The term Polymeric Nanoparticles (PNs) is defined as particulate dispersion in which the solid particle size range from 60-200 nm, where the drug particle can be encapsulated, dissolved, entrapped or can be attached to a nanoparticle matrix [1]. The main perspective of PNs is to reduce the drug volatility; also with the help of a multitude method; Rosuvastatin Calcium in formulating in greater quantity. They also furnish a remarkable improvement over traditional method in terms of effectiveness and efficiency for an administration of a medicament. PNs show high specificity for the delivery of any pharmaceutical agent to their desired location. Due to certain ideal characteristic features of PNs, such as opting of polymer and its potential to revise drug release pattern makes PNs a potent candidate as for cancer, contraceptive, antibiotics, vaccines [2].

The limitations of PNs are high-cost formulation with low yield, productivity is very difficult, on the industrial aspect the technology transfer to commercial production is also very difficult. Stability of PNs is a big issue owing to its nano size. Highly sophisticated technology is required for manufacturing PNs [3].

Rosuvastatin Calcium is one of the most potent statins for reducing low-density lipoprotein cholesterol (LDL-C) level. Rosuvastatin calcium used as a lipid-lowering agent by acting as HMG CoA reductase inhibitor, and it has low extrahepatic tissue penetration, Rosuvastatin Calcium elimination half-life is 19 h with low bioavailability of about 20 %, with the maximum amount of drug excreted through faeces (90 %) which leads to a reduction in bioavailable dose in blood that reflects in less therapeutic effect [4]. This above biopharmaceutics parameter is a reason for the selection to fabricate Rosuvastatin Calcium into PNs to enhance the bioavailability of it. Hence the hypothesis of the research is as follows; Rosuvastatin Calcium bioavailability is very less because of low solubility and low permeability (BCS Class II). It may lead to more toxicity due to its 19 h half-life without clearance.

So, polymeric nanoparticles were chosen to enhance the solubility, bioavailability and to decrease the toxicity of Rosuvastatin Calcium.

Another objective of this research is to optimize the polymeric nanoparticles by applying 2\(^{nd}\) factorial designs and to perform in vivo pharmacokinetic evaluation of designed polymeric nanoparticles to evince the intensification of bioavailability.

Materials
Rosuvastatin Calcium was procured from Microlabs Pvt. Ltd. India. Spans 80, Chitosan were obtained from LOBA Chemie Pvt. Ltd 107, Mumbai, India. Different instruments were used in the formulation and evaluation of polymeric nanoparticles like Magnetic Stirrer (REMI, India), Ultra Sonicator (Q Sonica, Germany), FT-IR Spectrophotometer (Bruker, India), Nanoparticles Size Analyzer (HORIBA, Japan), High-Performance Liquid Chromatography (HPLC, Shimadzu, Japan), Ultracentrifuge (REMI, India), Scanning Electron Microscopy (Zeiss Evo, USA).

Methods
Preparation of polymeric nanoparticles (PNs)
Polymeric nanoparticle (60-200 nm) was developed by using the solvent evaporation method. In this procedure, chitosan solution was done by using solvents like chloroform. To this organic phase required quantity of Rosuvastatin Calcium (20 mg) was dispersed. The emulsion is converted into polymeric nanoparticles like Magnetic Stirrer (REMI, India), Solid–Liquid Chromatography (HPLC, Shimadzu, Japan), Ultracentrifuge (REMI, India), Scanning Electron Microscopy (Zeiss Evo, USA).
Experimental design for formulation of PNs

In the ongoing study, 2^3 statistical designs were used with 3 levels, 2 factors and 8 runs were employed for the optimization study, which is carried out with the help of design expert software (State easy Inc, Minneapolis USA, design Expert 11). The independent variables are selected such as polymer concentration (A in mg), surfactant concentration (B in ml) and ultrasonication time (C in min) and they were set at high or low level based upon the result of the variable. According to this design, 8 PN formulations are prepared and characterized for particle size (Y1), zeta potential (Y2), which are dependent variable i.e. which was chosen as a response parameter. These designs elucidate the main effect of independent variable over dependent variable. Its optimization design is shown in table 1 [5-8].

