Preparation and Characterization of Solid Lipid Nanoparticles of Cinnacalcet HCl

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Authors’ contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Objective: The objective of the present research is to formulate solid lipid nanoparticles of cinnacalcet HCl to improve its oral bioavailability.

Methods: Cinnacalcet hydrochloride exhibits poor oral bioavailability of 20 to 25 % because of low aqueous solubility and first pass metabolism. The formulations were optimised using Box-Behnken Design. Solid lipid nanoparticles formulation was prepared using hot homogenization and ultrasonication method.

Results and Discussion: Precirol ATO 05, Soya lecithin and poloxamer 407 were selected as lipid, surfactant and co-surfactant respectively. For optimization the desirable goal was fixed for various responses entrapment efficiency, particle size and (time taken for diffusion of 85% drug) T85%. The optimized single dose of solid lipid nanoparticle obtained using box behnken design consisting of 30 mg of cinnacalcet HCl, 200 mg of precirol ATO 05, 250 mg of soya lecithin and 0.2% w/v of poloxamer. 407. The pharmacokinetic study revealed that optimized formulation was found to increase the oral bioavailability nearly 3 times compared to aqueous suspension of pure drug.
Conclusion: Thus optimized solid lipid nanoparticles explicating the potential of lipid-based nanoparticles as a potential carrier in improving the oral delivery.

Keywords: Precirol ATO 05; stability; Box-Behnken Design and oral bioavailability.

1. INTRODUCTION

Cinnacalcet HCl is used for the treatment of hypercalcaemia and secondary hyperparathyroidism in patients with parathyroid carcinoma and chronic kidney disease respectively [1]. It exhibits poor oral bioavailability of 20 to 25% owing to its poor aqueous solubility and first pass metabolism. A food effect study for Cinnacalcet HCl in healthy subjects revealed increased oral bioavailability in presence of high fat meal [2]. Solid lipid nanoparticles can significantly improve the bioavailability of Cinnacalcet HCl by forming a pre-absorptive solubilised phase and prevention of hepatic first pass metabolism by passing the portal circulation [3]. Hence solid lipid nanoparticles can be considered as a suitable drug delivery system to improve the poor oral bioavailability of BCS class IV drug Cinnacalcet HCl.

Solid lipid nanoparticles (SLNs) has the advantage of good loading for both lipophilic and hydrophilic drugs [4-6]. SLNs combine the advantage of colloidal, vesicular and polymeric carriers as physiologically acceptable systems, non toxic, biocompatible, scalability and also in imparting the controlled release of drug from lipid matrix [7-9]. Furthermore, SLNs augment the lymphatic transport of the lipophilic drugs, irrespective of the route of administration and therefore increase the systemic availability of drug molecule. In the present research, Precirol ATO 05 (PREC) was selected as the lipid carrier as it provides high drug entrapment efficiency (EE) [10]. Soya lecithin (SL) and poloxamer 407 (POL) were selected as surfactant and stabilizer respectively. Box-Behnken design (BBD) was used for optimisation of SLN formulation. Hence in the present research, preparation and characterization of SLN of Cinnacalcet HCl were attempted to improve oral bioavailability.

2. MATERIALS AND METHOD

2.1 Materials

Cinnacalcet Hydrochloride (CH) was obtained as gratis sample from RA Chem Pharma Ltd, Telengana, India. Precirol ATO 05 (PREC) was a gift sample from Gattefosse, Maharastra, India. Poloxamer 407 (POL) was procured from Sigma Aldrich. Methanol, chloroform, acetonitrile and tetra-butyl ammonium hydrogen sulphate (TBHS) was of HPLC grade (Merck, Mumbai, India). All other chemicals used were of analytical grade.

