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Enhancement Of Bioavilability of Perinodopril Using Lipid Based Nanocarrier Mediated Oral Drug Delivery System

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Abstract

Hypertension is a serious cardiovascular event which refers to rise in the arterial blood pressure. Perinodopril which has been classified as calcium channel blocker is utilized in the treatment of hypertension. Perinodopril comes under BCS class II drug (low solubility/high permeability) which shows variable absorption pattern due to solubility limitation. Therefore, nanostructured lipid carrier (NLC) of Perinodopril was developed which 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. Therefore, the objectives of the present work were to develop an optimized Perinodopril -NLC using Quality by design (QbD) and evaluating it for enhancement in intestinal uptake and solubilisation fate (in physiologically simulating gastro intestinal milieu) of Perinodopril which would further enhance the oral bioavailability. Physicochemical characterization of the drug by means of UV spectra, DSC and FT-IR concluded that Perinodopril is pure and authentic. Both medium chain triglycerides (MCT) and long chain triglycerides (LCT) were used in the solubility studies of Perinodopril. The drug exhibited the highest solubility in Capryol 90 (35±3.51 mg/mL). Among solid lipids, solubility of drug in Emulcire 61 was found to be the highest (62.41±4.02 mg/g). The highest solubility of drug in Emulcire 61 could be attributed to its inherent self-emulsifying property. Presence of alcoholic group in Emulcire 61 and in Capryol 90 which acts as hydrogen bond donor and presence of 5 oxygen and 3 nitrogen atom in Perinodopril which acts as hydrogen bond acceptors could form a stable complex which enhances the solubility of drug in these solid and liquid lipids

Keywords: Perinodopril, Antihypertensive, NLC, Lipid nanoparticles, carriers

INTRODUCTION : Hypertension, a worldwide epidemic at present, is not a disease in itself rather it is an important risk factor for serious cardiovascular disorders including myocardial infarction, stroke, heart failure, and peripheral artery disease. Hypertension is a serious cardiovascular event which refers to rise in the arterial blood pressure. Due to high blood pressure, heart has to work harder in order to pump adequate amount of blood to cope up with normal body functioning. If the same is not treated, it may lead to heart-related problems and may damage the organs like kidney, brain, and eyes. According to WHO, Geneva, in 2008, hypertension resulted in 45% mortality rate because of ischemic heart disease and 51%

mortality rate because of stroke. In 1980, 600 million people were suffering from hypertension while in 2015 this graph was raised to 1.1 billion raising a big concern for dealing with this condition effectively. High blood pressure being the main cause of heart disease is killing 7 million people every year worldwide.

THE SPECIFIC OBJECTIVES OF THE WORK WERE:

Development and optimization of oral NLC formulation of Perinodopril to increase its

- Aqueous solubility and bioavailability.
- In vitro evaluation of optimized formulation.

EXPERIMENTAL METHODS

PRE-FORMULATION STUDIES

Physicochemical Characterization

Melting Point

Drug filled capillary along with thermometer was inserted into HICON melting point apparatus. The temperature of thermometer was noted when drug was transitioned into liquid state[6].

Solubility

It was determined by shake flask method. Distilled water (20 mL), excess drug was dissolved and was kept on biological shaker for 48 h at 37 °C. Solution was then filtered and observed for solubility by UV spectrophotometric method[7].

UV spectra analysis

Drug was scanned after dilution in methanol (10 µg/mL) between 200-400 nm utilizing double beam spectrophotometer. [8]

Differential scanning calorimeter

DSC of Perinodopril was performed using Perkin Elmor Pyris 6 DSC. The sample was treated according to following specification:

Sample size: About 1 mg

Temperature: 40-300 °C

Fourier transform infrared absorption spectrum (FT-IR)

IR Prestige 21 was used to measure the IR absorption spectra of Perinodopril in KBr disc (Shimadzu Corp, Kyoto, Japan). To produce a disc, the sample was ground with KBr (1:10). Over a wave number range of 4000-350 cm-1, it was scanned at a rate of 4mm/s with a resolution of 2 cm-1. [9]