Evaluation parameters of PNs

Compatibility studies of drug and excipients

This test has been done by using Fourier transform infrared spectroscopy (FTIR). Pure drug and optimized formulation FTIR spectra analyzed separately, later the values are correlated for compatibility studies through reproducibility of functional groups in pure drug versus optimized formulation [9].

Percentage yield

The yield of any nanoparticles was decided by way of comparing the load of nanoparticles formed towards the total load of the drug and polymer used in PNs. The percentage yield is calculated as follows [9-11].

\[
\% \text{ Yield} = \frac{\text{Amount of Nanoparticles}}{\text{Amount of Drug and polymer}} \times 100
\]

Entrapment efficiency

The PNs is subjected to centrifugation, after centrifugation, the supernatant liquid is separated from the nanoparticle solution. The percentage yield is calculated as follows [9-11].

\[
\% \text{ Drug entrapment} = \frac{(W - w)}{W} \times 100
\]

Particulate characterization

The average particle size of PNs was found out by dynamic light scattering (DLS) at 90° angle and the sample holder’s temperature is about 25 °C by using (Nanopartic SZ-100 HORIBA Scientific, Japan). For ensuring the scattering intensity of light in the range of instruments, the sample had been diluted with proportion of 1:10 v/v by double distilled water. Zeta potential is defined as the difference in potential that exist in-between the surface of the solid particle that is dispersed or immersed in a conducting liquid or in the bulk of the liquid. Zeta potential is one of the key factors that affect the stability of colloidal dispersion; zeta potential was determined by using a Zetasizer (Nanopartic SZ-100 HORIBA Scientific, Japan). For a stable nanoparticle, the zeta potential should be >-30 mV. Each formulation was checked for their reproducibility of results while manufacturing [23].

In vitro drug release study

It was executed by the dissolution USP type 1 (basket type) equipment. The prepared PNs was filled in a capsule and taken in the basket. The basket shaft with PNs capsule was immersed into a dissolution jar contains 900 ml of phosphate buffer (7.4 pH) solution and 37±0.20 °C was maintained as bath temperature. Later 5 ml of sample is withdrawn from the dissolution jar at a specific time period i.e. 0.1, 2, 4, 8, 12, 16, 20 and 24 h, since in order to maintain a constant volume, the same 5 ml was restored in the dissolution jar. The sample withdrawn from the dissolution jar was examined by using UV spectrophotometer at 248 nm [20].

In vitro pharmacokinetic studies of rosvastatin calcium loaded PNs

The In vivo Pharmacokinetic (PK) data of PNs was determined by orally administering Rosuvastatin Calcium PNs to male albino wistar rats. The plasma drug concentration data is determined with the help of PK solver software. In this study male albino wistar rats are used of 180-250 g body weight. The animals were sorted into two groups with 6 animals each, on which the single-dose study was performed. The groups of the animals are dividing as follows:

Control Group: Conventional Rosuvastatin Calcium Tablet (Arvast Tablets) 20 mg/kg p.o.
Test Group: Rosuvastatin Calcium PNs Capsules (PNT) 20 mg/kg p.o.

Before administering the drug, the animals were fasted for 24h and they are free to access to water. Conventional Rosuvastatin Calcium (Arvast tablet) equivalent to animal dose was powdered and orally administered with the help of oral feeding needle. Rosuvastatin Calcium-loaded PNs equivalent to animal dose was administered orally with the help of feeding needle. 0.5 ml of blood samples was collected at time intervals of about 0.5, 2, 4, 8, 12, 24 h by retro-orbital puncture by capillary tube from there into glass tubes which priorly heparinized by anticoagulant (ammonium oxalate 1% solution). After collection of the blood sample, the sample was centrifuged with the help of microcentrifugator at 4000 rpm once the centrifugation is completed, the supernatant plasma is collected and stored at-20 °C for further analysis. The plasma drug concentration was determined using HPLC by reversed-phase C18 column (250 mm X 4.6 mm id, 5 µm Particle size); 80:20 v/v 500 µl of 0.5% formic acid and 2 mmol ammonium acetate, which act as a mobile phase with rate of flow 1.0 ml/min with 5 µl injection volume [23-28].

