Formulation and Optimization of Ketoprofen Loaded Solid Lipid Nanoparticles Using Central Composite Design

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Abstract

Ketoprofen is belongs to Non-steroidal antiinflammatory drugs (NSAIDs) and characterized by low solubility and bioavailability. The present study was planned to explore potential of ketoprofen loaded solid lipid nanoparticles (SLN) as a drug carrier system. Ketoprofen SLN was prepared by solvent injection technique. The formulation was optimized by experimental design considering the concentrations of drug and lipid. The optimized formulation demonstrated reduce particle size, better entrapment efficiency and sustained drug release pattern. The optimized formulation showed sustained release of drug from coating capsules containing lyophilized SLNs with cellulose acetate phthalate in the simulated gastrointestinal fluid. It was concluded that the Ketoprofen loaded SLN based formulation incorporated in capsules was suitable for oral application and give better therapeutic effects compared to conventional dosage form.

1 Introduction

Ketoprofen is a well-perceived medication, incorporated into the class of NSAIDs. It is a strong particular inhibitor of cyclooxygenase (COX) - 2 and has pain relieving and anti-inflammatory activity. It hinders the incendiary course and COX by restraining prostaglandin and thromboxane generation and lead to decrease in pain, fever, platelet total and inflammatory response. Other than hindering the prostaglandin and thromboxane generation, Ketoprofen additionally repress rabbit neutrophil and human lung lipoxgenase action. Ketoprofen is for the most part shown for symptomatic alleviation of Rheumatoid Arthritis, Osteoarthritis, Inflammatory arthropathies, Gout, Migraine and Headache.

The oral administration of ketoprofen causes gastrointestinal ulcers and bleeding in chronic use. Due to gastrointestinal bleeding it may cause anaemia. Also, use of ketoprofen is limited by its poor solubility and low bioavailability. Thus, the present study was approached to design and development of a drug delivery system which could enhance the solubility and improve the adverse effect of ketoprofen during oral administration using SLN.

Lipid based drug delivery has pulled in much consideration amid late years as creative procedure to beat lacking bioavailability of hydrophobic medications. SLN can likewise offer better patient consistence. A standout amongst the most well-known and monetarily feasible detailing approaches for taking care of these issues is SLN which have been demonstrated to be sensibly effective in improving the oral bioavailability of different ineffectively water-soluble SLN are isotropic blends of medication, oil/lipid, surfactant, and additionally cosurfactant, which structure fine emulsion/lipid beads, going in size from around 100 nm on weakening with physiological liquid. The medication, in this way, stays in solution in the gut, avoiding the disintegration step that much of as far as possible the retention rate of hydrophobic medications from the crystalline state. SLN can be enhanced with the assistance of stage outline, when such a framework is discharged in the lumen of the GIT, it scatters to shape a fine emulsion with the guide of GIT fluid.

Other advantages of this system include high drug loading capacity and controlled or sustained release of incorporated drug. The mechanisms for enhancement of solubility by SLN are mainly attributed to reduction in the particle size by using
different ingredients for SLN such as oleic acid, castor oil, olive oil and liquid paraffin as oil, Tween 20, Tween 80, Span 80 and Span 20 as surfactant, Propylene glycol, PEG 400, Transcutol P and glycerol as cosurfactant. Keeping in view of these, the present work was designed as follows:

2 Materials and Methods

2.1 Preparation of solid lipid nanoparticles of ketoprofen

Solid lipid nanoparticles were prepared by solvent injection technique. Ketoprofen (50mg) and specified amount of glyceryl monostearate was dissolved in 5ml of isopropyl alcohol with heating at melting temperature of glyceryl monostearate. Simultaneously the aqueous solution of specified amount of Poloxamer 407 was prepared in 25 ml of distilled water at the same temperature. When both the phases reached the same temperature the organic phase was quickly injected into the aqueous phase with continuous stirring at 400 rpm for 30 min on magnetic stirrer. To this dispersion 4 ml of 0.1N HCl was added to decrease the pH to around 1.5-2.0 to cause the aggregation of SLNs for the ease of separation.

Thereafter, the dispersion was centrifuged at 10,000 rpm for 60 min at 10°C in Remi Cooling centrifuge. The sedimented soft pellet was then separated and resuspended in 25 ml of distilled water containing 4% Poloxamer 407 (by weight) as stabilizer with stirring at 1000 rpm for 10 minutes and subjected to ultrasonication for 1 min to get a desired particle size.

