International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 6, 2023

Original Article

# FORMULATION AND *IN VIVO* EVALUATION OF PEMIGATINIB SUPER SATURABLE SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM

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*Received: 28 Jul 2023, Revised and Accepted: 06 Sep 2023*

**ABSTRACT**

**Objective:** Pemigatinib is an active component in treatment of cholangiocarcinoma, but the low solubility and bioavailability of Pemigatinib limit its wide application. The aim of the present study was to prepare and evaluate supersaturable self-nanoemulsifying drug delivery systems (sSNEDDS) followed by investigating and comparing the pharmacokinetic profiles of Pemigatinib and Pemigatinib sSNEDDS in rat plasma by HPLC.

**Methods:** Pemigatinib loaded SNEDDS were obtained by dissolving drug in the isotropic mixture of oil, surfactant, and co-surfactant. The conventional SNEDDS were converted to sSNEDDS by precipitation method by using an experimented polymer. An appropriate high sensitivity and selectivity was applied to the comparison of plasma pharmacokinetics in Pemigatinib and Pemigatinib sSNEDDS using Entrectinib as an internal standard (IS).

**Results:** The droplet of sSNEDDS ranges from 166.78±3.14 to 178.86±1.24 nm with PDI 0.212–0.256, transmission electron microscopy images revealed the spherical shape of the nanodroplets, emulsification time was 15 secs when added to physiological fluids, percent transmittance of the diluted formulation was 99.12±0.46, and viscosity was 574±26 centipoises indicating the good flow ability. FTIR and DSC studies indicated the amorphization of the drug. The dissolution profile of sSNEDDS indicated the faster release of drug compared to both pure drug suspension and SNEDDS formulation. $C_{max}$ of the sSNEDDS 3.52±0.13ng/ml was significant ($P$<0.05) as compared to the pure drug suspension formulation 2.82±0.42 ng/ml. The $AUC_{0-t}$, $AUC_{0-\infty}$ of sSNEDDS was increased, while the $T_{max}$ and $t_{1/2}$ was decreased. Moreover, the AUC value in the sSNEDDS group was significantly increased and the relative bioavailability was calculated to be 69% when compared with that of the Pemigatinib group.

**Conclusion:** These results concluded that Pemigatinib sSNEDDS when compared with pure drug after a single oral administration and the formulation modification of Pemigatinib into sSNEDDS can effectively enhance gastrointestinal absorption and relative bioavailability by improving solubility and dissolution rate.

**Keywords:** Pemigatinib, Cholangiocarcinoma, Solubility, sSNEDDS, Pharmacokinetics


DOI: https://dx.doi.org/10.22159/ijap.2023v15i6.48981. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

## INTRODUCTION

Biliary tract cancers (BTC)/cholangiocarcinoma represent a diverse group of epithelial cancers characterized by aggressive and chemoresistant tumors with poor long-term survival [1]. Surgery remains the only curative treatment; however, only 35% of patients can undergo curative surgery [2]. Often, the limitation of surgical resection includes the presence of vascular involvement and the presence of metastatic spread to regional lymph nodes, which are often evident at time of diagnosis, given the frequent asymptomatic status of early disease. Systemic therapy for cholangiocarcinoma represents the only feasible option for patients with locally advanced or metastatic cholangiocarcinoma.

In recent years, advancements in gene sequencing have better highlighted the genetic landscape of BTC and have shown that molecular profiles segregate with anatomical location. Numerous agents have been developed to target FGFR inhibition in this clinical context. Initial agents acquiring FDA approval included Pemigatinib in April 2020. Pemigatinib is a highly potent and selective inhibitor of FGFR1, FGFR2, and FGFR3, it is a BCS class-II compound and exhibits BCS class I properties in acidic media. The water solubility is about 0.144 mg/ml with log P value of 2.26. It is diprotic basic compound with pKa values of 3.1 and 5.7. It displays pH-dependent solubility (1.2 to 7.4), which decreases with increasing pH [3]. The poor solubility of the drug substance is the main inherent factor that influences the oral absorption of the drug [4]. In order to improve intrinsic solubility and to reduce the high pharmacokinetic variability observed with the existing tablet formulation, it is essential to develop an alternative formulation of Pemigatinib with improved characteristics.

