How to Cite:
Mahesh, P., & Somasundaram, I. (2022). Lipid nanocarrier system of perinodopril for enhancement of bioavailability. *International Journal of Health Sciences*, *6*(S1), 14067–14073.
https://doi.org/10.53730/ijhs.v6nS1.8573

Lipid nanocarrier system of perinodopril for enhancement of bioavailability

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***Abstract*---**Perinodopril comes under BCS class II drug (low solubility/high permeability) which shows variable absorption pattern due to solubilitylimitation. Therefore, nanostructured lipid carrier (NLC) of Perinodopril was developedwhich is suitable for drug with high log P value as it offers the advantage of high drug entrapment and loading capacity to lipophilic drugs. Tween 80 and Poloxamer 188 were reportedly P-gp efflux inhibitors which would be an added feature to the property of Perinodopril -NLC thus enhancing drug availability across intestine. So the objective of the current work was to evaluate the NLC of perinodopril formulation and to evaluate the same. The invivo estimation of the activity was carried out on Albino wistar rats that are maintained underroom conditions and the formulation was investigated for the Pharamcokinetic and pharmacodynamic paramteres in rat plasma. Also they were tested for their stability invitro. Results show that the nano particles measured as 0.207nm in size. The invitro drug release studies suggest that the formulations were releasing the drug in controlledfashion during 23 hrs. Stability studies proves the drug is very stable in the formulation.With R2 = 0.9683, the in vitro-in vivo correlation research clearly shows good agreement between in vitro drug solubilization during lipolysis and in vivo drug absorption during pharmacokinetic studies. This in vitro lipolysis research, which has an R2 close to 1, suggests that this model can match the in vivo dissolution profile in the gut.

***Keywords*---**Perinodopril, Antihypertensive, NLC, Lipid nanoparticles, carriers.

Introduction

High blood pressure, the most common causeof heart disease, claims the lives of 7 million individuals every year throughout the world. Perinodopril is a nonsulfhydryl prodrug that has been labeled as an ACE inhibitor and is used in the treatment of hypertension [1]. Perinodopril has a specific action on the coronary and skeletal muscle vasculature, according to the manufacturer. Additionally, Perinodopril improves blood flow by inhibiting the synthesis of certain natural compounds that constrict the blood vessels [2]. To achieve these goals, the current research focused on developing an improved Perinodopril- Nano Lipid based carrier (NLC) formulation through the use of Quality by design (QbD), which would further improve the oral bioavailability and, consequently, the therapeutic prospects of Perinodopril [3].

Because of high blood pressure, human heartneeds to beat harder in order to pump blood that is enough to keep up with the demands of regularbodily functioning [4]. Untreated diabetes can couple with hypertension cause heart disease andother complications, such as renal disease, brain damage, and vision loss [5]. The objective of the current research is development and optimization of oral NLC formulation of Perinodopril to increase its oral bioavailability the from optimized formulation and to perform invivo studies[6].

Analytical Methodology

Validation of UV method for the analysis of Perinodopril
Linearity

Perinodopril showed linear absorptionfrom 4-25 µg/mL in methanol, 2-30 µg/mL in HCl at pH 1.2 and 4-30 µg/mL in phosphate buffer saline at pH 7.4 and in Kreb's Ringer Soution at pH 6.5. The correlation coefficient (r2)was found to be 0.992, 0.990 and 0.993 in methanol, HCl (pH 1.2) and phosphate buffer saline (pH 7.4) respectively

Table 1. Calibration curve of Perinodopril in methanol (n = 3)

Concentration (µg/mL)	Mean Absorbance ± SD	Regressed absorbance
4	0.129±0.010	0.096
8	0.242±0.008	0.224
12	0.326±0.004	0.351
16	0.457±0.010	0.479
20	0.630±0.090	0.607
25	0.766±0.011	0.734

Stability indicating method for the estimation of perinodopril in developed formulation

Forced degradation studies : % drug degraded by different stress experiment is summarized. Degradation of drug product with the range of 5-20 % has been accepted as reasonable for chromatographic assay validation[7].

Table 2. HPLC quantification of forced degradation of Perinodopril under different stress condition

Stress testing condition	Number of peaks	Drug content (mg) mean±SD)	% Drug recovered	% Drug degraded
Acid induced	2	10±0.025	87.65±1.31	12.35±0.02
Base induced	2	10±0.036	82.98±2.19	17.02±0.05
Oxidative	3	10±0.027	91.54±0.021	8.46±0.03
Photolytic	2	10±0.041	83.61±1.58	16.39±0.04
Thermal	2	10±0.037	90.38±1.67	9.62±0.03

Acid conditions: The acid stress testing was done by adding hydrochloric acid (0.1M) to 1ml stock solution of Perinodopril in methanol(1mg/ml) and refluxing the mixture at 60 °C for 6 h. This solution was allowed to attain ambient temperature (final concentration for analysis -100 µg/ml) and analyzed via HPLC.