Statistical analysis

The plasma drug concentration versus time data was obtained by HPLC as plotted in PK solver software. The discrete plasma drug concentration time profile gives data like Cmax (peak plasma concentration), tmax (the time at which drugs attain peak plasma concentration), AU C0–infinite and AU C0–t. Biological half-life (t1/2), MRT are also determined by using PK solver software. The ANOVA studies were used to differentiate various pk parameters which are statistically evaluated [29, 30].

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RESULTS

From the data obtained from FTIR spectra (fig. 1), it was inferred that the desired frequencies of fingerprint regions were reproducible in a physical mixture of Rosuvastatin Calcium and polymer, when compared to Rosuvastatin Calcium. It was confirmed that the drugs and excipients used in the formulations were found to be compatible with each other.

Particle size

The mean particle sizes for all the formulations are presented in table 1 and fig. 2. In general, the particle sizes for all the Rosuvastatin Calcium PNs formulations were found to be in the range of 157.0±15.4 to 310.1±69.3 nm, based on the effect of the independent variable in the process of formulation. But the acceptance criteria, the PS of polymeric nanoparticle should be 60-200 nm. As per the acceptance criteria, the formulation PN1 (5 mg A factor; 0.5 ml of B factor and 10 min of C factor) shows 157.0±15.4 nm. The formulation PN2 (10 mg A factor; 1.0 ml of B factor and 10 min of C factor) shows 199 ±50.9 nm. The formulation PN5 (5 mg A factor; 0.5 ml of B factor and 20 min of C factor) shows 165.3±31.6 nm. The formulation PN7 (5 mg A factor; 1.0 ml of B factor and 20 min of C factor) shows 159.9±16.1 nm. Remaining formulation PN3, PN4, PN6 and PN8 formulations particle size was found to be more than desired range.

Zeta potential

The zeta potential for all the formulations is presented in table 1 and fig. 2. In general, the zeta potential for all Rosuvastatin Calcium PNs was found to be in the range of -4.7±0.12 mV to -33.5±1.54 mV, primarily based on the effect of surfactant in the process of formulation. But the acceptance criteria of ZP of polymeric nanoparticles should be found between -30 to -60 mV. As per the acceptance criteria, the formulation PN7 (5 mg A factor; 1.0 ml of B factor and 20 min of C factor) shows a maximum ZP of -33.5±1.54 mV. The remaining formulation was found to be less than desired range.

![Fig. 1: Drug excipients compatibility studies-FTIR studies of (A) Rosuvastatin calcium pure drug and (B) Optimized rosuvastatin calcium PN](image)

![Fig. 2: Particle characteristics; (A) PS, PI; (B) ZP of PN 7; (C) SEM images of optimized polymeric nanoparticle (PN7)](image)

Table 1: Optimization of the polymeric nanoparticle by 2³ factorial design and evaluation of the effect of independent variables on dependent variables by 2³ factorial design

