How to Cite:
Pg, M., & Somasundaram, I. (2022). Evaluation and invivo studies of solid lipid nano carrier mediated drug delivery system of perinodopril. *International Journal of Health Sciences*, *6*(S3), 8000–8008. https://doi.org/10.53730/ijhs.v6nS3.7894

Evaluation and invivo studies of solid lipid nano carrier mediated drug delivery system of perinodopril

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***Abstract*---**High BP is one of the most predominant causes of heart diseases and cerebrovascular problems. Perinodopril is an ACE inhibitor that is a non sulfhydryl derivative that is used for the treatment of hypertension. To enhance the effect of the drug it was formulated into Lipid based nano carrier system (NLC) to improve the bioavailability and thereby the therapeutic potential. 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 under room 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 controlled fashion 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 cause of 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 heart needs to beat harder in order to pump blood that is enough to keep up with the demands of regular bodily functioning [4]. Untreated diabetes can couple with hypertension cause heart disease and other 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

Methods

Animals

Wistar albino rats were maintained in plastic cage and kept under conventional laboratory settings, which included maintaining the temperature at 25.2 degrees Celsius and the relative humidity at 55 percent RH, as well as providing them with easily available to feed and water [6].

Pharmacokinetic studies

Perinodopril suspension (perinodopril dispersed in 2 percent Na-CMC and Perinodopril-NLC were given the drug in oral route to rats at a dosage of 12 mg/kg by an 18-gauge oral feeding needle [7] to evaluate the pharmacokinetics of Perinodopril suspension.

Determination of Perinodopril in plasma

Perinodopril in plasma was estimated by liquid-liquid extraction. Normally 0.2ml of the plasma of the rat and 0.5ml of the acetonitrile was mixed and centrifuged at low RPM for one min. To this medium, added 1ml of the ethyl acetate and again centrifuged for about 10 min at 4000 rpm [8].

Pharmacodynamic study

The assessment of the drug for its antihypertensive activity in the developed formulation in preclinical setting was performed in hypertensive rats. After 2 weeks the animals were dividied into 3 groups having 4 rats in everygroup [9].

Stability Studies

For the assessment of stability of developed Perinodopril loaded NLC formulation in accordance with ICH guidelines, three batches of prepared formulation were stored for 6 months at40 ± 2 °C and 75 ± 5 % RH [10].

Results & Discussion

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) suggests that nanoparticles are homogenous in size. When using the improved formulation, the zeta potential was -10.170.59 mV.

Table 1.
Size and PDI of placebo NLC in different medium. Data expressed as mean ± SD, n = 3 Mean of the Particle Sizes Mean PDI

Time (h)	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±8.8	93.4±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