Self-nanoemulsifying drug delivery systems (SNEDDS) is an effective, smart and more adequate formulation approach for poorly soluble drugs, compared to wide range of lipid-based systems. SNEDDS can enhance oral bioavailability by improving the drug solubility, dissolution behavior in GIT and gut permeability [5-7]. In addition, the drug loading capacity of conventional SNEDDS ranges only from 50–90% of the equilibrium solubility of drug and this result in more amount of formulation to reach the therapeutic level [8]. In addition, conventional SNEDDS consists of plenty of surfactants and co-surfactants to prevent precipitation of the drug when diluted by GI fluids. However, a higher composition of surfactants may lead to gastric irritation [9]. The above-mentioned limitations of conventional SNEDDS can be solved by minimizing drug precipitation in GIT and reducing the amount of surfactant. A new class of supersaturable formulation, namely supersaturable SNEDDS has been developed as a thermodynamically stable system containing a precipitation inhibitor and less amount of surfactant [10, 11]. The solubility of Pemigatinib can be enhanced by formulating into sSNEDDS.

Pharmacokinetics is a discipline which studies the absorption, distribution, metabolism, excretion, and toxicity of drugs *in vivo* and also shows the great significance for the development and safety evaluation of drug [12, 13]. For further research and development Pemigatinib sSNEDDS, we systematically studied the pharmacokinetic comparison of pure drug and Pemigatinib sSNEDDS *in vivo* in the present study with Entrectinib as internal standard (IS) [14]. This assay has some merits, such as precise sample preparation, good linearity and specificity, and negligible carryover [15]. The current study was aimed to study *in vivo* pharmacokinetic parameters of Pemigatinib sSNEDDS.

## MATERIALS AND METHODS

### Materials

Pemigatinib and Entrectinib were procured from Aelida Pharmaceuticals, Haryana, India. Captex®300, was purchased from HI Media Private limited, Mumbai, India. HPMC K4M, ortho-

phthalaldehyde, acetonitrile, methocel, NaOH, dimethylsulfoxide, methanol were procured from SD fine chemicals limited, Mumbai, India. Kolliphor®RH40 and Transcutol® HP were obtained from BASF, Germany. Wistar rats were procured from Sanzyme Private Limited, Hyderabad.

**Preparation and evaluation of pemigatinib loaded sSNEDDS**

For the preparation of Pemigatinib loaded sSNEDDS, first solubility was established, then surfactant and co-surfactants were selected based on the ability to emulsify the oil component [16, 17]. Pemigatinib loaded SNEDDS were obtained by dissolving drug in the isotropic mixture of oil, surfactant, and co-surfactant. Then the mixture was vortexed and subjected to sonication to get a transparent solution. The conventional SNEDDS were converted to sSNEDDS by precipitation method by using experimented polymer. Supersaturable SNEDDS of Pemigatinib was obtained bya simple admixture method [18]. The selected precipitation inhibitor was incorporated into the preparedformulation. The formulations were vigorouslyvortexed to get a uniform emulsion. Then thefinal formulations were maintained stable at 37±0.5 °C for 24 h to attain equilibrium. The prepared sSNEDDS were evaluated for size distribution and zeta potential, surface morphology, self-emulsification time, transmittance percentage, viscosity, drug release, dilution and pH stability, thermodynamic stability, and stability studies [19-21]. The results are published in Future Journal of Pharmaceutical Sciences.