2.2 Preparation of Solid Lipid Nanoparticles (SLN)

Systematic optimisation of SLN of Cinnacalcet HCl was accomplished employing Box-Behnken design (BBD) with the help of design expert ver. 8.0.1 software (Stat-Ease, Minneapolis, MN). For each critical response contour plot and 3D plot were plotted using response surface methodology [11]. ANOVA study was conducted to identify the significant model term. Optimisation of SLN of Cinnacalcet HCl were carried out by setting up the upper and lower limit of different critical responses. The overlay plot was constructed to identify the design space [12]. The SLN formulation of Cinnacalcet HCl was prepared by hot homogenization and probe sonication. Cinnacalcet HCl (30 mg), PREC and SL were dissolved in 10 mL of 1:1 ratio of chloroform and methanol. The organic solvents were evaporated by rota evaporator (Ika, Germany) at 65°C i.e. 5°C above the melting point of PREC (lipid). Simultaneously aqueous phase was prepared by dissolving the POL in 10 mL of 1:1 ratio of chloroform and methanol. The organic solvents were evaporated by rota evaporator (Ika, Germany) at 65°C i.e. 5°C above the melting point of PREC (lipid). Simultaneously aqueous phase was prepared by dissolving the POL in 10 mL of distilled water (TKA, Millipore, Germany) and heated at 65°C. The aqueous phase was added to molten lipid phase in hot condition and homogenized (T25 Digital Ultra-Turrax, Ika India Private Ltd, India) for 10 min at 12,000 rpm, while the system was maintained at 65°C. The obtained coarse hot oil in water emulsion was subjected to probe sonication to get nanoemulsion (Sonics, USA) for 2 min at amplitude of 70% with on and off of pulse in 2 sec and 2 sec respectively. The formulation was cooled to room temperature to obtain SLN of Cinnacalcet HCl [13].

3. CHARACTERIZATION OF SOLID LIPID NANOPARTICLES

3.1 Percentage entrapment efficiency (% EE)

A simple, rapid and precise reverse phase ultrafast liquid chromatographic method for
analysis of Cinnacalcet HCl was adopted from the literature [14]. Chromatography was performed on a 250 mm × 4.6 mm i.d., 5 µm particle, C18 column with 50:50 (v/v) acetonitrile: tetrahydroammonium hydrogen sulphate (TBHS-10 mM) as mobile phase at a flow rate of 1 mL/min with photo diode array detector (PDA) detection at 223 nm. Cinnacalcet HCl was eluted with retention time of 4.3 min. 1 mL of the Cinnacalcet HCl SLNs dispersion was transferred to eppendorf tubes. The tubes were subjected to cooling centrifugation (Remi Instrument Ltd., Mumbai, India) at 10,000 rpm for 30 min at 4°C. Then 0.5 mL of supernatant was collected and mixed with 0.5 mL of ethylacetate followed by vortexing for 10 min. The same procedure was followed as described under drug content for UFLC analysis [15,16].

\[
\text{(% EE)} = \frac{\text{Weight of drug used in formulation} - \text{Weight of unbound drug in supernatant}}{\text{Weight of drug used in formulation}} \times 100
\]

3.2 Particle size (PS)

Mean particle size were measured by using zetasizer nano ZS (Malvern Instruments, UK). About 100 µL of each Cinnacalcet HCl SLN formulation was diluted (50 times) with double distilled water up to 5000 µL [17].

3.3 In vitro drug release studies

In vitro release studies of pure drug and cinnacalcet HCl -SLNs were done in 0.1N HCl (pH 1.2) for 2 h followed by pH 6.8 phosphate buffer for 22 h, by using dialysis method. SLN dispersion equivalent to 30 mg Cinnacalcet HCl was placed in dialysis bag with sealing at one end. The dialysis bag was inserted into a beaker containing 100 mL of medium and the temperature was maintained at 37 ± 0.5°C. Samples were collected and were replaced with fresh medium. The collected samples were suitably diluted and analyzed by UFLC. From the in vitro release study data T85% (time taken for release of 85% of drug) was calculated [18].

3.4 Polydispersity Index (PDI) and Zeta Potential (ZP) of Optimized SLN Formulation

Polydispersity index (PDI) and zeta potential (ZP) were determined for optimized formulation. by using zetasizer nano ZS (Malvern Instruments, UK) after 50 times dilution with double distilled water.

3.5 Stability Study

Optimized SLN Formulation was placed in humidity controlled oven (TH90 S/G, Thermolab, India) at 25±2°C/60±5% RH for a period of six months as per the (ICH) Q1A (R2) guidelines. Samples were collected and evaluated for EE, PS, PDI, ZP and T85% with a frequency of 0, 1, 3 and 6 months [19].

