Invivo Pharmacokinetic studies to investigate the enhancement of bioavailability of Lovastatin

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ABSTRACT

The main aim of this study is to intensify the bioavailability of drug which is having lower bioavailability (<5 %) like Lovastatin in the form of Solid lipid nanoparticle (SLN) carrier and Nanostructured lipid carrier (NLC) and also to choose the best carrier molecule among this two by performing the invivo pharmacokinetic studies. The NLC (N3) and SLN (S6) was formulated by homogenization technique by using various formulation variable like lipid concentration (Witepsol) and surfactant concentration (span 80) and process variables like homogenization time (5000 Revolutions Per Minute) and albino wistar rats were used for the evaluation of invivo pharmacokinetic studies. From the obtained outcome, it was winded up that the formulation of Nanostructured Lipid Carried and SLN was carried out by a optimized hot homogenization technique. The optimized preparation N3 and S6 evaluated for invivo pharmacokinetic studies and compare the enhancing efficiency of bioavailability between the SLN and NLC. From the invivo pharmacokinetic data, NLC confirms enhancement of bioavailability by 10.56% when compared to SLN and conventional dosage form that have bioavailability 7.5% and 5.6%. From the outcome data of the research and in-vivo pharmacokinetic data, it came to an conclusion that the Lovastatin encapsulated Nanostructured Lipid Carrier presented an increased bioavailability than SLN, by intensifying the Area Under Curve and Mean Residence Time in plasma drug concentration profile. Hence using Nanostructured lipid carrier in the formulation of drugs in Bio pharmaceutical Classification System class II, like Lovastatin which have low bioavailability will assure a better drug delivery system.

INTRODUCTION:

SLNs are submicron sized spherical particles of 50 - 500 nm in diameter. SLNs are capable of solubilizing lipophilic molecules as it contains solid lipid core matrix. Emulsifiers (Surfactants) were used in their formulation to stabilize the lipid core. Because of their remarkable properties, they are used as an optimistic nanocarrier in the formulation of Chemotherapeutic drugs.1,2

An ideal SLN should have following characteristics:

- Should have a caliper to enhance the performance of pharmaceuticals and neutraceuticals
• Interaction of phases at the interfaces
• Larger surface area
• Smaller size

Lipid nanoparticles are solid in body and room temp. as it consist of hydrophobic lipids which are rigid in nature. They are enclosed by a phospholipids monolayer. Usage of increased concentration of surfactants plays an important role in the stabilization of these aggregates. These have a lesser toxic level, when compared with ceramic or polymer nanoparticles as SLNs are easily biodegradable.

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Lipid decreases plasma profile variability and increases oral bioavailability. SLNs are promising colloidal system of carrier which is used in spite of polymer which is used in O/W emulsions to attain parenteral nutrition, in contrast solid lipid is been used in the place of liquid lipid during the formulation of the emulsion. In the early 90’s SLNs are recognized as a most predominant lipid based colloidal carriers. It is one among the well known lipid carrier to enhance the bio-availability of hydrohobic drugs.

NLC is the new revolutionary drug carrier which replaces the SLN in various formulations. Nanostructured lipid carrier consists of 2 mixtures: liquid and solid lipid phase which were linked by a spatial arrangements. Solid lipid and liquid lipid ratio in NLC can be extended till 95%. The ability of the drug load to avoid the crystalline character of lipid matrix by controlling the conversion of amorphous form to crystals and enhanced drug loading efficiency is achieved by this alternative spatial arrangement. Due to the presence of both the lipid phases in the Nanostructured Lipid Carrier the nanoparticles will be in indefinite form. During storage, the expulsion of recrystallized drug is not possible as the mixture of both the lipid phase will be in the form of blocks or chain. Hence, Nanostructured Lipid Carrier is another choice of carrier for conventional systems such as ointments, suspensions and solutions. When juxtaposed with Solid Lipid Nanoparticle there was a reduction in melting point as the Nanostructured lipid carrier contains oil in it.

The bioavailability of the Lovastatin was found to be reduced i.e., five percent; and metabolized effectively through first pass effect (Hepatic CYP3A and CYP2C8 substrate) with a low half life of 2 – 5 hrs about 10% of the drug is excreted in unchanged form through urine and 83% in stool. Lovastatin fails to maintain required amount of plasma drug concentration to ensure its pharmacological action because of

• Lack of pharmacokinetic data
• Low bioavailability
• Low permeability
• Low solubility

Hence, The main aim of this study is to intensify the bioavailability of drug which is having lower bioavailability (<5%) like Lovastatin in the form of Solid lipid nanoparticle (SLN) carrier and Nanostructured lipid carrier (NLC) and also to choose the best carrier molecule among this two by performing the invivo pharmacokinetic studies.