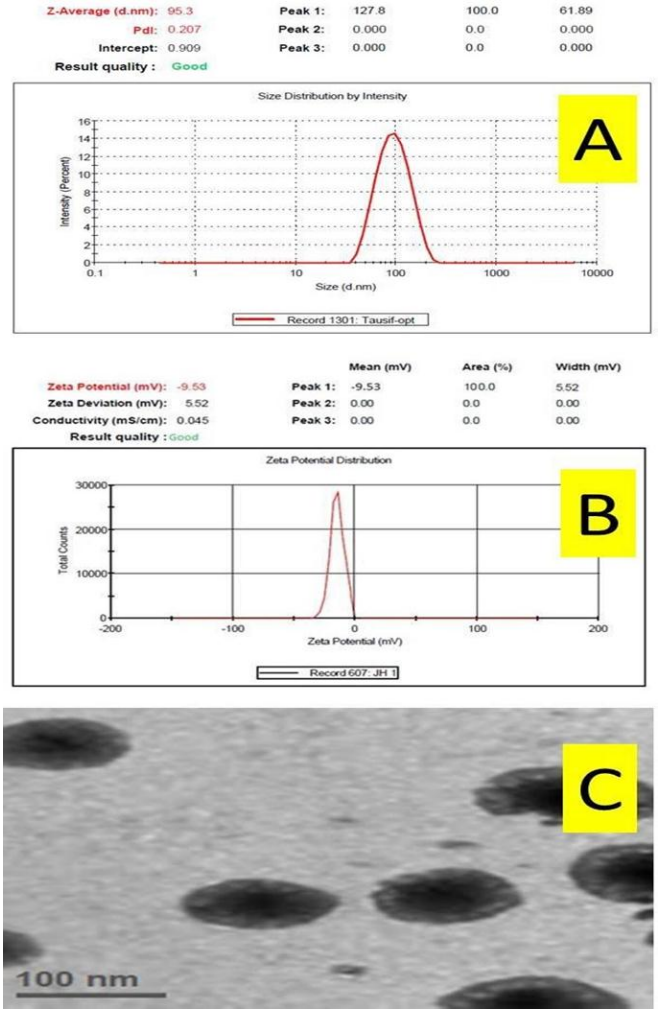

Figure 1. (A) particle size analysis, (B) Zeta-potential and (C) T.E.M images of the optimized Perinodopril -NLC

In vitro release study

From the study in 1.2 pH and 7.4 pH values for Perinodopril solution and commercially available Perinodopril formulation It wasconcluded that 37.4±5.21% of the medicationwas released from the NLC at pH 7.4 immediately for immediate action, followed by a steady release of 55.49 percent of the drug for a period of over 23 hours after the initial release.

Table 2
In vitro release profile of Perinodopril -NLC,Perinodopril -suspension and marketed formulation at pH 1.2 and 7.4.Perinodopril = perinodopril, %CDR = % cumulative drug release, Mkt = marketed. Data presented as mean±standard deviation, n = 3 for each formulation.

Time (hr)	% CDR of Perinodopril-NLC at pH 1.2	% CDR of Perinodopril-Susp at pH 1.2	% CDR of Mkt at pH 1.2	% CDR of Perinodopril-NLC at pH 7.4	% CDR of Perinodopril-Susp at pH 7.4	% CDR of Mkt at pH 7.4
0.5	24.1±2.37	1.1±3.31	13.3±5.54	29.3±3.32	1.3±6.36	15.1±3.65
1	33.4±5.23	1.9±4.88	19.1±6.12	37.4±5.21	2.4±5.69	21.1±5.65
2	41.3±3.55	3.8±3.01	26.5±7.21	48.1±2.21	4.2±7.54	27.3±6.32
4	56.4±7.15	8.5±5.27	34.8±5.25	63.5±3.36	9.8±5.23	34.7±7.32

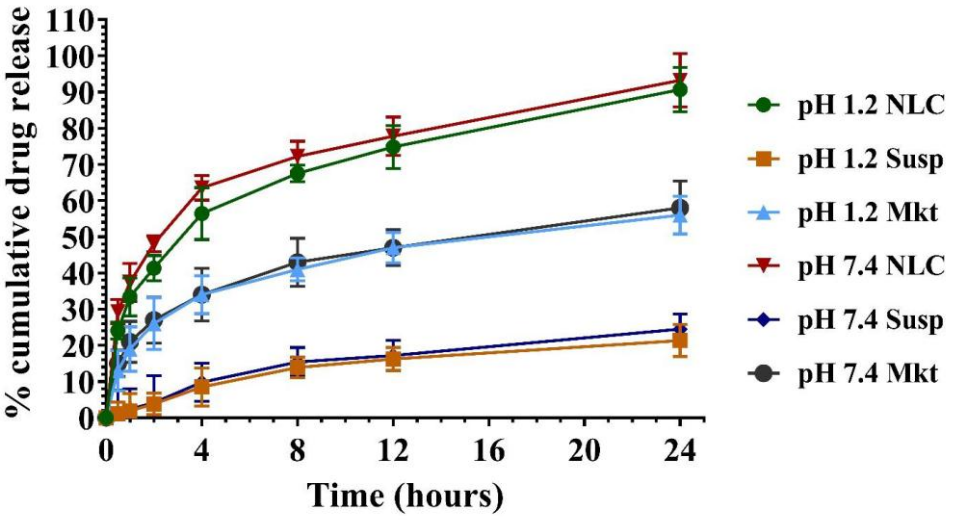

Figure 2. The percentage cumulative drug release in vitro study ofPerinodopril -NLC, Perinodopril suspension &the marketed formulation at pH's 1.2 and 7.4. values were expressed as mean±SD, n = 3

Stability Studies

There was no statistically significant difference in mean particle size and PDI of Perinodopril -NLC in stomach pH 1.2 and intestinal fluid pH 7.4 as compared to baseline.