3.6 FT-IR Spectroscopy Study

FT-IR analysis of pure drug Cinnacalcet HCl, physical mixture (PM) in 1:1 ratio of Cinnacalcet HCl and lipid (PREC), Cinnacalcet HCl and surfactant (SL), Cinnacalcet HCl and stabilizer (POL), were studied on IR Affinity-1, (Shimadzu, Japan) using potassium bromide discs. Samples were analyzed at a scanning speed of 2 mm/s with resolution of 4 cm⁻¹ over the region 4000–400 cm⁻¹.

3.7 Differential Scanning Calorimetry (DSC)

DSC thermal analysis of pure drug Cinnacalcet HCl, physical mixture (PM) in 1:1 ratio of Cinnacalcet HCl and lipid (PREC), Cinnacalcet HCl and surfactant (SL), Cinnacalcet HCl and stabilizer (POL) was performed using DSC-60 (Shimadzu, Japan). Indium was used as standard for calibration of instrument. The experiment was performed at a rate of 10°C rise/min in the temperature range of 25 to 225°C.

3.8 Pharmacokinetic Study

Two samples vis-à-vis aqueous suspension of pure drug Cinnacalcet HCl and optimized SLN formulation were administered orally to white albino rabbits of weight of 2 kg. Standard curve of Cinnacalcet HCl in rabbit serum was prepared by solvent extraction method using ethyl acetate as extracting solvent [20]. Two samples were aqueous suspension of Cinnacalcet HCl and optimized SLN. They were treated with hygienic food and fresh water twice daily.

The dose for rabbit was calculated as follows:

\[
\text{Total dose (in humans)} = (90×0.07×2)/1.5 = 8.4 \text{ mg of 2 kg rabbit = 9 mg}
\]
The calculated dose of Cinnacalcet HCl (9 mg) was administered to albino rabbits. Aqueous suspension of pure drug Cinnacalcet HCl and optimized SLN formulation were administered to animals with the help of wood and feed tube (Ryle's tube). Marginal ear vein of rabbit was selected for collection of blood (1 mL) at following time points such as 0, 1, 2, 4, 6, 8, 12 and 24 h. Serum was collected after 10 min centrifugation at 3000 rpm. Cinnacalcet HCl was extracted from serum samples by solvent extraction method. Pharmacokinetic parameters like Cmax, Tmax and AUC were determined for both samples.

4. RESULTS AND DISCUSSION

4.1 Preparation of Solid Lipid Nanoparticles (SLN)

Table 1 depicts a set of 17 experimental runs which are prepared using a 3-factor at 3-level BBD. Each formulation were further characterized as explained above to study the effect of various factors such as A-PREC, B-SL and C-POL on each of the critical responses such as EE, PS and T85%. The use of non polar solvent chloroform contributed in quick solubilization of solid lipid i.e. PREC and polar solvent methanol contributed in solubilization of cinnacalcet hydrochloride. The combination of both solvents has significant impact on drug entrapment efficiency.

4.2 Response surface analysis

Fig. 1 represents the contour plot and 3D plot of EE response. The value of EE ranges from 61 % (run 6) to 85.96 (run 5). The % EE increased with the increase in the concentration of PREC which acts as solubiliser for lipophilic drug [9]. PREC helps in formation of less ordered crystals with many lattice defects which supports in accommodating large amount of Cinnacalcet HCl. Fig. 2 represents the contour plot and 3D plot of PS response. The value of PS ranges from 161.5 nm (run 10) to 357.5 nm (run 7). Higher concentration of PREC caused coalescence which resulted in increased particle size. This can also be attributed to additional space provided by lipid for entrapment of drug [21]. Particle size of SLN formulations decreased with increase in the concentration of surfactant soy lecithin. The use of mixed surfactants i.e. POL as non-ionic and SL as zwitterions surfactant resulted in electrostatic and steric stabilization of particles. Interpenetration of long polyethylene chains of poloxamer 407 limits freedom of the particles and prevents agglomeration [22]. Fig. 3 represents the contour plot and 3D plot of T85% response. The value of T85% ranges from 14.2 h (run 7) to 24.2 h (run 15). Release of cinnacalcet HCl was affected by the concentration of lipid, surfactant and co-surfactant in aqueous phase. The release rate was directly proportional to concentration of surfactant (SL) and inversely proportional to concentration of solid lipid (PREC) [23].

