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Original Article

Combination of Ginseng and Curcumin Loaded Polymeric Nanoparticles: A Novel Approach to Check Synergistic Effect for the Topical Treatment of Diabetic Retinopathy

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ABSTRACT

Background: Diabetic Retinopathy (DR) is the worst complication of diabetes which is treated by the invasive methods. The proposed study involves the development of novel combinational therapy for the topical management of diabetic-retinopathy. **Materials and Methods:** Formulation involves the combination of previously investigated curcumin nanoparticles with newly fabricated ginseng nanoparticles. Both drugs were loaded individually in the PLGA 50:50 polymer. The ginseng-PLGA nanoparticles were optimized by using 3^2-factorial design to investigate the impact of process parameter (HPH pressure) and polymer (PLGA concentration) by using size of nanoparticle, PDI and % entrapment as the response. Prepared nanoparticles were investigated for various parameters viz. zeta potential, XRD, DSC, SEM, TEM and *in vitro* drug release. Formulation efficacy was investigated on STZ induced diabetic Wistar Rats. **Results:** The particle size, PDI, and %EE for ginseng nanoparticles were found to be 167.5-350.8 nm, 0.264-0.699, and 69-95.6%, respectively. The batch F8 (HPH pressure 20 kPsi and PLGA 100 mg) with particle size 168.1 nm, PDI 0.264 and 92.3% entrapment efficiency was selected as the optimized batch and further spray dried. Zeta potential of optimized formulation was found to -21.5 mV. Optimized batch showed 78.58±1.54% cumulative drug release at the end of 10 hr. The XRD, DSC, TEM and SEM analysis confirmed the entrapment of drug in polymeric strand. In the lateral stage, the nanoparticles of curcumin and ginseng were investigated on Wistar rats which showed significant control over the VEGF, TNF-α and IL-6 in comparison to treatment of individual ginseng nano-particles. **Conclusion:** The obtained results confirmed the impact of combinational therapy over the diabetic retinopathy.

Keywords: Combinational Treatment, Ginseng Nanoparticles, Curcumin Nanoparticles, VEGF, Interleukins, Diabetic Retinopathy, Ophthalmology, Alternative Medicine.

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INTRODUCTION

The diabetes mellitus is one of the core chronic disorder which affects progressively to all parts of body including ocular system.[1] Impact of increased glucose level is significantly high on the cornea and retina in comparison to rest of the ocular parts.[2] As per latest survey published, the prevalence of DR in Indian population is 16.9%[3] and more than 4.1 million Americans are suffering from retinopathy with 8,99,000 cases of vision threatening.[4] Cascade of DR includes formation of AGEs, inflammation at retinal site, development of TNF-α, increased level of VEGF, development of weak capillaries at retinal site in response to oxidative stress which is associated with rupturing and blood leakage.[5] Presently, DR is managed by vitrectomy, laser treatment or intravenous injections. These methods are invasive with the probability of secondary infection.[6] There is need to develop the formulation which can be administered topically by patient.

Recent studies reveal the role of ginseng in controlling DR. A study showed its potential to control VEGF and TNF-α expression in diabetic rats.[7] Ginseng also showed control over the neovascularization.[8] Administration of ginseng confirmed the reduction in retinal edema developed because of the high levels of VEGF and AGEs.[9] It also has the potential to impede retinal cell apoptosis, which plays a leading role in the early stages of DR. Study performed by Dong C. *et al.* on STZ induced

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diabetic rats showed that ginseng has the potential to control the cascade of DR due to antioxidant property.[10] Furthermore; recent research also observed the capacity of ginseng on the integrity and stability of blood-retinal-barrier along with the ability to control the accumulation of AGEs.[11] Yang H. *et al.* confirmed the potential of ginseng to control the gene expression that accelerates the development of diabetic retinopathy.[12] However, all these investigations were made either on a cell line or after oral or parenteral administration. There is a need to explore ginseng by developing a topical formulation that can be administered in the eye to target the retinal site. Since the retina is present to the posterior segment of eye, deep penetration can be achieved by formulating nano formulations. Therefore; by considering the possible usefulness of ginseng in management of DR, we have prepared the ginseng loaded PLGA nanoparticles and thoroughly investigated by various parameters which proved its suitability for the *in vivo* administration.