**Pharmacokinetic studies**

**Study design**

Healthy Wistar rats (Weighing 150-180 g) were selected for this study, all the animals were healthy during the period of the experiment. All efforts were made to maintain the animals under controlled environmental conditions (Temperature 25 °C, Relative Humidity 45% and 12 h alternate light and dark cycle) with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply. Rats were fed with standard diet and water ad libitum Rats were divided in to two groups (n=6 in each group) at random. The rats were fasted for 24 h prior to the experiments. After 4 h of dosing, food was reoffered. First group was administered with pure Pemigatinib (as such) made suspension with 0.5% methocel and second group was administered prepared Pemigatinib sSNEDDS diluted in 0.5% methocel by oral route at a dose of 1.171 mg/kg. Then, 500 µl blood samples were collected from the femoral artery at certain times 0, 0.50, 1, 1.50, 2, 2.50, 3, 4, 5, 6, 8, 12, 16, 20, 24 h post dose and transferred into Eppendorf tubes containing heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5 min to 10 min and stored frozen at-20 °C until analysis. The protocol of animal study was approved by the institutional animal ethics committee with ref no: 1447/PO/Re/S/11/CPCSEA-70/A. Chromatographic separation of Pemigatinib was achieved on Agilent Zorbax XDB C18 (250×4.6 mm, 5 µm) column maintained at ambient temperature and PDA-UV detection set at 262 nm. Consisted of mobile phase 0.1% OPA pH 2.5 buffer (60%):Acetonitrile(40%) pumped at a flow rate of 1.06 ml/min gave the highest desirability. The retention time of the drug and IS was found to be 3.258 and 4.43 min respectively [22-25].

**Pharmacokinetic analysis**

The Pharmacokinetic parameters employed to evaluate were maximum plasma concentration (Cmax), time to attain Cmax i.e., Tmax, and $t_{½}$ values, area under plasma concentration-time curve from zero to the last sampling time ($AUC_{0-t}$), area under plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$). $AUC_{0-t}$ was calculated by the linear trapezoidal rule [26-34].

The pharmacokinetic parameters were performed by a non-compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean±SD.

**Statistical analysis**

Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $P<0.05$ was considered statistically significant [24-27].

**RESULTS AND DISCUSSION**

Solubility of Pemigatinib was established in Captex® 300 and Kolliphor® RH 40 and Transcutol® HP were selected as surfactant and co-surfactant, respectively. The composition of oil, surfactant and co-surfactant was identified using phase diagram. HPMC K4M was selected as precipitation inhibitor which resulted in effective supersaturation and increased self-emulsification time. The droplet of sSNEDDS ranges from 166.78±3.14 to 178.86±1.24 nm with PDI 0.212–0.256, transmission electron microscopy images revealed the spherical shape of the nanodroplets, emulsification time was 15 secs when added to physiological fluids, percent transmittance of the diluted formulation was 99.12±0.46, and viscosity was 574±26 centipoises indicating the good flow ability, the results were presented in table 1. FTIR and DSC studies indicated the amorphization of the drug. The dissolution profile of sSNEDDS indicated the faster release of drug compared to both pure drug suspension and SNEDDS formulation. The formulation was found to be stable and transparent at all pH values. Any kind of separation or precipitation was not observed at different temperatures cycles. No significant difference was observed with all the samples exposed at different storage conditions. The optimized sSNEDDS were further evaluated for *in vivo* pharmacokinetic studies.

**Table 1: Physico-chemical parameters of formulated Pemigatinib sSNEDDS**

| Size | PDI | Emulsification time | Transmittance | Viscosity |
|---|---|---|---|---|
| 166.78±3.14 to 178.86±1.24 nm | 0.212–0.256 | 15 sec | 99.12±0.46 | 574±26 centipoises |

All values are expressed as mean standard deviation, n=3, SD

**Table 2: Pharmacokinetic parameters of pemigatinib sSNEDDS formulation and pure drug**

| Pharmacokinetic parameters | Pemigatinib pure drug | Pemigatinib sSNEDDS |
|---|---|---|
| $C_{max}$ (ng/ml) | 2.82±0.42 | 3.52±0.13 |
| $AUC_{0-t}$ (ng. h/ml) | 12.2±1.52 | 17.4±2.61 |
| $AUC_{0-inf}$ (ng. h/ml) | 15.7±1.32 | 22.5±2.54 |
| $T_{max}$(h) | 2.50±0.03 | 1.50±0.01 |
| $t_{1/2}$ (h) | 6.50±0.02 | 4.50±0.02 |