4.3 ANOVA of the Experimental Design

Table 2 represents the summary of ANOVA for different factors and its significance with respect to quadratic model. After conducting the design matrix the resultant model F-value and P-value justify the quadratic model is significant. A, C, BC, C² are significant model terms for response EE as P-values of the model terms are less than 0.05 (α = 0.05). Similarly in case of PSA, B, C, AB, AC, BC, A² are significant model terms. In case of T85%A, B, C, AB, A², B², C² are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. It can be predicted that there is a high level of correlation between actual and predicted value. Table 3 represents the summary of the BBD quadratic model in the process of optimisation of the SLN. For each of critical response predicted R² value is very close to the adjusted R². High Precision ratio of each response depicts a good signal to noise ratio.

4.4 Optimisation of SLN of Cinnacalcet HCl and Construction of Overlay Plot to Identify the Design Space

For optimisation the desirable goal was fixed for various responses EE, PS and T85%. Fig. 4 portrays the overlay plot with design space and also depicts the selected optimized SLN composition. The optimised single dose of SLN obtained using BBD consisting of 30 mg of Cinnacalcet HCl, 200 mg of PREC, 200 mg of SL and 0.2 % of POL. The summary of the optimisation process along with predicted and experimental value of responses of the optimised formulation are expressed in Table 4.

4.5 Polysdispersity Index (PDI) and Zeta Potential (ZP) of Optimized SLN Formulation

The PDI and zeta potential for the optimized SLN formulation was found to be 0.25 and - 21.5 mV.
PDI values less than 0.3 are indicative of narrow size distribution. Zeta potential value greater than 20 indicate that repulsion force sufficient to prevent aggregation of globules.

Table 1. Composition of Solid Lipid Nanoparticles as per BBD along with the experimental results of various critical responses

| Run | PREC | SL | POL | EE (%) | PS (nm) | T85% (h) |
|-----|------|----|-----|--------|--------|---------|
| 1   | -1   | 0  | 1   | 66.87  | 227.9  | 17.2    |
| 2   | 0    | 0  | 0   | 75.85  | 240.6  | 15.2    |
| 3   | 1    | 0  | 1   | 81.26  | 259.2  | 20.5    |
| 4   | 0    | -1 | 1   | 78.35  | 185.7  | 19.4    |
| 5   | 1    | -1 | 0   | 85.96  | 329.5  | 23.4    |
| 6   | -1   | 0  | 1   | 61.29  | 198.4  | 14.2    |
| 7   | 0    | -1 | -1  | 73.21  | 357.5  | 22.4    |
| 8   | 0    | 0  | 0   | 75.54  | 233.3  | 15.4    |
| 9   | 0    | 1  | 1   | 68.21  | 162.7  | 18.3    |
| 10  | 0    | 1  | -1  | 82.47  | 161.5  | 21.2    |
| 11  | 0    | 0  | 0   | 78.23  | 231.6  | 15.2    |
| 12  | 1    | 0  | 0   | 84.57  | 287.2  | 17.5    |
| 13  | 0    | 0  | 0   | 75.84  | 231.2  | 15.5    |
| 14  | 0    | 0  | 0   | 75.54  | 238.2  | 15.6    |
| 15  | 1    | 0  | -1  | 84.21  | 341.8  | 24.2    |
| 16  | -1   | 1  | 0   | 64.81  | 168.1  | 17.4    |
| 17  | -1   | -1 | 0   | 72.23  | 276.1  | 14.3    |

Table 2. Summary of ANOVA for different factors and its significance with respect to quadratic model

| Source | EE | PS | T85% |
|--------|----|----|------|
| F value | P value | F value | P value | F value | P value |
| Model  | 43.0 | <0.0001 | 56.2 | <0.0001 | 54.4 | <0.0001 |
| A: PREC | 293.9 | <0.0001 | 148.2 | <0.0001 | 185.2 | <0.0001 |
| B: SL | 5.6 | 0.0517 | 138.8 | <0.0001 | 9.9 | 0.0169 |
| C: POL | 18.7 | 0.0037 | 107.2 | <0.0001 | 57.3 | 0.0001 |
| AB | 4.65 | 0.0772 | 10.38 | 0.0129 | 60.5 | 0.0001 |
| AC | 0.71 | 0.3884 | 7.6 | 0.0216 | 0.4 | 0.5741 |
| BC | 43.9 | 0.0003 | 54.35 | 0.0002 | 7.4 | 0.9335 |
| A² | 1.0 | 0.3698 | 38.6 | 0.0009 | 6.9 | 0.0331 |
| B² | 4.9 | 0.0761 | 0.1 | 0.7806 | 56.1 | 0.0004 |
| C² | 7.3 | 0.0272 | 3.75 | 0.0804 | 108.6 | 0.0001 |