The optimized batch was prepared similarly and subjected to lyophilisation by addition of mannitol as a cryoprotectant then the nanoparticulate suspension was kept in deep freezer at 4°C for 24 hrs and lyophilized product was used for further studies.

2.2 Optimization

2.2.1 Experimental Design

The optimization technique was utilized to obtain systematic formulation design in order to minimize the number of trials, and analyse the response surface to investigate the effect of independent variables on the response. In this study, Central Composite Design (CCD) was adopted for optimization of the formulation of solid lipid nanoparticles. CCD is a response surface design which is widely used technique for formulation and process optimization. The amount of glyceryl monostearate (X1) and poloxamer 407 (X2) were taken at three levels (-1, 0 and +1) as formulation factors on the basis of previous trials (Table 1).

The particle Size, entrapment efficiency, and cumulative drug release were taken as dependent or response variables. All other formulation and process parameters were kept invariant throughout the study.

The software suggested 13 trial runs for 2 factors out of which four trial runs were for the two levels (-1, +1) of selected independent variables, five were for the centre points (0) to include the effect of unknown variables other than the selected variables and four runs for the extreme levels (-1.41421, +1.41421) of the two variables (Table 2 & 3).

Table 1: Independent Variables used for optimization

| Variables | Levels | Amount (mg) |
|-----------|--------|-------------|
| Factor-1: | -1     | 100         |
| Glyceryl Monostearate | +1     | 200         |
| Factor-2: | -1.41421 | 59          |
| Poloxamer 407 | 1.41421 | 241         |

Table 2: Experimental design (using design expert 9.0.3)

| Std | Run | Factor-1: Amount of Glyceryl monostearate (X₁) | Factor-2: Amount of Poloxamer 407 (X₂) |
|-----|-----|-----------------------------------------------|---------------------------------------|
| 6   | 1   | 1.41421                                      | 0                                     |
| 4   | 2   | 1                                            | 1                                     |
| 1   | 3   | -1                                           | -1                                    |
| 10  | 4   | 0                                            | 0                                     |
| 8   | 5   | 0                                            | 1.41421                               |
| 12  | 6   | 0                                            | 0                                     |
| 5   | 7   | -1.41421                                     | 0                                     |
| 9   | 8   | 0                                            | 0                                     |
| 3   | 9   | -1                                           | 1                                     |
| 13  | 10  | 0                                            | 0                                     |
| 2   | 11  | 1                                            | -1                                    |
| 7   | 12  | 0                                            | -1.41421                              |
| 11  | 13  | 0                                            | 0                                     |
Table 3: Batch Specifications

| Std | Run | Factor-1: Amount of Glycerol monostearate (X₁) | Factor-2: Amount of Poloxamer 407 (X₂) |
|-----|-----|----------------------------------|----------------------------------|
| 6   | 1   | 241                              | 468.7                            |
| 4   | 2   | 200                              | 625                              |
| 1   | 3   | 100                              | 312.5                            |
| 10  | 4   | 150                              | 468.7                            |
| 8   | 5   | 150                              | 881.2                            |
| 12  | 6   | 150                              | 468.7                            |
| 5   | 7   | 59                               | 468.7                            |
| 9   | 8   | 150                              | 468.7                            |
| 3   | 9   | 100                              | 625                              |
| 13  | 10  | 150                              | 468.7                            |
| 2   | 11  | 200                              | 312.5                            |
| 7   | 12  | 150                              | 184.3                            |
| 11  | 13  | 150                              | 468.7                            |

2.3 Formulation of enteric coated capsules containing the SLNs of ketoprofen

2.3.1 Preparation of coating solution

A 10% w/v Cellulose Acetate Phthalate (CAP) coating solution was prepared using acetone as solvent and 0.8% polyethylene glycol 600 as plasticizer. 10g of CAP was dissolved in 100 ml of acetone and 0.75 ml of polyethylene glycol 600 was added to the solution. The mixture was stirred properly on a magnetic stirrer to get a homogeneous solution.

