

References

➤Fernandes *et al.*, 2003, J Control Release (88)1: 127-134.