Table 3. Summary of design of experiment with various parameters fitting to quadratic model

| Responses | EE | PS | T85% |
|-----------|----|----|------|
| R² | 0.9718 | 0.9661 | 0.9962 |
| Adj. R² | 0.9685 | 0.9773 | 0.9784 |
| Pred. R² | 0.8414 | 0.8787 | 0.7997 |
| Adequate Precision | 22.70 | 25.33 | 21.83 |
| Std. Dev | 1.66 | 11.3 | 0.69 |

PDI values less than 0.3 are indicative of narrow size distribution. Zeta potential value greater than 20 indicate that repulsion force sufficient to prevent aggregation of globules.
Table 4. Constraints for the process of optimisation of SLN of CH using design of experiment

| Name of factor | Lower Limit | Upper Limit | Optimized Coded value | Optimized Actual value |
|----------------|-------------|-------------|-----------------------|------------------------|
| A: PREC (mg)   | 100         | 300         | 0                     | 200                    |
| B: SL (mg)     | 50          | 150         | 1                     | 250                    |
| C: POL (%)     | 0.1         | 0.3         | -1                    | 0.2                    |

| Responses OR CQAs | Desirable Lower Limit | Desirable Upper Limit | Predicted responses | Experimental responses |
|-------------------|-----------------------|-----------------------|---------------------|------------------------|
| EE (%)            | 70                    | 100                   | 72.40               | 73.47 ± 1.18           |
| PS (nm)           | 10                    | 200                   | 184.81              | 186.5 ± 7.1            |
| T85% (h)          | 18                    | 24                    | 21.23               | 21.2 ± 0.4             |

Response data are the mean values ± SD, n = 6

PRECpritol ATO 888T: PREC, Soya Lecithin: SL, Poloxamer 407: POL, Entrapment efficiency: EE, Particle Size: PS and Time for 85% cumulative drug release: T85%

Table 5. Stability study of optimised SLN

| Time (months) | Optimised SLN |          |          |
|---------------|---------------|----------|----------|
|               | EE (%)        | PS (nm)  | T85%     |
| 0             | 73.47 ± 1.18  | 186.5 ± 7.1 | 21.2 ± 0.4 |
| 1             | 71.12 ± 2.5   | 172 ± 2.5 | 21.1 ± 0.22 |
| 3             | 70.34 ± 3.6   | 174 ± 9.7 | 21.5 ± 0.35 |
| 6             | 70.78 ± 2.1   | 175 ± 3.2 | 21.8 ± 0.45 |

Mean ± SD, n = 6

Entrapment efficiency: EE, Particle Size: PS and Time for 85% cumulative drug release: T85%

Table 6. Pharmacokinetic data of pure drug CH, Optimized SLN and Lyophilized SLN

| Pharmacokinetic parameters | Aqueous suspension of CH | Optimized SLN |
|----------------------------|--------------------------|---------------|
| \( K_E \)                  | 0.0846 ± 0.003           | 0.1139 ± 0.04 |
| \( C_{max} (\text{ng/mL}) \) | 573.02 ± 23              | 1440.13 ± 67  |
| \( t_{max} (\text{h}) \)   | 6 ± 0.26                 | 6 ± 0.14      |
| AUC (ng.hr/L)              | 15238.98 ± 546           | 44704.68 ± 215|

Mean ± SD, n = 6

Fig. 1. Contour plots and 3D-Response surface plot showing the influence of significant factor on entrapment efficiency (EE)
Fig. 2. Contour plots and 3D-Response surface plot showing the influence of significant factor on particle size (PS)

Fig. 3. Contour plots and 3D-Response surface plot showing the influence of significant factor time taken for release of 85% o drug

Fig. 4. Overlay contour plots depicting the design space and delineate the optimized formulation of solid lipid nanoparticle (SLN) of cinacalcet hydrochloride
4.6 Stability Study

The results of stability study are shown in Table 5. The stability of optimized SLN formulation was evaluated by determining EE, particle size, zeta potential and PDI with a frequency of 1, 3 and 6 months at 25±2°C/60±5% RH. The particle size, T85% and EE did not show any significant change during stability study.