2.3.2 Coating of capsules

The solid lipid nanoparticles of the optimized batch were lyophilized and the product equivalent to 5mg of drug was filled in a hard gelatin capsule. The capsule was coated with the enteric coating polymer solution of CAP by dipping method. The filled capsule was dipped into the prepared enteric coating solution and then withdrawn from the solution at a controlled speed. The applied coating remained wet for several minutes until the solvent evaporated and coat become dry. Once a layer is cured, another layer was applied on the top of it by repeating the process. The above step was repeated 5-7 times to get a desired coating thickness. The thickness of the coat depends on the viscosity, density, and surface tension of coating solution.

2.3.3 Drug release studies on coated capsules

The in-vitro drug release studies were carried out in two different dissolution medium, Simulates Gastric Fluid (SGF) 0.1 N HCl (pH 1.2) for 2 hrs and Simulates Intestinal Fluid phosphate buffer (pH 7.4) for next 8 hrs using USP type- II Dissolution apparatus. The temperature was maintained at 37±0.5°C and stirring rate was 100 rpm. The enteric coated capsule was placed in a dialysis bag with small amount of dissolution medium and sealed at both the ends with the help of clips. Samples (5 ml) were withdrawn from the dissolution medium at specified time intervals and were replaced with fresh dissolution media. The samples were analysed for drug content by measuring absorbance using UV-visible spectrophotometer at 259 nm and 260 nm for dissolution in SGF and SIF respectively. The cumulative release of ketoprofen was calculated over the entire study duration of 12 hrs.

3 Results and Discussions

3.1 Drug-excipient interaction studies

The compatibility of drug with excipients was studied using techniques like FTIR and DSC to find any kind of destructive interaction between drug and lipid used in the study.

The characteristic peaks of FTIR of Ketoprofen and glyceryl monostearate were present in the physical mixture, thus indicating that there was no significant evidence of chemical interaction between drug and lipid, which confirms the stability of drug in presence of glyceryl monostearate (Fig 1).

DSC thermogram of pure drug Ketoprofen, Glyceryl Monostearate, physical mixture of drug and Glyceryl monostearate and drug loaded SLNs of optimised batch are shown depicted in the overlay profiles shown in Fig 2.

The thermogram of physical mixture suggested that there were no appearance of new peaks or disappearance of existing peak in the curve, the melting point shows slight deviation from respective pure samples. Hence, it was concluded that the drug and excipient did not undergo any considerable interaction.

3.2 Characterization of solid lipid nanoparticles

The Solid lipid nanoparticle were evaluated for various parameters as described below

The particle size and polydispersity index of different batches are shown in Table 4.

The particle size of prepared formulations F1 to F13 was found to be in the range of 101.8 – 427.0 nm. From the above results, it was concluded that the particle size increases with the increase in amount of glyceryl monostearate. The size of lipid nanoparticles is highly dependent on lipid concentration that can be explained in terms of tendency of lipid to coalesce at high lipid concentration. The increased amount of lipid provides an

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additional space for drug molecules to get entrapped, thus decreasing the total surface area (Fig 3).

Fig 1: FTIR spectrum of physical mixture of Ketoprofen and glyceryl monostearate

Fig 2: Overlay profiles of DSC Analysis of (a) Ketoprofen, (b) Optimised batch, (c) Physical mixture of drug and Glyceryl Monostearate, (d) Glyceryl Monostearate

Fig 3: Particle Size distribution of F10 formulation
On increasing the concentration of poloxamer 407, the particle size was found to decrease. This might be due to the surfactant-induced reduction in surface tension between aqueous phase and organic phase. In addition, surfactant helps to stabilize the newly generated surfaces and prevents particle aggregation.

The Entrapment Efficiency ranged from 60.55% – 92.70% which indicated that increase in amount of glyceryl monostearate also increased the entrapment efficiency of drug because of the increased concentration of mono-, di-, and triglycerides which act as solubilizing agents for highly lipophilic drug and provide a less ordered solid lipid matrix and left enough space to accommodate drug molecules. The Entrapment Efficiency was decreased with increasing concentration of surfactant in aqueous phase because of the well-known fact that the aqueous solubility of drug increases with increase in surfactant concentration Fig 4.

![Fig 4: Entrapment Efficiency of different formulations](image)

The release profile of ketoprofen loaded solid lipid nanoparticle showed the cumulative drug release from 39.84% – 67.08% over a period of 12 hrs (Fig 5 and Fig 6).