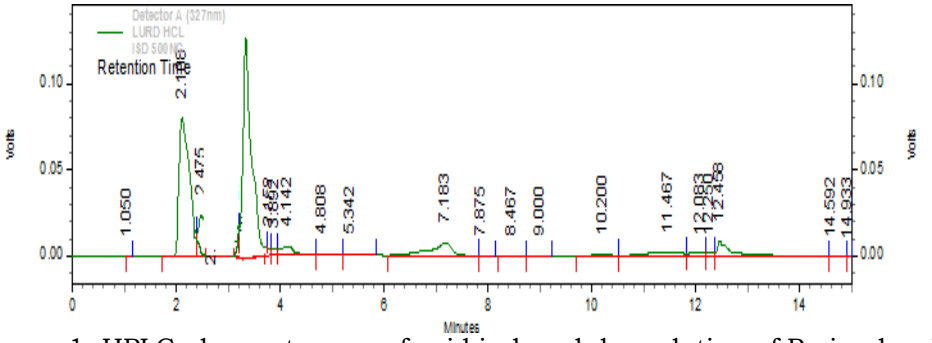


Figure 1: HPLC-chromatogram of acid induced degradation of Perinodopril

Oxidation conditions: For inducing oxidativestress, hydrogen peroxide is the most commonly used oxidizing agent. The prepared stock solution of Perinodopril (1mg/ml) was subjected to 0.1– 3% hydrogen peroxide solution at neutral pH and room temperature for seven days. The mixture was diluted with 10 ml methanol (final concentration for analysis was 100 µg/ml) and analysed through HPLC[8].

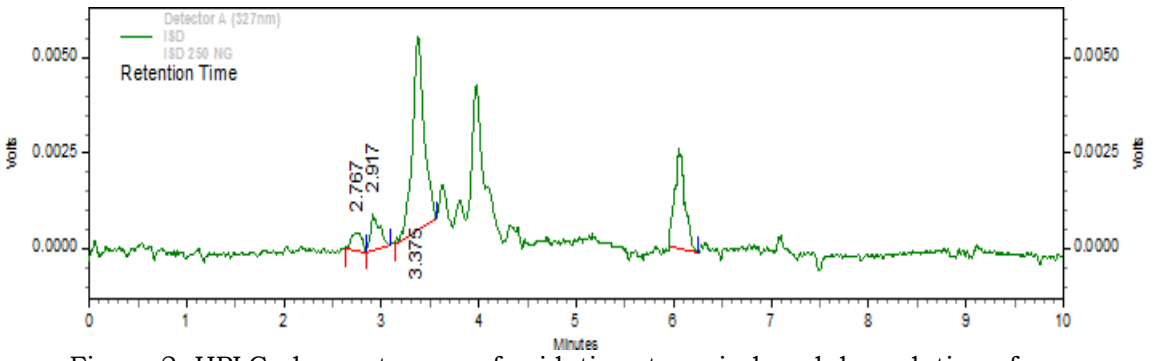


Figure 2: HPLC-chromatogram of oxidative stress induced degradation of Perinodopril

Size, PDI and Zeta Potential

The mean particle size and particle distribution index (PDI) of the improved Perinodopril and NLC were determined to be 85.7±7.3 nm and 0.207±0.029, respectively. The low value of the particle size distribution index (PDI) suggeststhat nanoparticles are homogenous in size. When using the improved formulation, the zeta potential was -10.170.59 mV.

Table 3. Size and PDI of placebo NLC in different medium. Data expressed as mean ± SD, n = 3

Time (h)	Mean of the Particle Sizes				Mean PDI	
	In water	In SGF	In FaSSIF	In FaSSIF	In water	In SGF
0.5	88.1±4.59	88.9±5.59	91.1±3.658	95.6±4.39	0.221±0.0089	0.225±0.0018
1	88.9±8.89	91.4±8.89	3.4±7.365	114.7±6.68	0.223±0.0085	0.226±0.0031
2	90.1±5.987	94.5±7.01	95.7±4.568	128.3±7.19	0.221±0.0173	0.228±0.0047
3	91.3±7.78	99.2±4.21	151.4±9.14	0.225±0.0075		0.234±0.0051
6	94.8±4.69		107.2±6.87	207.6±6.6		0.236±0.0135

Pharmacokinetic Studies

Perinodopril suspension and Perinodopril - NLC were studied with and without cycloheximide to determine their plasma drug concentration-time profiles. At each time point, there was a statistically significant difference in the plasma concentration of Perinodopril -NLC when compared to Perinodopril -NLC with cycloheximide and Perinodopril suspension (all p0.01). A significant improvement in oral bioavailability was seen in the pharmacokinetic characteristics demonstrated by the formulation (Perinodopril-NLC) [9].