In our previous finding we observed the beneficial effect of curcumin in the control of cascade of DR.[13] However; the results were slightly upside in comparison to the normal group. Henceforth; the previously optimized curcumin nanoparticles were further combined with the newly prepared ginseng nanoparticles and investigated pre-clinically to compare the impact of individual and combinational drug therapy.

MATERIALS AND METHODS

Materials

The Ginseng as well as the PLGA 50:50 [poly (D, L-lactide-co-glycolide)] was obtained as the gift sample from the 'The Korean Society of Ginseng, South-Korea and Evonik Pvt. Ltd., India respectively. Rest of all ingredients were of the analytical grade.

Development of Ginseng Nanoparticles

Nanoparticles were prepared by using the precipitation method in which organic phase [PLGA and drug (50 mg) dissolved in dimethyl sulphoxide] was added gradually in aqueous phase [PVA (1%) and tween 80 (0.45%)] in presence of probe sonicator. Further, the dispersion was passed through the high pressure homogenizer operating at different pressure (fixed cycles 10) and checked for the Particle size, Poly-Dispersity Index (PDI) by using Malvern Zeta-sizer ZS 90. Organic solvent was evaporated by overnight magnetic stirring. Obtained dispersion was subjected for cold centrifugation and supernatant was tested for the Entrapment Efficiency (%EE).[6]

Optimization and Evaluation of Ginseng Nanoparticles

For optimization of concentration of PLGA (X1) and pressure of HPH (X2), a 3^2 factorial design was used. Using the particulate size (R1), PDI (R2) and %EE (R3) as the responses, selected independent variables were examined at -1: low, 0: moderate and +1 highest levels (Table 1). The particle size and PDI (<0.3) is connected with the stability, efficacy and compatibility with ocular site. It has been observed that the particle size below 200 nm penetrates deep in the eye and useful to target the posterior segment of the eye (i.e. retina).[6,17-19] The % EE was analysed spectrophotometrically by recording absorbance at 236 nm. Entrapment was calculated by using formula 1:

$$E.E.(\%) = \frac{Total\ amount\ of\ the\ drug - Amount\ of\ the\ free\ drug}{Total\ amount\ of\ the\ drug} \times 100 \quad (1)$$

The gathered information was analyzed by using Design expert software version 13 and suitable batch was selected by the 'desirability search approach'.

Further the selected batch was checked for Drug Loading (%DL) and % yield after the spray drying. Nanoparticles may subject to a series of stability problems such as aggregation, fusion and leakage of encapsulated drugs in to storage the medium. One of the approaches to resolve this kind of problems is the spray drying of the nanoparticles. To perform the spray drying the inlet and outlet temperature of spray dryer (Labultima-LU-222 Advanced) was fixed to 140°C and 90°C respectively with the flow rate of 2 mL/min. The major solvent was water with traces of DMSO remaining even after the overnight stirring. Spray drying further ensure the complete evaporation of used organic solvent to make it more suitable for ocular administration.

The % DL (formula 2) and % yield (formula 3) was obtained as 7.66% and 75% respectively.

$$DL\ (\%) = \frac{Total\ amount\ of\ the\ drug - Amount\ of\ the\ free\ drug}{\text{Weight of spray dried nanoparticles}} \times 100 \quad (2)$$

$$\%\ Yield = \frac{Total\ weight\ of\ spary\ dried\ nanoparticles}{Drug + polymer\ weight + dispersing\ agent} \times 100 \quad (3)$$

Prepared nanoparticles of ginseng were investigated for *in vitro* dissolution study by using dialysis sac which was soaked in dissolution medium (phosphate buffer pH 7.4) for 8 hr. One end of sac was sealed and 1 mL formulation (1 mg/mL) was loaded through the another open end. The remaining end was sealed carefully and suspended in 100 mL dissolution medium in a beaker. The system was placed on the magnetic stirrer at 37±0.50°C and 50 rpm. At time interval of 1 hr samples were withdrawn for 10 hr by maintaining the sink condition. The aliquots were analysed for drug concentration spectrophotometricaly.[15] The obtained data was subjected for mathematical treatment to calculate the drug release kinetics.

Further, for the surface morphology and entrapment of drug the SEM and TEM study was performed. In addition to the size, a smooth surface is essential to increase the ocular residence with minimum sensitization by foreign particles. The entrapment of drug was further confirmed by using XRD and DSC study of drug and ginseng loaded nanoparticles.