All values are expressed as mean standard deviation, n=3, SD

The development of sensitive and specific assay of a drug is crucial to the study of drug pharmacokinetics. The HPLC method was first developed to monitor the concentration of Pemigatinib to determine its suitability and sensitivity. The method was further optimized for the determination of Pemigatinib in the rat plasma and has been validated to be sensitive to investigate the pharmacokinetics in rats [27].

The mobile phase 0.1% OPA pH 2.5 buffer (60%): Acetonitrile (40%) was used in the system. Noticeable separation was shown between Pemigatinib and IS, with retention times of about 3.25 and 4.43 min, respectively. Good resolution was achieved between analyte and IS and no substance from several different sources of rat plasma was observed interfering with the separation and quantization of Pemigatinib [28, 29].

Fig. 1 shows the plasma concentration–time curve in Wistar rats after a single oral dose (1.171 mg/kg) of Pemigatinib sSNEDDS formulation as compared to Pemigatinib pure suspension. At all the indicated time points, the Pemigatinib plasma concentrations in rats treated with sSNEDDS formulation was significantly higher than those treated with pure drug. Pharmacokinetic parameters of Pemigatinib after oral administration of the two formulations in Wistar rats are shown in table 2.

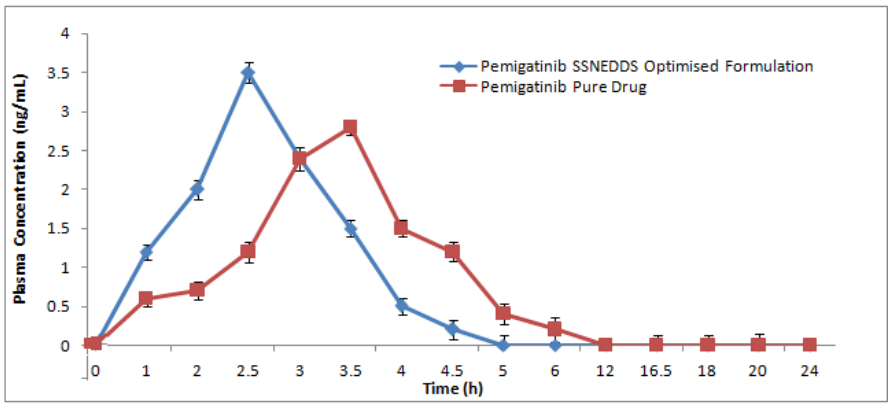


**Fig. 1: Plasma concentration profiles of Pemigatinib sSNEDDS and pure drug, Note: All values are expressed as mean standard deviation, n=3, SD**

The blood concentration of Pemigatinib is extremely low following oral administration and its application can be greatly restricted by its poor intestinal absorption. It is necessary for drugs to have a certain level of solubility to penetrate biomembranes [30]. In our study, the solubility of Pemigatinib sSNEDDS was greatly improved compared with that of pure Pemigatinib, so, Pemigatinib sSNEDDS can have good intestinal absorption *in vivo*. The plasma concentration of sSNEDDS increased gradually within the first 3.5 h after oral administration, and then slowly decreased to the lower concentration during the next 5 h, and then the concentration remained constant for the 25 h of measurement. Pemigatinib from sSNEDDS was rapidly absorbed by rats, with the maximum plasma concentration achieved within 3.5 h after dosing. $C_{max}$ of the sSNEDDS 3.52±0.13 ng/ml was significant ($P$<0.05) as compared to the pure drug suspension formulation 2.82±0.42 ng/ml. Here, the blood concentration of Pemigatinib sSNEDDS is higher than that of Pemigatinib. These differences suggest that the formulation modification induced a dramatically enhancement in the absorption of Pemigatinib [29].