RESULTS & DISCUSSION

Authentication of Perinodopril

UV spectra analysis

UV spectra of Perinodopril in methanol (10 µg/mL) showed λmax at 325.6 nm as shown. (Reported = 327 nm)

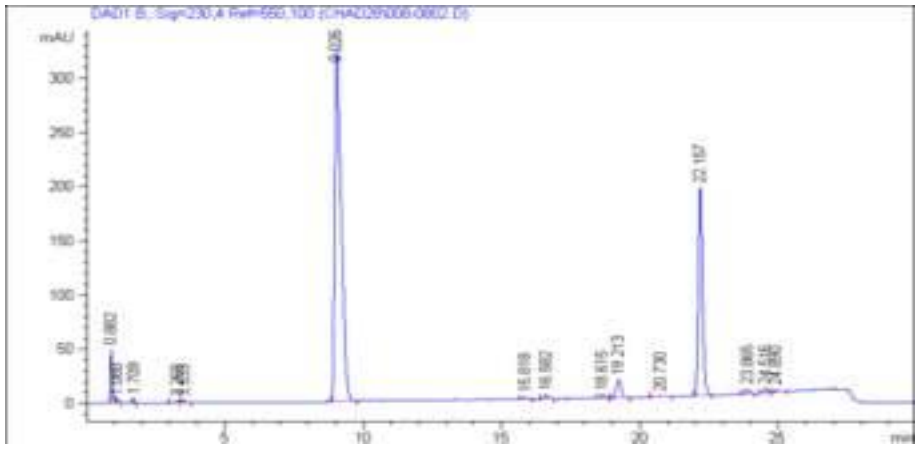

Figure 1. UV scan of 10 µg/mL **Perinodopril** ***in methanol from 400 to 200 nm***

Differential scanning calorimeter

A sharp endothermic peak was obtained at 171.092 °C showing crystalline nature of drug. This DSC value is in accordance with reported value of 168.02 °C

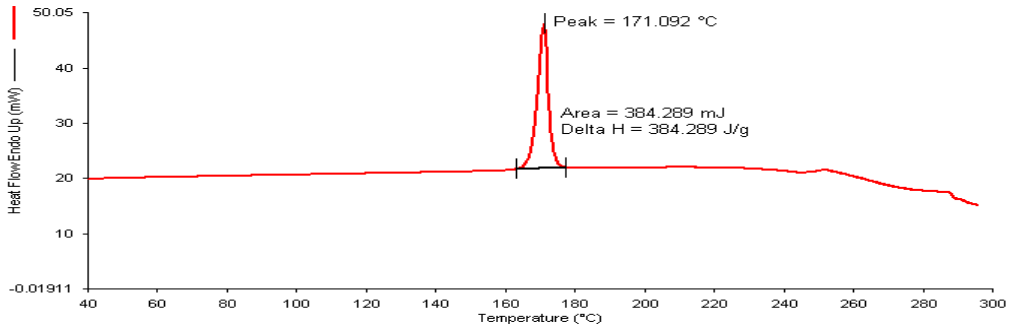

Figure 2. DSC scan of Perinodopril from 40 to 300 0C at 10 °C/mi

PREPARATION OF PERINODOPRIL LOADED SOLID LIPID NANOPARTICLES.

Solvent evaporation with probe sonication was used to make perinodopril. In a beaker, solid lipid (Cetyl Alcohol) and liquid lipid (Propylene Glycol Monocaprylate) were mixed in a 7:3 ratio with Perinodopril. To generate the lipid phase, ethanol and acetone (1:1) were added to it and the beaker was kept at 70 °C.

DRUG–EXCIPIENTS COMPATIBILITY STUDY

Tween 80 and Poloxamer 188, in a 2:1 ratio, were chosen as the surfactant of choice because they produced an optically clear formulation with a lower mean particle size and a higher PDI than any other surfactant. With or without phase separation, the formulation can be made.