Preclinical Evaluation

The effectiveness of prepared formulation and combinational approach was checked by using hyperglycemia induced Wistar rats as per the approved protocol by CPCSEA, New Delhi (MET-IOP-IAEC/Oct.2023/08). The rats of weight 200-250 g were divided in six groups (n=6) as I-vehicle control, II-Diabetes control, III-Vehicle treatment (topical drop of saline water), IV-Formulation treatment-1 (drop of nanoparticles-concentration 5 mg/mL), V-Formulation treatment-2 (drop of nanoparticles-concentration 10 mg/mL), VI-Formulation treatment-3 (drop of nano-dispersion containing 5 mg/mL curcumin and 5 mg/mL ginseng). Hyperglycemia was induced by intraperitoneal injection of STZ (65 mg/kg) in group II-VI, and confirmation of hyperglycemia was made three days later by observing glucose levels exceeding 250 mg/dL. After a week of diabetes, VEGF and interleukins level were checked in group I and II as per the standard procedure. Treatment in group III-VI was initiated after confirmation of significant difference in VEGF and interleukins level in group II in comparison to Group-I. After the four week of treatment the vitreous fluid was evaluated for VEGF, TNF-α and IL-6.[6,15]

RESULTS

In the early part of research, the nine batches of ginseng-PLGA nanoparticles were developed by using the precipitation method. The R1, R2 and R3 were found to be in the range of 167.5-350.8 nm, 0.264-0.699 and 69-95.6 % respectively as shown in Table 1. A summary of statistically examined data is provided in Table 2. Predicted models and terms were considered to be significant as the 'p value <0.05'.

Following polynomial equations were recommended by software;

$$R1= 252.44-75.60\ X1 + 23.70\ X2 \quad (4)$$

From equation 4 following conclusion can be drawn;

a) As the HPH pressure increases there is decrease in particle size because of increased shear stress. Increased shearing results in breakdown of particles in smaller size.

b) As the concentration of polymer increases, the particle size also increases. It is because, as the concentration of PLGA increases, it results in increases in viscosity of organic phase which ultimately reduces the impact of shear stress of high pressure homogenizer.

However; impact of HPH pressure is more significant that the HPH pressure.

$$R2= 0.4690-0.1227\ X1 + 0.0410X2 \quad (5)$$

Equation 5 indicates positive impact of conc. of PLGA and negative impact of HPH pressure on PDI. Therefore; following conclusion can be drawn;

a) As the concentration of PLGA increases PDI increases which is because of increase in thickness of nanoparticles that may leads to uneven surface.

b) As the HPH pressure increases, PDI decreases. The major contributing factor is the shearing force which tries to reduce the unevenness of particles and convert in the uniform shaped and sized particles.

$$R3= 83.43 + 8.32\ X1 + 5.10\ X2 \quad (6)$$

Both the independent variables showed positive impact on the percent entrapment of drug (equation 6), i.e. as the HPH pressure and PLGA concentration increases the entrapment of drug also increases. Increased polymeric concentration is responsible for the availability of more sites for binding and ultimately entrapment of drug. Moreover; increased HPH pressure leads to place drug in the polymeric strands which also increases the entrapment of the drug.

The 3D surface plot can be used to connect the interaction between the independent variables and its influence on the responses (Figure 1). The suitable batch was further selected by 'desirability search method'. Software suggested 100 possible solutions with desirability 1, out of which batch 9 was same as of prepared batch 8. As a result, batch 8 [Particle size 168.1 nm, PDI 0.264 (Figure 3) and 92.3% entrapment] was chosen as the final batch for further investigation (Figure 2).

The zeta potential of optimized batch was measured and found to be -21.5 mV (Figure 3). The obtained results of optimized batch confirmed the nanoparticles are stable and suitable for intended use.

The optimized batch confirmed the drug release of 78.58±1.54% at the end of 10 h (Figure 4A) with the characteristic biphasic drug release pattern. The chosen polymer grade is known for the rapid drug release through the diffusion and erosion mechanism on both surface and bulk side. Furthermore; used polymer is biodegradable and non-toxic for the long term use. The data obtained from drug release study was subjected for mathematical treatment to find out the drug release kinetic profile. The release constant was calculated from the slope of the appropriate plots and the regression coefficient (R^2) was determined. A Hixon-Crowel cube root (R^2= 0.995) was found to be best fitted model in comparison to First order (R^2=0.957), Zero order (R^2=0.988) and Higuchi (R^2=0.963).