**Table 4: Particle size, zeta potential and Polydispersity Index different formulations of Solid lipid nanoparticle**

| Formulation | Average Diameter (nm) | Polydispersity Index | Zeta Potential (mV) |
|-------------|-----------------------|----------------------|---------------------|
| F1          | 385.8                 | 0.467                | -15.1               |
| F2          | 305.0                 | 0.131                | -11.9               |
| F3          | 348.8                 | 0.125                | -17.6               |
| F4          | 356.7                 | 0.136                | -2.21               |
| F5          | 101.8                 | 0.201                | -11.1               |
| F6          | 326.8                 | 0.466                | -8.49               |
| F7          | 224.6                 | 0.076                | -14.4               |
| F8          | 273.5                 | 0.178                | -4.65               |
| F9          | 207.8                 | 0.007                | -15.7               |
| F10         | 241.9                 | 0.078                | -                   |
| F11         | 425.9                 | 0.269                | -1.64               |
| F12         | 427.0                 | 0.239                | -4.65               |
| F13         | 263.4                 | 0.149                | -                   |

![Fig 5: In vitro drug release profile of F1-F6](image)

![Fig 6: In vitro drug release profile of F6-F13](image)
The solid lipid nanoparticles displayed a biphasic drug release pattern with initial burst release followed by sustained release of drug. The burst release may be ascribed to the drug associated with the surface of particles. The results displayed that the release was chiefly dependent on the concentration of lipid. An increase in the lipid concentration caused a decrease in the release rate because lipid content increases the packing density of lipid molecules in given space; as a consequence of which the release is reduced. However, the percent cumulative drug release increased with corresponding increase in poloxamer 407 concentration which could be attributed to the decrease in particle size and increase in surface area available for dissolution.

3.3 Response surface methodology optimization

The optimization of formulation variables was done using the central composite design technique and the various parameters are given in table 5.

Table 5: Central Composite design Used in Formulation of SLNs and Independent Variables Influencing Responses

| Run | Factor 1 Glyceryl Monostearate (mg) X1 | Factor 2 Poloxamer 407 (mg) X2 | Response 1 Particle size (nm) Y1 | Response 2 Entrapment Efficiency (%) Y2 | Response 3 Cumulative Drug Release (%) Y3 |
|-----|---------------------------------------|---------------------------------|---------------------------------|----------------------------------------|----------------------------------------|
| 1   | 241 (1.41421)                         | 468.7 (0)                       | 385.8                           | 92.708                                 | 44.238                                 |
| 2   | 200 (1)                               | 625 (1)                         | 305                             | 78.095                                 | 57.642                                 |
| 3   | 100 (-1)                              | 312.5 (-1)                      | 348.8                           | 81.154                                 | 55.611                                 |
| 4   | 150 (0)                               | 468.7 (0)                       | 356.7                           | 80.666                                 | 53.255                                 |
| 5   | 150 (0)                               | 881.2 (1.41421)                | 101.8                           | 63.639                                 | 67.087                                 |
| 6   | 150 (0)                               | 468.7 (0)                       | 326.8                           | 79.437                                 | 52.717                                 |
| 7   | 59 (-1.41421)                         | 468.7 (0)                       | 224.6                           | 60.559                                 | 55.708                                 |
| 8   | 150 (0)                               | 468.7 (0)                       | 273.5                           | 78.774                                 | 52.844                                 |
| 9   | 100 (-1)                              | 625 (1)                         | 207.8                           | 66.649                                 | 66.346                                 |
| 10  | 150 (0)                               | 468.7 (0)                       | 241.9                           | 80.514                                 | 51.467                                 |
| 11  | 200 (1)                               | 312.5 (-1)                      | 425                             | 93.478                                 | 50.408                                 |
| 12  | 150 (0)                               | 184.3(-1.41421)                | 427                             | 87.35                                  | 39.84                                  |
| 13  | 150 (0)                               | 468.7 (0)                       | 263.4                           | 80.288                                 | 51.32                                  |

The results of optimization of ketoprofen solid lipid nanoparticles (particle size, entrapment efficiency and cumulative drug release) were fitted into various polynomial models. It was observed that the response particle size was fitted best into the response surface linear model while entrapment efficiency and cumulative drug release were best fitted into modified model. Further to estimate the significance of model they were subjected to ANOVA analysis. The results of ANOVA analysis showed that the models to be significant with non-significant lack of fit and quadratic terms were generated for all the response variables.