4.7 FT-IR Spectroscopy Study

FT-IR study for the pure drug Cinnacalcet HCl showed absorption bands at 1517 cm\(^{-1}\) assigned to CH\(_3\) group, absorption bands at 1338 cm\(^{-1}\) assigned to CH\(_2\) group, absorption bands at 2909 cm\(^{-1}\) assigned to NH group, absorption bands at 796 cm\(^{-1}\) assigned to CF\(_3\) group and absorption bands at 805 cm\(^{-1}\) assigned to benzene group. The physical mixtures of Cinnacalcet HCl with different excipients such as PREC, SL and POL showed absorption bands in similar range hence the Cinnacalcet HCl and excipients are compatible with each other. The overlaying FT-IR spectrum was shown in Fig. 4.

4.8 Differential Scanning Calorimetry (DSC)

Fig. 5 represents the DSC thermograms of Cinnacalcet HCl, PM of Cinnacalcet HCl with PREC, SL and POL. The DSC thermogram of Cinnacalcet HCl exhibited a sharp endothermic peak at 181.90 °C (T\(_{\text{fus}}\)), with onset at 178.33°C and latent heat of fusion (ΔH\(_{\text{fus}}\)) was found to be -28.26 mJ, indicated the crystalline nature of the drug whereas the DSC thermogram of PM showed slightly broadened endothermic peaks nearer to the melting point of cinacalcet HCl.

4.9 Pharmacokinetic Study

The serum concentration-time profile is shown in Fig. 6. The pharmacokinetic parameters are given in Table 6. The T\(_{\text{max}}\) for the aqueous suspension of pure drug and optimized SLN was found to be 6 h. The C\(_{\text{max}}\) value of pure drug, and optimized SLN formulation was found to be 573 ng/mL and 1440.13 ng/mL respectively. Optimized SLN showed nearly 2.5 times increase in C\(_{\text{max}}\) indicating better absorption from formulations. Similarly AUC values for formulations showed nearly 3 times increase in area for optimized SLN indicating better bioavailability. Routray et al, 2020 also reported 2.5 times improvement in bioavailability for SLN formulation of cinacalcet HCl by using compritol ATO 888 as solid lipid and poloxamer 407 as surfactant [24] The pharmacokinetic profile of optimized SLN was found to be superior compared to aqueous suspension of pure drug.
Fig. 6. FT-IR spectra of pure drug cinacalcet HCl (a), physical mixture of cinacalcet HCl and PREC (b), physical mixture of cinacalcet HCl and SL (c), physical mixture of cinacalcet HCl and POL (d)
Fig. 7. DSC thermograms of pure drug cinacalcet HCl (a), physical mixture of cinacalcet HCl and PREC (b), physical mixture of cinacalcet HCl and SL (c), physical mixture of cinacalcet HCl and POL (d)

Fig. 8. Pharmacokinetic profile of pure drug cinacalcet HCl and Optimized SLN in albino rabbit serum following oral administration
5. CONCLUSION

In the present study, BBD was used for optimisation of SLN formulation. Controlled release profiles for nearly 24 h were obtained by incorporating Cinnalcalcet HCl into the solid matrix of PREC based lipid nanoparticles. The use of mixed surfactants SL and POL resulted in the formation SLNs with decreased particle size. For optimisation the desirable goal was fixed for various responses EE, PS and T85%. The optimized single dose of SLN obtained using BBD consisting of 30 mg of Cinnalcalcet HCl, 100 mg of PREC, 150 mg of SL and 50 mg of POL. The optimized SLN formulation showed improvement oral bioavailability (2 times). Thus it can be concluded that SLN formulation can be considered as a promising approach to improve oral bioavailability.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The current pharmacokinetic study was approved (approval no 88) by IAEC of Roland institute of pharmaceutical sciences (Regd. no 926/PO/ac/06/CPCSEA)

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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