The results of SEM and TEM is shown in Figures 4B and C respectively. The SEM analysis confirmed spherical, smooth and fracture less structure of prepared ginseng nanoparticles, whereas; TEM analysis showed the entrapment of drug in the

polymer with size less than 200 nm. Moreover; XRD and DSC study showed the absence of the peaks in the nanoparticle system in comparison to the pure drug, which further confirmed the entrapment of the drug in the polymer (Figures 4D and E).

In vivo Investigations

A group treated with the vehicle showed significant increase in VEGF level and on the other hand marked control on VEGF level was observed with the entire treatment group. Furthermore; dose dependent control on VEGF was also observed for the ginseng administration (Figure 5A). Moreover; the combination of curcumin and ginseng nanoparticles showed synergistic effect on the VEGF level. It downregulated the level of VEGF near to the normal. Additionally; the diabetic retinopathy is also associated with inflammation which leads to the increased level of local cytokines. Henceforth, vitreous fluid was analysed by standard procedure for the concentration of cytokines as TNF- (Genlisa KB2145) and IL-6 (Genlisa KLM1405) to confirm the control on diabetic retinopathy. Vehicle treated group showed significant increase in the TNF- and IL-6 levels. On the other hand, ginning nanoparticles treated group showed dose-dependent control on the inflammation (Figures 5B and C). Moreover; the significant control on the level of the cytokines was observed for the combinational therapy in comparison the individual drug treatment.

DISCUSSION

This study involves the investigation of the combination of previously studied curcumin nanoparticles along with newly fabricated ginseng nanoparticles after the topical instillation. Both the nanoparticles were prepared by using biodegradable and biocompatible PLGA 50:50 polymers. In the initial part of study, the nanoparticles of ginseng were prepared by using the precipitation method. The optimization was performed by using 3^2 factorial design to assess the effect HPH pressure and PLGA concentration on the particulate size, PDI and drug entrapment. Software suggested the polynomial equations to correlates the impact of independent variables over the responses. From eq. 4 and 5 it can be concluded that as the HPH pressure increases the particle size and PDI decreases because of increased shear stress, whereas; with increasing concentration of PLGA, both responses increase which might be due to increased viscosity of organic phase along with accumulation of polymer in surrounding to the drug.[14] Increased HPH pressure as well as PLGA concentration leads to increase the entrapment of drug[15,16] as shown in equation 6. The batch 8 with HPH pressure 20 kPsi and 100 mg PLGA concentration having particle size 168.1 nm, PDI 0.264 (Figure 2) and 92.3% entrapment was chosen by using the desirability search approach. Particle size <200 nm, PDI <3 and possible higher entrapment of drug were the selection criteria. The optimize batch was spray dried and tested for the zeta potential which was found to be -21.5 mV. The particle size and zeta potential both are correlated with the stability as well as the cellular uptake. Particle

Table 1: Optimization of nanoparticles with Coded levels and translation in actual units along with responses.

Batch	Coded level of variables		Particle Size nm Y1	PDI Y2	%EE Y3
	HPH Pressure kPsi X1	PLGA Mg X2			
1	10 (-1)	50 (-1)	307.1	0.553	69
2	10 (-1)	100 (0)	336.9	0.581	74
3	10 (-1)	150 (+1)	350.8	0.699	80
4	15 (0)	50 (-1)	212.3	0.388	80
5	15 (0)	100 (0)	251	0.382	86
6	15 (0)	150 (+1)	272.7	0.521	89
7	20 (+1)	50 (-1)	167.5	0.433	85
8	20 (+1)	100 (0)	168.1	0.264	92.3
9	20 (+1)	150 (+1)	205.6	0.4	95.6

Table 2: Summary of results of regression analysis and ANOVA for measured responses.

Response	Model	F value	*p* value	R^2	SS	DF	MS	Model Significance
R1	Linear	166.31	<0.0001	0.9823	37662,3	2	18131.15	Significant
R2	Linear	8.13	0.0196	0.8304	0.1004	2	0.0502	Significant
R3	Linear	103.84	<0.0001	0.9719	571.06	2	285.53	Significant

SS: Sum of Square; DF: Degree of freedom; MS: mean square.