The relationship between the independent variables with responses in terms of coded factors can be shown as:

- Equation - 1
  \[ Y_1 = +299.08 + 50.17 \times X_1 - 90.11 \times X_2 \]

- Equation - 2
  \[ Y_2 = +79.94 + 0.52 \times X_1 - 7.93 \times X_2 + 5.91 \times X_1^2 - 2.22 \times X_2^2 + 5.42 \times X_1^3 - 3.78 \times X_1^4 \]

- Equation - 3
  \[ Y_3 = +52.32 - 3.77 \times X_1 + 9.63 \times X_2 - 0.88 \times X_1 \times X_2 - 1.17 \times X_1^2 + 0.57 \times X_2^2 - 5.14 \times X_1^3 \times X_2 + 5.78 \times X_1^2 \times X_2^2 \]

Where,
- \( X_1 = \) Glyceryl Monostearate
- \( Y_1 = \) Particle size
- \( X_2 = \) Poloxamer 407
- \( Y_2 = \% \) Entrapment Efficiency
- \( Y_3 = \% \) Cumulative drug Release
3.3.1 Solution of numerical optimization

Design expert 9.0.3 was used for formulation optimization of SLNs with an objective to keep glyceryl monostearate and Poloxamer 407 within the range of experimental level. The goal of optimization was to minimize the particle size and maximizing the cumulative drug release and entrapment efficiency was kept within of range experimental values. Since optimization techniques are basically meant to make compromises, in order to achieve the desired goals. In order to get the desired goal lower limits and upper limits were set for different time points as shown in table 6.

Based on the desirability approach for optimization one solution was found which indicated a solution with Glyceryl monostearate at -1 level and concentration of Poloxamer 407 at 1 level which should yield a particle size of 158.8 nm, % Entrapment efficiency 65.97% and % Cumulative drug release 66.63% with desirability of 0.914 (Table 7).

Table 6: Constraints of Numerical Optimization

| Constraints name        | Goal         | Lower limit | Upper limit | Lower weight | Upper Weight | Importance |
|-------------------------|--------------|-------------|-------------|--------------|--------------|------------|
| X1: Glyceryl monostearate| Is in range  | -1          | 1           | 1            | 1            | 3          |
| X2: Poloxamer 407       | Is in range  | -1          | 1           | 1            | 1            | 3          |
| Y1: Particle size       | minimize     | 101.8       | 400         | 1            | 1            | 3          |
| Y2: % Entrapment efficiency| Is in range | 60.559      | 93.478      | 1            | 1            | 4          |
| Y3: % Cumulative drug release | maximize | 39.84       | 67.087      | 1            | 1            | 5          |

Table 7: Solution of Numerical Optimization

| Glyceryl monostearate | Poloxamer 407 | Particle size | % Entrapment Efficiency | % Cumulative drug release | Desirability | 1 Solution found |
|-----------------------|---------------|---------------|-------------------------|---------------------------|--------------|-----------------|
| -1                    | 1             | 158.80        | 65.974                  | 66.635                    | 0.914        | Selected        |

3.3.2 Response surface analysis

The response surface plot portraying the combined effect of glyceryl monostearate and poloxamer 407 on particle size of solid lipid nanoparticles is shown in Fig 7.

The graph clearly indicates that concentration of glyceryl monostearate and poloxamer 407 had significant effect on the particle size. The particle size increased with the increase in concentration of glyceryl monostearate and decreased with the increase in concentration of poloxamer 407 as it reduced the surface tension and facilitate the particle partition.

Fig 7 shows the response surface plot representing the combined effect of glyceryl monostearate and poloxamer 407 on cumulative drug release of ketoprofen SLNs. The graph indicated that the release rate was decreased as the amount of glyceryl monostearate increased. Poloxamer 407 increased the percent cumulative drug release because of the corresponding decrease in particle size, which in turn increased the surface area available for dissolution.