The results indicated that Pemigatinib could be absorbed from the rat gastrointestinal tract and the hepatic first-pass effect may be one of the limitations of its health-promoting effects. To improve its bioavailability, new kinds of pharmaceutical preparations like sSNEDDS have been adopted [25]. $T_{max}$ of both sSNEDDS formulation and pure drug suspension was 1.50±0.01 h and 2.50±0.03 h, respectively. As expected, this absorption rate of Pemigatinib was rapidly increased, accompanied by an increase in the peak plasma concentration; this is likely to be due to faster dissolution and absorption of sSNEDDS [27, 32].

AUC is an important parameter in evaluating bioavailability of drug from dosage form, as it represents the total integrated area under the blood concentration-time profile and represents the total amount of drug reaching the systemic circulation after oral administration [26]. $AUC_{0-\infty}$ for sSNEDDS formulation was higher (22.5±2.54 ng. h/ml) than the pure drug suspension formulation 15.7±1.32 ng. h/ml. Statistically, $AUC_{0-t}$ of the sSNEDDS formulation was significantly higher ($P$<0.05) as compared to pure drug suspension formulation, which suggested an increase in the relative bioavailability of sSNEDDS. In the study, the increased $C_{max}$ values contributed to the significantly enhanced $AUC_{0-t}$ and $AUC_{0-\infty}$ of the sSNEDDS when compared with the pure drug. These results indicated the Pemigatinib sSNEDDS concentration remarkably increased over time in rats *in vivo*, and the relative bioavailability of Pemigatinib sSNEDDS to Pemigatinib was 69%, which suggested Pemigatinib sSNEDDS could maintain the effective concentration, dissolution, and membrane permeability in rats *in vivo* for a long period of time [31, 33].

The distribution of Pemigatinib sSNEDDS into the tissues was slow and this is indicated by the long distribution half-life, $t_{1/2}$ of 4.50±0.02 h when compared to pure drug (6.50±0.02 h), which shows that Pemigatinib sSNEDDS was also rapidly absorbed [29, 34].

Overall, big changes are being observed in the mean plasma concentration-time profiles and pharmacokinetic parameters between pure Pemigatinib and Pemigatinib sSNEDDS after a single oral administration, which suggested that the formulation modification induced a remarkable enhancement in gastrointestinal absorption and relative bioavailability of Pemigatinib by improving solubility and membrane permeability in the present study. Thus, the above pharmacokinetics study of Pemigatinib sSNEDDS may be more helpful for the farther development and clinical study of Pemigatinib sSNEDDS for the treatment of BTC in the near future.

## CONCLUSION

The numerous clinical experiments show that the absorption, distribution, metabolism, excretion, and toxicity process of drugs are important indicators of drugs ability. According to the physical properties of drug candidates, the drug structure will be designed rationally and this study illustrates this fact by transforming poorly soluble Pemigatinib into Pemigatinib sSNEDDS will enhance the solubility. The result of main pharmacokinetic comparisons of Pemigatinib and Pemigatinib sSNEDDS showed that the pharmacokinetic parameters have remarkable differences, which suggested that the formulation modification of Pemigatinib can effectively enhance gastrointestinal absorption and relative bioavailability by improving solubility and membrane permeability. The resulting pharmacokinetic data can aid the understanding of the kinetic profile of Pemigatinib sSNEDDS and lay the foundation for future drug research in the *in vivo* studies for the treatment of BTC/cholangiocarcinoma.

## ACKNOWLEDGMENT

The authors thank GITAM School of Pharmacy, GITAM Deemed to be University, Hyderabad, for their continuous support in completion of this research work.

## FUNDING

This research received no external funding

## AUTHORS CONTRIBUTIONS

R. M. and S. K. completed the research work, execution, and writing did the work plan, review, and corrections. Both authors agree with the submission and publication. All authors have read and agreed to the published version of the manuscript.

**CONFLICTS OF INTERESTS**

Declared none

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