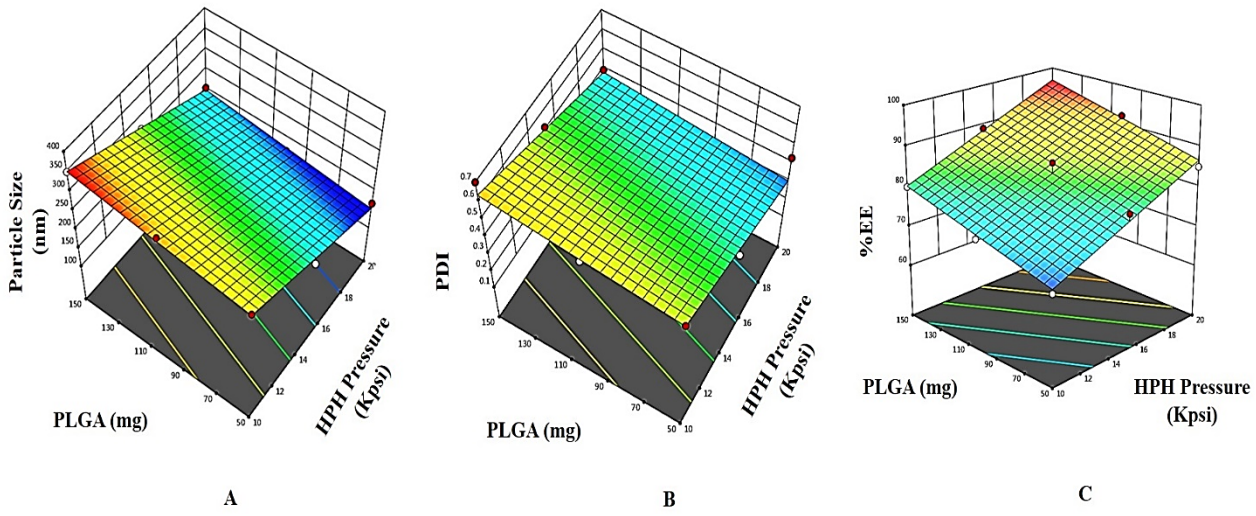

Figure 1: Three Dimensional (3D) response surface plot for response A) Particle Size B) PDI and C) %EE.

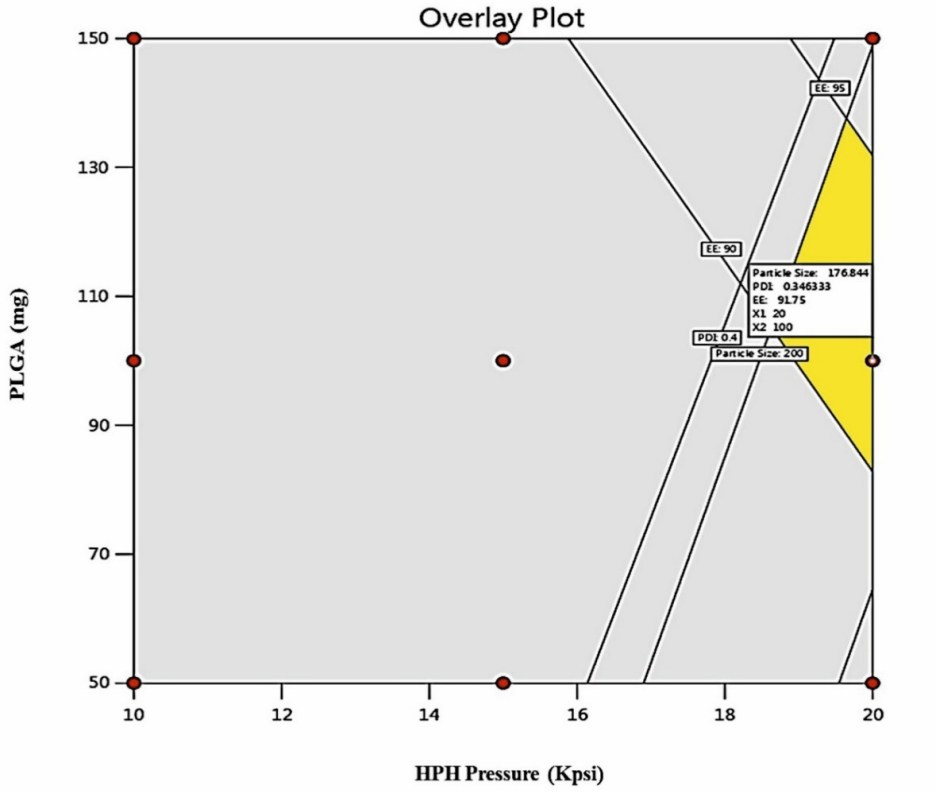

Figure 2: Desirability plot.