| Run | Factor A: polymer concentration [Level code/mg] | Factor B: surfactant concentration [Level code/ml] | Factor C: ultra sonication time [Level code/min] | Dependant variables | Other variables | %EE | %Yield |
|-----|---------------------------------------------|-----------------------------------------------|-----------------------------------------------|--------------------|----------------|------|--------|
| PN1 | -1/5                                        | -1/0.5                                       | -1/10                                         | PS Y1 nm           | ZP Y2 mV       | PI ~ | %EE    | %Yield |
| PN2 | 1/10                                       | 1/1.0                                        | -1/10                                         | 157.0±15.4         | -4.7±0.12      | 1.341±0.12 | 90.40±2.42 | 93.54±2.80 |
| PN3 | -1/5                                        | 1/1.0                                        | -1/10                                         | 210.3±53.8         | -7.6±0.32      | 0.913±0.10 | 79.28±3.84 | 80.66±4.42 |
| PN4 | 1/10                                       | 1/1.0                                        | -1/10                                         | 285.4±60.0         | -5.9±0.26      | 0.557±0.14 | 72.80±3.44 | 76.54±4.58 |
| PN5 | -1/5                                        | -1/0.5                                       | 1/20                                          | 165.3±31.6         | -14.9±1.36     | 0.928±0.12 | 89.40±2.44 | 92.34±3.56 |
| PN6 | 1/10                                       | -1/0.5                                       | 1/20                                          | 310.1±60.3         | -14.3±1.36     | 0.547±0.14 | 64.84±3.60 | 68.26±4.78 |
| PN7 | -1/5                                        | 1/1.0                                        | 1/20                                          | 159.9±16.1         | -33.5±1.54     | 0.587±0.16 | 94.20±2.46 | 96.80±2.08 |
| PN8 | 1/10                                       | 1/1.0                                        | 1/20                                          | 230.6±60.2         | -21.4±1.62     | 0.376±0.18 | 76.84±3.66 | 79.66±2.86 |

Acceptance criteria: Particle Size (PS) = 60-200 nm; Zeta Potential = ±30 to ±60 mV; Polydispersity Index (PI) = ±0.7 for monodisperse particles; percentage entrapment efficiency (%EE) =>85 %; Percentage yield (% yield) =>85 %; *All data are measured as mean±SD, n=3.
Polydispersity index

The polydispersity index for all the formulations was shown in Table 1 and Fig. 2. The polydispersity index for Rosuvastatin Calcium PNs was found to be in the range of 0.376±0.18 to 1.341±0.12, primarily based on the effect of homogenization speed or ultrasonication time in the process of formulation. But the acceptance criteria of PI should be <0.7 for monodisperse nanoparticles. As per the acceptance criteria, the formulation PN4, PN6, PN7 and PN8 shows good polydispersity index like 0.557±0.14, 0.547±0.14, 0.587±0.16 and 0.376±0.18. Remaining formulations were found to be greater than 0.7.

Percentage entrapment efficiency and percentage yield

The desired percentage entrapment efficiency and yield for polymeric nanoparticles should be more than 85 %. As per the results shown in Table 1, the efficiency of entrapment was found to be 64.84±3.60 % to 94.20±2.46 % and % yield was found to be in the range of 68.26±4.78 to 96.80±2.08 %. By comparing all the formulations, PN6 shows the very least amount of percentage entrapment efficiency and percentage yield.

In vitro drug release and in vitro release kinetics studies

The percentage amount of drug release studies were done for PN7 optimized formulation (Table 2 and Fig. 3). The percentage amount of drug release of PN7 was found to be 96.54±2.02 % in 24 h. The regression value (r²) for Zero order, First order, Higuchi model, Hixson crowell model and Korsmeyer Peppas model was determined to be 0.982±0.02, 0.702±0.02, 0.966±0.04, 0.842±0.02 and 0.981±0.04. In vivo pharmacokinetic studies

The comparative in vivo pharmacokinetic studies data between ARVAST (20 mg/kg) conventional Rosuvastatin Calcium tablet vs. polymeric nanoparticle suspension (PN7) (20 mg/kg) orally administered was shown in Table 3. The Tmax (h), Cmax (μg/ml), AUC∞ (μg/ml/h) and MRT∞ (h) of ARVAST was found to be 0.2 h, 0.2634 μg/ml, 7.542 μg/ml/h, 0.8 h and PN7 was found to be 0.6 h, 0.1982 μg/ml, 44.2780 μg/ml/h, 12 h.