Lipolysis Study

In the dynamic lipolysis investigation, the percent of Perinodopril in aqueous phase from Perinodopril-NLC and Perinodopril suspension was 72.34±4.616 percent and 3.01±0.905 percent, respectively, with a p0.001 significance level for each. Perinodopril concentration in the aqueous phase of the NLC was

considerably greater than the concentration of the drug in the lipid phase (20.1±1.77) and sediment (3.3±0.63),with a p-value of 0.005.

Table 3
Concentration of drug from its suspension and formulation in different medium. Data expressedas mean±SD (n = 3)

Medium	Perinodopril	Perinodopril - suspension (%)
Aqueous phase	72.34±4.616	3.01±0.905
Lipid phase	20.1±1.77	13.79±1.62
Sediment	3.3±0.63	83.11±6.042

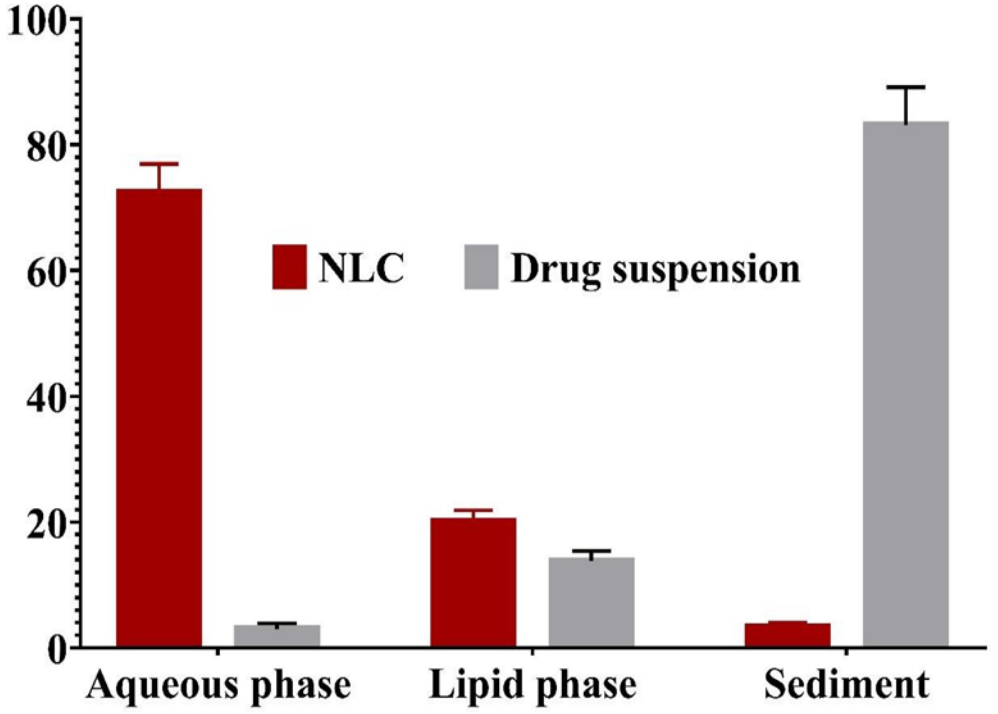

Figure 3. Lipolysis study of Perinodopril in different phases. values were expressed asMean ± SD, n = 3% of Perinodopril in different Phase

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).

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)	Time (h)
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 between in 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 vivo inside gut.