MATERIALS AND METHOD

Lovastatin got as a gift sample form Aurobindo Pvt. Ltd. Witepsol, Oleic acid and other analytical chemicals are purchased from Himedia Pvt. Ltd. Mumbai.

In-vivo Pharmacokinetic studies of Nanostructured Lipid Carrier and Solid Lipid Nanoparticles loaded Lovastatin

PK solver software was used to study the pharmacokinetics of Nanostructured Lipid Carrier (n3) and Solid Lipid Nanoparticles (S6). For this study, 24 healthy albino Wistar rats (male) with a weight of 0.18-0.25 Kg were selected and divided into three groups (Six in each):

B1: Positive Control - Lovastatin - Mevercor(4mg/kg) in CMC - Oral administration.
B2 : Test 1 - Lovastatin NLC(4mg/kg) - Oral administration
B3 : Test 2 - Lovastatin SLN(4mg/kg) - Oral administration

Before starting the experiment, the rats were kept for fasting for a day. But the consumption of the water has been allowed without any exception. The abstract for this study was proposed to IAEC and got approval. By the use of oral feeding needle, drug solution was given orally by retro-orbital puncture. Blood samples were collected in the volume of 0.5ml at the interval of 0, 1, 2, 4, 6, 8, 10, 12 hours. The samples were taken in a capillary tube by retro orbital puncture and then it is transferred to the heparinized glass tube to prevent coagulation, as it contains 1% Ammonium oxalate sol., a anticoagulant. The 1.5ml of the 8 samples were kept in a centrifuge for micro centrifugation at 5000 revolutions per minute for 5 minutes to separate the plasma as soon as possible and 0.75ml of plasma was collected into herfindoff tube. To this plasma solutions 0.5ml of 10% trichloroacetic acid was added and again kept in the centrifuge with 4000 revolutions per minute for 15 minutes at 4°C. After 15 minutes, the drug got separated from the plasma solutions. To this separated drug samples phosphate

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buffer solution of pH 7.4 was added and stored at -20°C. The final samples were injected into the injector of HPLC to determine the amount of Lovastatin present in it.

**Quantification of Lovastatin in Plasma**

Quantification of Lovastatin in Plasma was carried out by using HPLC (Schimadzu, Japan)

Run time: 10 – 20 min

Injection Volume: 5 μl

Flow rate: 1.0 ml/min

Mobile Phase: methanol: 2 mM ammonium acetate and 500 μl of 0.5% formic acid (80:20 v/v)

Column: reversed phase C18 column (250 mm X 4.6 mm i.d., particle size - 5 μm)

After completion of the run time, the wavelength maxima of Lovastatin was found to be 241 nm. At this wavelength the drug concentration was found to be 0.04-0.24 μg/ml with a R value of 0.999.

From the obtained data, a graph was plotted against the Conc. (μg/ml) Vs. Peak area (%) to construct a Calibration curve. From the unknown peak of the sample the concentration of the drug present in the plasma (plasma drug concentration) was determined

**Pharmacokinetic data analysis**

**Statistical analysis**

The PK analysis presented various PK identities, which includes Mean Residence Time, AUC$_{0-\infty}$, $t_{max}$, $C_{max}$ to improve the bioavailability in Lovastatin loaded Nanostructured lipid carrier. The comparative study between the control and treatment groups were evaluated with the help of ANOVA and the confidence interval (test : reference) was calculated using log transformed data. The formulation was considered to be statistically insignificant when the p value was more than 0.05 with the confidence interval of 85% and statistically significant when the p value was less than 0.05 with confidence interval of 95%

**RESULTS AND DISCUSSION**

**Invivo Pharmacokinetic Studies**

**HPLC results for Quantification of Lovastatin in plasma**

The pharmacokinetic parameters of SLN and NLC are shown in Tables 1, 2 and 3 and Figures 1 and 2. Invivo pharmacokinetic plasma drug concentration profiles were shown in Figure No 2. In Table 1 the decreased in $C_{max}$ and; increased area under curve,$A_{0-\infty}$, mean residence time and $T_{max}$ manifests that the Lovastatin encapsulated Nanostructured lipid carrier have better bioavailability than the drugs available in market.