Response surface plot in Fig 8 shows a nonlinear relationship between glyceryl monostearate and poloxamer 407 on entrapment efficiency of SLNs. It could be clearly inferred from the plot that the entrapment efficiency of the drug was increased with increase in concentration of glyceryl monostearate. This
may be due to the fact that a higher concentration of lipid would provide more space for the drug content and would also reduce the escaping of drug into the external phase thus ensuring high entrapment efficiency. Entrapment efficiency was decreased with increase in poloxamer 407 as it increased the aqueous solubility of drug which precluded the accommodation of drug in lipid matrix (Fig 9).

Fig 8: Response surface plot showing the combined effect of glyceryl monostearate and poloxamer 407 on percent entrapment efficiency of solid lipid nanoparticles.

Fig 9: Response surface plot showing the combined effect of glyceryl monostearate and poloxamer 407 on percent cumulative drug release of solid lipid nanoparticles.

Fig 10: Response surface plot showing the combined effect of glyceryl monostearate and poloxamer 407 on desirability of solid lipid nanoparticles.

In the same way, the melting enthalpy values of different lipids in SLN formulations showed drastic depression compared to their bulk lipids from 73.205 J/g to 510.071 J/g respectively. These lower melting enthalpy values suggested less ordered lattice arrangement of the lipid within nanoparticles compared to the bulk. For the less-ordered crystal or amorphous state, the conversion of crystalline ketoprofen to the amorphous form which could be attributed to complete dissolution of the drug in the molten lipid matrix (Fig 11). The melting point of glyceryl monostearate in SLNs was depressed showing slight shift to lower temperature side when compared to the corresponding bulk lipid. This melting point depression could be due to the small particle size (nanometer range), the high specific surface area, and the presence of surfactant - in other words, the depression can be attributed to the Kelvin effect. Kelvin realized that small, isolated particles would melt at a temperature lower than the melting temperature of bulk materials.
melting of the substance requires less energy than the perfect crystalline substance, which needs to overcome lattice force. Therefore this decrease in the melting point and enthalpy values is associated with numerous lattice defects and the formation of amorphous regions in which the drug is located.

3.3.4.2 Transmission electron microscopy

Transmission Electron Microscopy (TEM) was conducted to investigate the morphology of Ketoprofen loaded SLNs. It was evident from the TEM images that nanoparticles were almost spherical with smooth morphology, appeared as black dots, well dispersed and separated on the surface (Fig 12).

3.3.4.3 In-vitro drug release profile of optimized batch

Fig 13 shows the drug release profile of optimised batch. It was observed that the 65.867% of drug was released over a period of 12 hrs using phosphate buffer (pH 7.4) as a dissolution medium.

3.4 In-vitro dissolution profile for enteric coated capsules

The coating capsules of containing lyophilized SLNs with cellulose acetate phthalate significantly reduced the release of drug in the simulated gastrointestinal fluid. The drug release from the prepared capsules was studied and it was found that about 4% of ketoprofen was released after 2 hrs, while more than 57% was released after 12 hrs followed the mechanism of sustained release of drug (Fig 14). Hence, prevent the excessive exposure of drug to stomach mucosal lining. The in vitro study data can be corroborated with further in vivo studies in animal models. Thus, paving the way for the development of a promising drug delivery system for more effective therapeutic management of rheumatoid arthritis.

4 Conclusion

The objective of the present investigation was to explore potential of ketoprofen loaded SLN as a drug carrier system. Ketoprofen SLN were prepared by solvent injection technique. The formulation was optimized by experimental design considering the concentrations of drug and lipid. The optimized formulation exhibited sustained drug release. Further the SLN
were filled in capsule, and it exhibited more than 57% was released after 12 hrs followed the mechanism of sustained release of drug. The above findings concluded that the prevention of the excessive exposure of Ketoprofen to stomach mucosal lining and it decrease the adverse effect of drug. Hence, prevent the excessive exposure of drug to stomach mucosal lining.

Table 8: Drug release kinetic data obtained from optimized batch

| Model                | Slope  | R²     |
|----------------------|--------|--------|
| Zero order           | 5.1671 | 0.8634 |
| First order          | -0.0398| 0.9286 |
| Higuchi equation     | 0.0462 | 0.9714 |
| Korsemeyer Peppas equation | 0.5896 | 0.9909 |

5 Conflicts of interest

None

6 Authors’ contributions

All authors contributed equally on experimental and drafting of the manuscript. All authors read and approved the final manuscript.

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