Table 4. Formulations with and without cycloheximide, plasma drug concentrations throughout time.values were expressed as mean±SD, n=4

Time(h)	Conc. (suspension)(ug/mL)	Conc. (Perinodopril-NLC) (ug/mL)	Conc. (Perinodopril-NLC +Cycloheximide) (ug/mL)

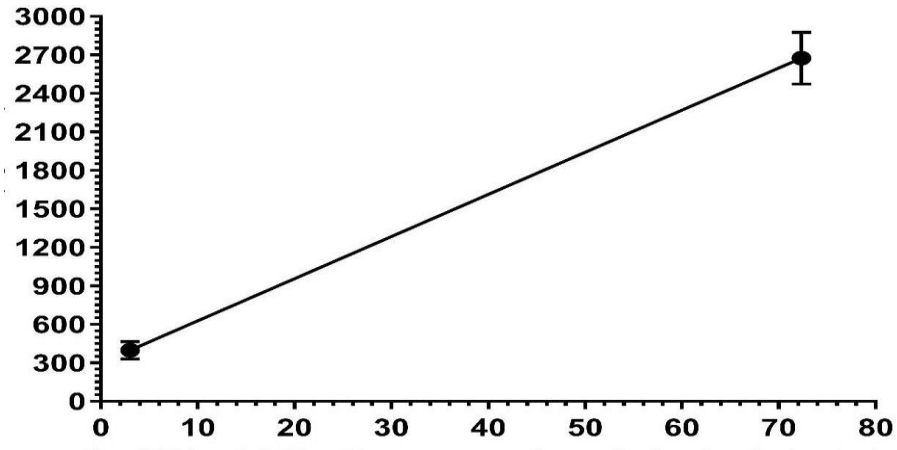
0.5	398.14±67.29	2674.21±142.19	1983.21±293.56
2	2354.25±177.65	6987.64±296.23	3459.2±198.2
8	1123.54±128.47	3642.54±227.9	1781.3±226.57
12	371.28±66.57	2943.71±256.88	1187.59±259.72
24	149.32±24.59	1347.58±143.84	387.84±67.51

Table 5. Pharmacokinetic data acquired following oral administration of drug suspension to rats, both inthe presence and absence of cycloheximide (Cx).values were represented as mean±SD,n=4

Parmameters	Perinodopril suspension	Perinodopril-NLC	Perinodopril-NLC with-Cx
AUC0 to t (ngh/mL)	18710.44±1759.25	78725.72±1948.62	27426.5±12325.28
Cmax (ng/mL)	2355.52±356.27	6988.46±597.8	1892.67±359.63
Tmax (h)	2.0±0.00	2.0±0.00	2.0±0.00
Ka(h-1)	0.081298±0.021	0.048416±0.038	0.061079±0.053
AUC0 to ∞ (ngh/mL)	20547.06±1124.52	106555.5±34257.51	29024.76±1539.84
AUMC0 to t(ng.h2/mL)	119942.5±27548.29	676093.7±13326.49	201920.17±983.17
AUMC0 to ∞(ng.h2/mL)	186611.6±18526.91	1918742±22356.47	396370.6±34691.67
T1/2 (h)	8.49±2.13	14.29±4.19	11.28±3.97
Relative bioavailability	-----	4.201	1.905

In vitro-in vivo correlation study with R2 = 0.9683 clearly indicates good agreement betweenin vitro drug solubilized during lipolysis study and in vivo drug absorption during pharmacokinetic study. This in vitro lipolysis study with R2 closer to 1 indicates that this model can mimic in vivo dissolution profile in vivoinside gut[10].

Figure 3. In vitro- in vivo correlation of AUC of Perinodopril obtained after oral



dosing vs % of drugsolubilized in aqueous phase during lipolysis study

% of Perinodopril solubilized in aqueous phase during lipolysis study

Summary and Conclusion

Confocal microscopy was performed to assess the depth of penetration of drug through intestine. After treating Perinodopril suspension and Perinodopril-NLC with rhodamine 123, formulations were placed into the 5-6 cm segments of small intestine. Fluorescence signal was detected at different depth of the intestine after 20 min and 1 h of treatment. Filling of formulation into intestine, dissolution media and maintenance of temperature was same as for *in vitro* gut permeation study. After 20 min and 1 h of treatment small intestine was cut open and positioned on the slide such that inner part of intestine faces up. The optimized Perinodopril Formulation was found to be stable at different simulated gastric fluid. Confocal study depicted maximum deposition of Perinodopril into the depth of the small intestine. Perinodopril displayed significantly higher permeation across small intestine due to of P-gp inhibiting activity of the chosen excipients resulting in sufficient improvement in the oral bioavailability of Perinodopril. A significantly higher drug partition into aqueous phase of drug from Perinodopril anticipated that Perinodopril might have higher absorption *in vivo*. This was further confirmed by *in vivo* pharmacokinetic study which demonstrated that Perinodopril could improve oral bioavailability of drug which could be attributed to the lipid based excipients utilized in NLC. *In vivo* antihypertensive activity clearly demonstrated that oral administration of NLC of Perinodopril in rats are a suitable approach to maintain blood pressure for over 24 h duration. Thus, oral administration of NLC loaded Perinodopril has proved to be a remarkable delivery system in the management of hypertension.

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