FORMULATION OF PERINODOPRIL-NLC

The compound Perinodopril -NLC was synthesised using a solvent evaporation process. Whilst preparing Perinodopril -NLC, the selection of organic phase (ethanol and acetone) was based on the solubility of each phase in both the lipid phase and the Perinodopril phase. In an organic solvent, the drug and lipids are fully combined. After evaporation, organic solvents leave behind medication that has been solubilized in lipids. Because the drug is concentrated mostly in the solid core, the release of the drug is sluggish because the mobility of the drug is greatly decreased in the crystalline core.

Table 1. Formulation of Perinodopril

FORMULATION	FORMULATIONS														
INGRIDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
ORGANIC PHASE															
Perinodopril (mg)	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Cetyl Alcohol (mg)	100	200	-	-	-	-	-	-	-	100	200	-	-	-	-
Glyceryl Monostearate-(mg)	-	-	100	200	-	-	-	-	-	-	-	100	200	-	-
Propylene glycol Monocaprylate	-	-	-		100	200	-	-	-	-	-	-	-	100	200
Ethanol : Acetone (1:1)	10	10	10	10	10	10				10	10	10	10	10	10
AQUEOUS PHASE															
Poloxamer (mg)	100	100	100	100	100	100	-	-	-	100	100	100	100	100	100
Tween 80	0.5	1	-		-	-	-	-	-	0.5	1	-	-	-	-
Mannitol	10	10	10	10	10	10	-	-	-	10	10	10	10	10	10
Glycerol mono oleate	-	-	-		-	-	10	-	-	-	-	-	-	10	-
Distilled water(mL)	-	-	-		-	-	10	-	-	-	-	-	-	10	-

ANALYTICAL METHODOLOGY

Validation of UV method for the analysis of Perinodopril

Linearity : Perinodopril showed linear absorption from 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 2. 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.

Table 3. 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, neutralized to pH 7 by adding 0.1 M sodium hydroxide, diluted with 10 ml methanol (final concentration for analysis -100 µg/ml) and analyzed via HPLC.

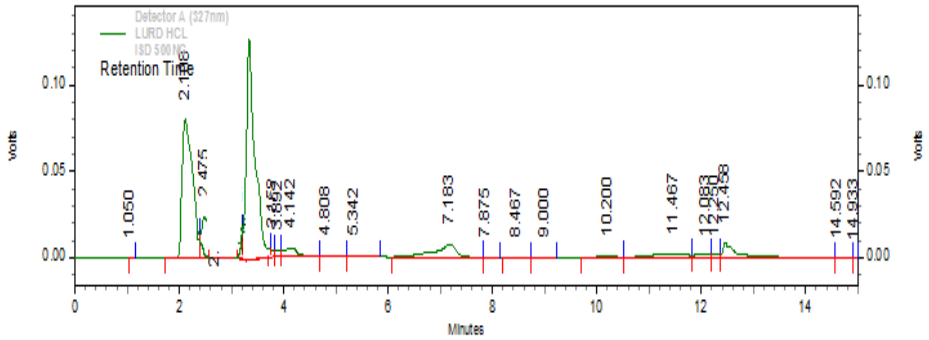

Figure 3:HPLC-chromatogram of acid induced degradation of Perinodopril

Oxidation conditions: For inducing oxidative stress, 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 analyzed through HPLC