Table 2: In vitro drug release kinetic study data of optimized polymeric nanoparticle (PN7)

| S. No. | Kinetic model and its regression value | ARVAST (20 mg/kg) conventional rosuvastatin calcium tablet-oral administration | Polymeric nanoparticle suspension (PN7) (20 mg/kg)-oral administration |
|--------|--------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------|
| 1      | Zero order (r²)*                     | 0.982±0.02                                                                     | 06±0.0                                                        |
| 2      | First order (r²)*                    | 0.702±0.02                                                                     | 0.1982±0.002                                                  |
| 3      | Higuchi model (r²)                   | 0.966±0.04                                                                     | 0.842±0.02                                                   |
| 4      | Hixson crowell model (r²)*           | 0.981±0.04                                                                     | 0.502±0.02                                                   |
| 5      | Korsmeyer Peppas model (r²)*         |                                                                                 |                                                               |
| 6      | Korsmeyer Peppas release exponent (n)*|                                                                                 |                                                               |

All data are measured as mean±SD, n=3

Table 3: Comparative in vivo pharmacokinetic studies data

| Parameter                              | ARVAST (20 mg/kg) conventional rosuvastatin calcium tablet-oral administration | Polymeric nanoparticle suspension (PN7) (20 mg/kg)-oral administration |
|----------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------|
| T_max (h)                             | 02±0.0                                                                       | 06±0.0                                                        |
| C_max (μg/ml)                         | 0.263±0.002                                                                 | 0.1982±0.002                                                  |
| AUC∞ (μg/ml/h)                        | 7.542±0.12                                                                  | 44.2780±0.24                                                  |
| MRT∞ (h)                              | 12±1.0                                                                       |                                                               |
| F_rel= (AUC)_{test}/(Dose)_{test} / (AUC)_{std}/ (Dose)_{std} | Bioavailability enhanced by 5.80%                                                  |

Note: Increase in AUC_{∞}; MRT; T_{max}: Decrease in C_{max} in PNs shows better bioavailability than conventional dosage form (All data are measured as mean±SD, n=3)

Table 4: Comparative stability study data for PN7 before and after conducting stability studies

| Parameter (PN7) | Initial values during preparation* | Final values after conducting stability studies for 3 mo (4 ±2 °C)* |
|-----------------|-----------------------------------|---------------------------------------------------------------|
| PS nm           | 159.9±36.1                        | 161.1±16.1                                                   |
| ZP mV           | -33.5±1.54                        | -30.5±1.40                                                   |
| PI              | 0.587±0.16                        | 0.580±0.12                                                   |

*All data are measured as mean±SD, n=3
Stability studies

The comparative stability study data for PN7 before and after conducting stability studies was shown in table 4. The PS nm, ZP mV and PI of PN7 during preparation was found to be 159.9±36.1 nm, -33.5±1.54 mV, 0.587±0.16 and PN7 after performing stability studies i.e. after 3 mo on storing in 4±2°C was found to be 161.1±16.1 nm,-30.5±1.40 mV, 0.580±0.12.

RESULTS AND DISCUSSION

Optimization of polymeric nanoparticle

The 2^3 optimization design table 1 and fig. 1 revealed the outcome of independent variables on dependent variables on Rosuvastatin Calcium PN7s. From the above data, it was concluded that there was a powerful tie-up between particle size and polymer concentration, i.e. the particle size of PN7s was bigger by raising the concentration of polymer. Among all the formulations (PN1-PN8), PN7 formulation showed desired particle size of about 159.9±36.1 nm at low-1 level polymer (5 mg). The minimization of particle size was due to low level of polymer concentration with high level of surfactant (table 1). And also the particle size reduction was resulted due to increase in ultrasonication time, which separated the big particle aggregates into small separated particles. Increase in surfactant concentration in the preparation of PN7s showed a simultaneous increase in the zeta potential with the decrease in particle size, which confirmed the good stability of PN7s in phase, so that the utmost conductivity of the particle, which may lead to enhancement of zeta potential or surface charge potential, leads to good stability of nanoparticles and also keep the particle in motion without sedimentation. Among all formulations (PN1-PN8), PN7 formulation showed the required zeta potential of about-33.5±1.54 mV at high-1 level (1 ml of surfactant concentration). Increase in concentration of the surfactant and homogenization time showed a parallel increase in the ZP in mV and % EE of about 94.20±2.46. The Optimized Rosuvastatin Calcium PN7s (PN7) were analyzed for surface morphology studies by SEM (fig. 2), in which the PN7s were visualized as smooth spherical surfaced particles. By this it was observed that it will lead to improvement of drug loading efficiency and easy diffusion of the drug into physiological barriers due to its spherical, smooth nanometric surface. The Rosuvastatin Calcium PN7s (PN7) formulation showed the maximum %yield and %entrapment efficiency of about 96.80±2.08 and 94.20±2.46%, respectively. From the above-mentioned data, it may also conclude that the drug concentration was distributed uniformly in the PN7s [1-23].