Figure 1: Calibration curve for Lovastatin by HPLC

Figure 2: Comparative in-vivo pharmacokinetic study data for Lovastatin formulations (Marketed, NLC and SLN)

Conc. of drug in blood was determined upto 12h with the help of HPLC and the results were listed in table 2. Lovastatin has high plasma concentration ($C_{max}$) i.e.,24.13 μg/ml, by administering conventional dosage form (Mevacor tablet). The maximum drug concentration declines rapidly in conventional dosage form due to faster clearance. The higher clearance concentration may be due to unchanged drug will be cleared out of body, due to inability of drug to reach bioavailable dose and target site receptors. The maximum plasma conc. of drug after the taking of Lovastatin NLC through oral administration was found to be 16.56 μg/ml and administration of Lovastatin SLN through oral administration was found to be 16.24 μg/ml for duration of 3 h respectively. The AUC concentration of drug after the administration of Lovastatin tablet Mevacor, Lovastatin NLC and Lovastatin SLN through oral administration was found to be 108.76 μg/ml/hr ;
Table 1: Comparative in-vivo pharmacokinetic studies data between Lovastatin formulations (Marketed, NLC and SLN) treatment groups

| Parameters          | B1: Mivacor (4 mg/kg) | (4 mg/kg) | B2: Nanoparticle lipid carrier (N3) Suspension | B3: SLN Suspension (4 mg/kg) |
|---------------------|-----------------------|-----------|-----------------------------------------------|-----------------------------|
| AUC 0-α (μg/ml/h)   | 108.76                | 180.20    | 143.68                                        |
| Cmax (μg/ml)        | 24.13                 | 16.56     | 16.24                                         |
| Tmax (h)            | 2                     | 3         | 3                                             |
| AUMC 0-α (μg/ml/h)  | 336.54                | 1128.60   | 768.84                                        |
| MRT 0-α (h)         | 3.99                  | 8.26      | 7.42                                          |
| T<sub>1/2</sub>     | 2.38                  | 5.40      | 5.46                                          |

B1, B2 & B3 are oral suspensions and Mivacor is the Marketed plain formulation of Lovastatin *

Table 2: Comparative Plasma Drug Concentration study data for Lovastatin formulations

| Duration (hours) | Mevacor (4 mg/kg) | N3 Suspension (4 mg/kg) | S6 Suspension (4 mg/kg) |
|------------------|-------------------|-------------------------|-------------------------|
| 0                | 0                 | 0                       | 0                       |
| 1                | 18.92             | 12.24                   | 11.6                    |
| 2                | 24.13             | 16.56                   | 16.24                   |
| 4                | 2.34              | 15.78                   | 15.68                   |
| 6                | 0.14              | 15.12                   | 15.46                   |
| 8                | 0.14              | 14.96                   | 14.98                   |
| 10               | 0.14              | 12.24                   | 14.86                   |
| 12               | 0.14              | 8.24                    | 13.24                   |

Table 3: ANOVA data for pharmacokinetic studies

| Source of variance | Mean of squares (MS) | Sum of squares (SS) | Degree of freedom (Df) | F Value | Table value at 5% significant level |
|--------------------|----------------------|---------------------|------------------------|---------|-----------------------------------|
| Between the treatments | 67751               | 20,325.02          | 3                      | 1.19    | 0.0424                            |
| Within the treatments    | 119288              | 4,29,412.3         | 37                     |         | P<cal < Ftab Accepted at 5% significant level |
| Total                   | 449737.32           | 39                  |                        |         |                                   |

B1, B2 & B3 are oral suspensions and Mivacor is the Marketed plain formulation of Lovastatin *

180.20 μg/ml/hr; 143.68 μg/ml/hr for 12 h respectively. The AUMC concentration of drug after the administration of Lovastatin tablet Mevacor, Lovastatin NLC and Lovastatin SLN through oral administration was determined to be 336.54, 1128.60, 768.84 (μg/ml/hr) for 12 h respectively. NLC formulations attain a notable higher plasma concentration and enhance T<i>1/2</i> when compared to other marketed and SLN formulation. This leads to longer mean residence time (MRT = 8.26 h) of drug through NLC administration and provides an opportunity for enhanced systemic bioavailability of Lovastatin i.e., 10.56%. This enhanced bioavailability and absorption of drug from Lovastatin NLC was due to small particle size, chain and block like lipid nature of NLC and protection of drug from degradation pathways like first pass metabolism and enzymatic degradation. These discussed data proves that, NLC confirms enhancement of bioavailability by 10.56% when compared to SLN and conventional dosage form that have bioavailability 7.5% and 5.6%. Hence, NLC was a suitable drug delivery career for Lovastatin which enhance the bioavailability<sup>31</sup>,<sup>32</sup>.
CONCLUSIONS

From the outcome data of the research and in-vivo pharmacokinetic data, it was winded p that the Lovastatin encapsulated Nanostructured Lipid Carrier presented greater bioavailability than SLN, by improving the Area Under Curve and Mean Residence Time in plasma drug conc. proϑile. NLC confirms enhancement of bioavailability by 10.56% when compared to SLN and conventional dosage form that have bioavailability 7.5% and 5.6%. Hence using Nanostructured lipid carrier in the formulation of drugs in Biopharmaceutical Classification System class II, like Lovastatin which have low bioavailability will assure a better drug delivery system.

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Conflict of Interest

Authors declared no conflict of interest.

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