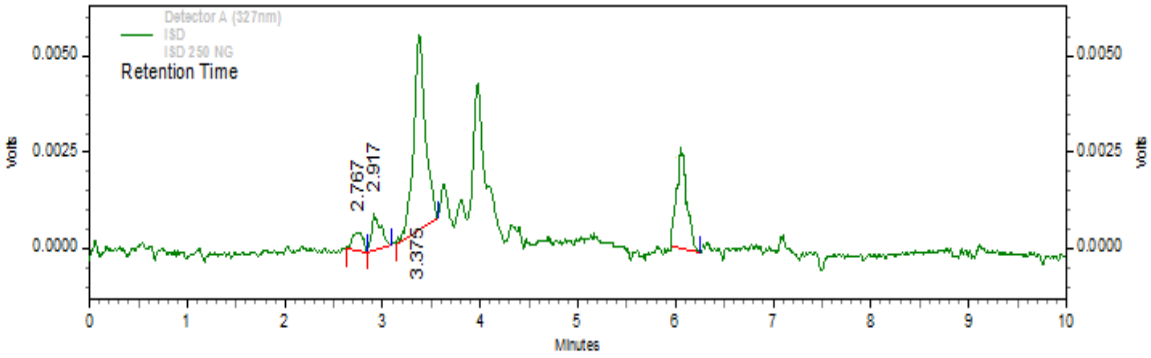

***Figure 4:HPLC-chromatogram of oxidative stress induced degradation of* Perinodopril**

DESIGN AND EVALUATION OF PERINODOPRIL LIPID BASED NANOSTRUCTURE

Excipients screening

Screening of lipids

Screening of liquid lipids

Perinodopril's solubility investigations were conducted using both medium chain triglycerides (MCT) and long chain triglycerides (LCT) as lipid carriers. The medication had the greatest solubility in Capryol 90 (353.51 mg/mL), which was the most used solution. As a liquid lipid, it was chosen for use in the creation of the NLC formulation. The fact that medicines are generally more soluble in MCT than in LCT is due to the fact that MCT has a greater emulsifying capacity than LCT in contrast to the latter.

Screening of solid lipids

The solubility of the medication in Emulcire 61 was found to be the greatest of the solid lipids tested (62.414.02 mg/g).The fact that Emulcire 61 has the highest solubility of any medication tested might be due to the fact that it has an intrinsic self-emulsifying characteristic. [10]

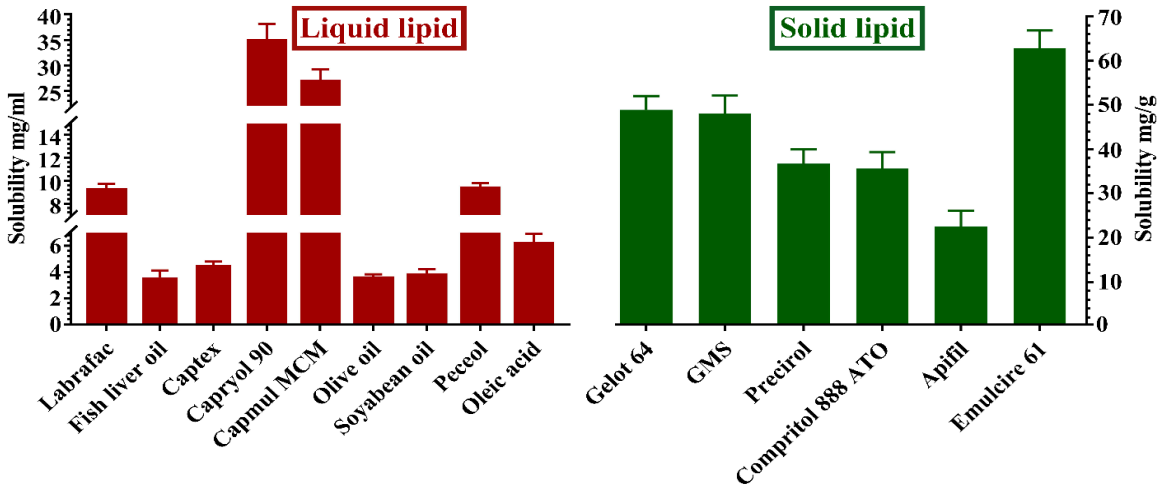

Figure 5. The solubility of the drug in various liquid lipids (mg/mL) and solid lipids (mg/g) was determined using the methods: The data is presented as the mean standard deviation (n = 3).

SUMMARY AND CONCLUSION

Insights of Research work done & incurred results

UV method validation for determination of Perinodopril in pH 1.2, 7.4, methanol and Krebs Ringer solution was performed for the study of *in vitro* release profile of drug and estimation of drug in oil respectively.. The method was found to be linear in the concentration range of 4-24 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 Krebs Ringer solution.

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