In vitro drug release studies

In vitro drug release studies for Rosuvastatin Calcium PN7s (PN7) formulation showed a better-controlled drug release of 96.54±2.02 % in 24 h compared to the conventional ARVAST tablet 20 mg formulation (fig. 3). The In vitro release kinetics studies of Rosuvastatin Calcium Polymeric Nanoparticles (PN7) were shown in table 2. The Rosuvastatin Calcium release kinetics records for PN7 followed the zero-order release kinetic model in which the regression values (r2) were found to be 0.962 with shows good linearity. Rosuvastatin Calcium loaded PN7s (PN7) followed zero order kinetics, from which the drug was released in a predetermined and controlled manner. It was confirmed as an ultimate model for the discharge of the drug in order to attain the required therapeutic action without toxic effects. Higuchi release kinetic pattern showed r2=0.966, it confirmed diffusion type of drug release. Release exponent (n) value from peappas release kinetic data for PN7 formulation was found to be 0.502 (n = 0.45-0.89). It implied that the drug release from PN7s followed a non-fickian diffusion mechanism i.e. The drug was released from the polymer through polymer relaxation and diffusion [24, 25].

In vivo pharmacokinetic studies

The in vivo pharmacokinetic information is shown in table 3. From the data, it shows that there was a significant difference in 'p' value as<0.05 among the pharmacokinetic parameters of conventional Rosuvastatin Calcium formulation and Polymeric Nanoparticles (PN7) with T_{max} (h) of about 2 h and 6 h; and the maximum concentration of drug (C_{max} μg/ml) of 0.2634 μg/ml and 0.1982 μg/ml. Area Under Curve (AUC_{0-∞} μg/ml/h) was about 7.542 μg/ml/h and 44.2780 μg/ml/h, Mean Residence Time of the drug (MRT_{0-∞} h) was shown as 8 h and 12 h. The in vivo pharmacokinetic data confirms that increase in AUC_{0-∞}, T_{max}, MRT_{0-∞} with reduce in C_{max} in PN7s when compared to ARVAST conventional tablet. The relative bioavailability was calculated by considering conventional formulation as standard. It confirmed that PN7s showed the enhancement of bioavailability of about 5.80 % than conventional dosage form [26, 27].

Stability studies

Short-term stability studies are done for the optimized polymeric nanoparticles (PN7) at 4 ±2°C. The parameters were evaluated at three months’ time interval. From the results of stability studies, it was observed that there was no drastic change in PS, ZP and PI of PN7. From the results (table 4 and fig. 4), it was confirmed that the drug-loaded PN7 were stable at stored temperature [28-30].

CONCLUSION

PN7s show a significant enhancement of bioavailability by minimizing the dose-dependent adverse side effects of Rosuvastatin Calcium. From the above research, it was confirmed that the PN7s shows control drug release pattern and also a potential drug delivery carrier for low soluble and poorly bioavailable drugs to enhance the bioavailability.
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AUTHORS OF CONTRIBUTIONS

We declare that this work was done by the all authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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CONFLICT OF INTERESTS

No conflict of interest is associated with this work.

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