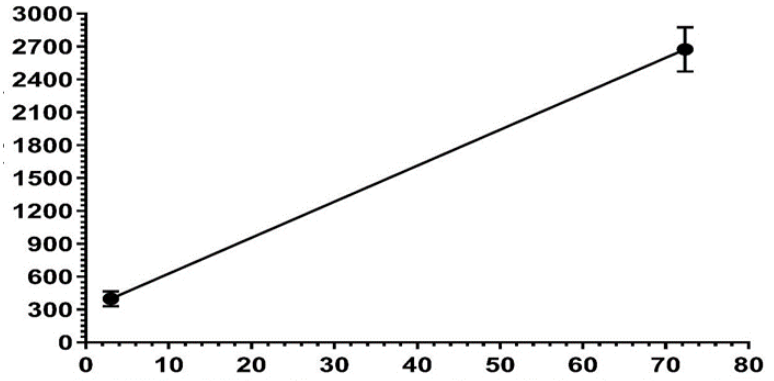

Figure 4. In vitro- in vivo correlation of AUC of Perinodopril obtained after oral dosing vs % of drugsolubilized in aqueous phase during lipolysis study % of Perinodopril solubilized in aqueous phase during lipolysis study

Summary and Conclusion

Chromatographic method was employed inorder to determine the Perinodopril concentration in blood plasma for determining pharmacokinetic parameters. C18 reverse phase column was utilized. Acetonitrile and water (50:50) were taken as solvent system; the flow rate was modified to 1mL/min. This methodology was observed to be linear in between the range of concentration of 50-10000 ug/mL. The Limits of Determination and Quantification was determined to be 8.86 ug/mL and 26.87 ug/mL. % RSD as determined for accuracy, precision and robustness was found to be less than 2%.

References

1. Basalious E, Shawky N, Badr-Eldin S. SNEDDS containing bioenhancers for improvement of dissolution and oral absorption of lacidipine. I: Development and optimization. Int J Pharm. 2010;391(1-2):203-211. doi:10.1016/j.ijpharm.2010.03.008
2. Beg S, Sharma G, Thanki K, Jain S, Katare O, Singh B. Positively charged self- nanoemulsifying oily formulations of olmesartan medoxomil: Systematic development, in vitro, ex vivo and in vivo evaluation. Int J Pharm. 2015;493(1-2):466-482. doi:10.1016/j.ijpharm.2015.07.048
3. Beg S, Swain S, Singh HP, Patra CN and Rao MB. Development, Optimization, and Characterization of Solid Self-Nanoemulsifying Drug Delivery Systems of Valsartan Using Porous Carriers. AAPS Pharm SciTech 2012;13(4):1416-1427.
4. A, Solinis MA, Rodriguez-Gascon A, Almeida AJ and Preat V. Nanostructured lipid carriers: Promising drug delivery systems for future clinics. Nanomed 2016;12:143-161.
5. Beveridge T, Gratwohl A and Michot F. Cyclosporine: pharmacokinetics after a single dose in man and serum levels after multiple dosing in recipients of allogenic bone-marrow grafts. CurrTher Res 1981;30:5-18.
6. BioLineRx to Develop and Commercialize Novel Peptide Drug Candidates Discovered by Compugen [Online]. Available from: http://www.biolinerx.com, 5:27, 14 Apr2016.

7. Bruno BJ, Miller GD and Lim CS. Basic and recent advances in peptide and protein drug delivery. Therdeliv 2013;4(11):1443-67.
8. Carey RM and Padia RH. Angiotensin AT2 receptors: control of renal sodium excretionand blood pressure. Trends Endocrinol Metab2008;19(3):84-87.
9. Christopher JHP, Natalie LT and William NC. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs 2007;7:231-248.11.
10. Chadha R, Bhandari S, Kataria D, Gupta S. Exploring Lecithin/Chitosan Nanoparticles of Ramipril for Improved Antihypertensive Efficacy. J Nanopharm Drug Deliv 2013;1(2):173-181. doi:10.1166/jnd.2013.1014.