size below 200 nm ensures the development of Brownian motion which maintain the prepared colloidal particle in the dispersion state. Furthermore; smaller particle size also ensures the rapid movement of prepared polymeric nanoparticles through the different barriers of the ocular system. Additionally; small particle size (<200 nm) also ensures the uptake of nanoparticles by both corneal as well as the non-corneal mechanism.[17-19] The zeta potential above or equal to±20 mV is the prerequisite for the nanoparticles which is the responsible force for the repulsion of nanoparticles when they colloids with each other. It also helps the maintain the stability of particles. As the zeta potential was found to be -21.5 mV it clearly indicates the stability of prepared nano particles. The *in vitro* drug release study showed the characteristic biphasic drug release pattern which involves initial burst release with controlled release behaviour in lateral stage. The PLGA 50:50 is known grade for relatively rapid drug release due to same proportion of lactic and glycolic acid which equalizes the hydrophilic and lipophilic characteristics in the polymer. This

nature further helps for movement of nanoparticles from the sandwich of lipoidal and hydrophilic barriers before the retina.[20,21] The drug release was best explained by Hixon-Crowel cube root model with highest R^2 value which indicates drug release takes place change in the surface area and size of particle through the dissolution process. The SEM and TEM analysis showed the spherical shape of prepared nanoparticles with smooth surface. This morphology is essential for non-scratching effect over the cornea after instillation in eye cavity which otherwise may activates the ocular defence mechanism with high tear secretion that shorten the retention time. The TEM results also showed the entrapment of the drug with particle size below 200 nm which make prepared nanoparticles suitable for ocular administration. The entrapment of drug was further confirmed by comparative XRD and DSC study. All these results showed the stability and suitability of prepared ginseng nanoparticles for further *in vivo* testing. In lateral stage, the efficacy of prepared ginseng nanoparticles was studied individually as well as in combination of the previously optimized and evaluated curcumin nanoparticles on the diabetic Wistar rats. Prepared ginseng nanoparticles showed dose dependent downregulation VEGF which confirms the involvement of ginseng in the management of DR after the topical instillation.[6] This impact confirms the movement of prepared nanoparticles to the back of the eye and further drug release. Furthermore; the ginseng nanoparticles also showed significant control over the inflammation as tested through the

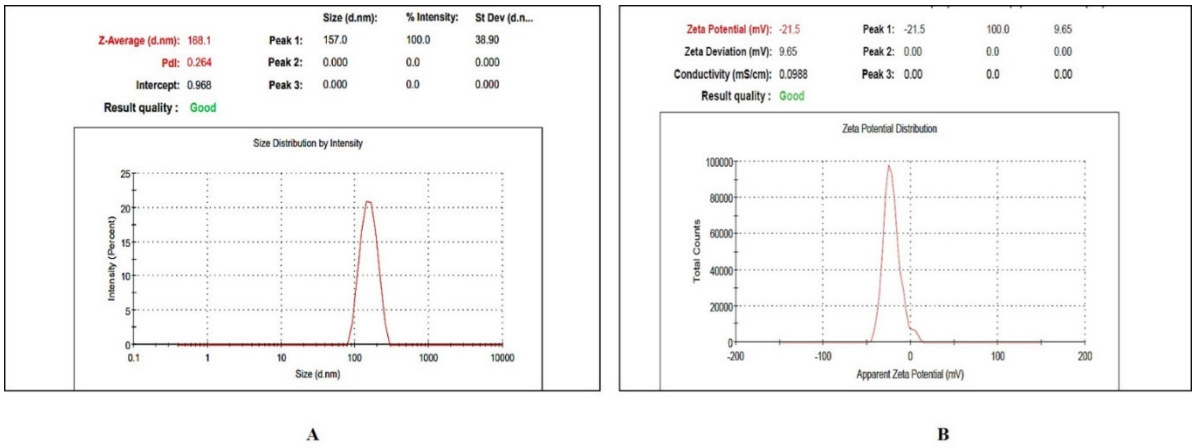

Figure 3: Characterization of optimized batch A) Particle size, PDI and B) Zeta potential.

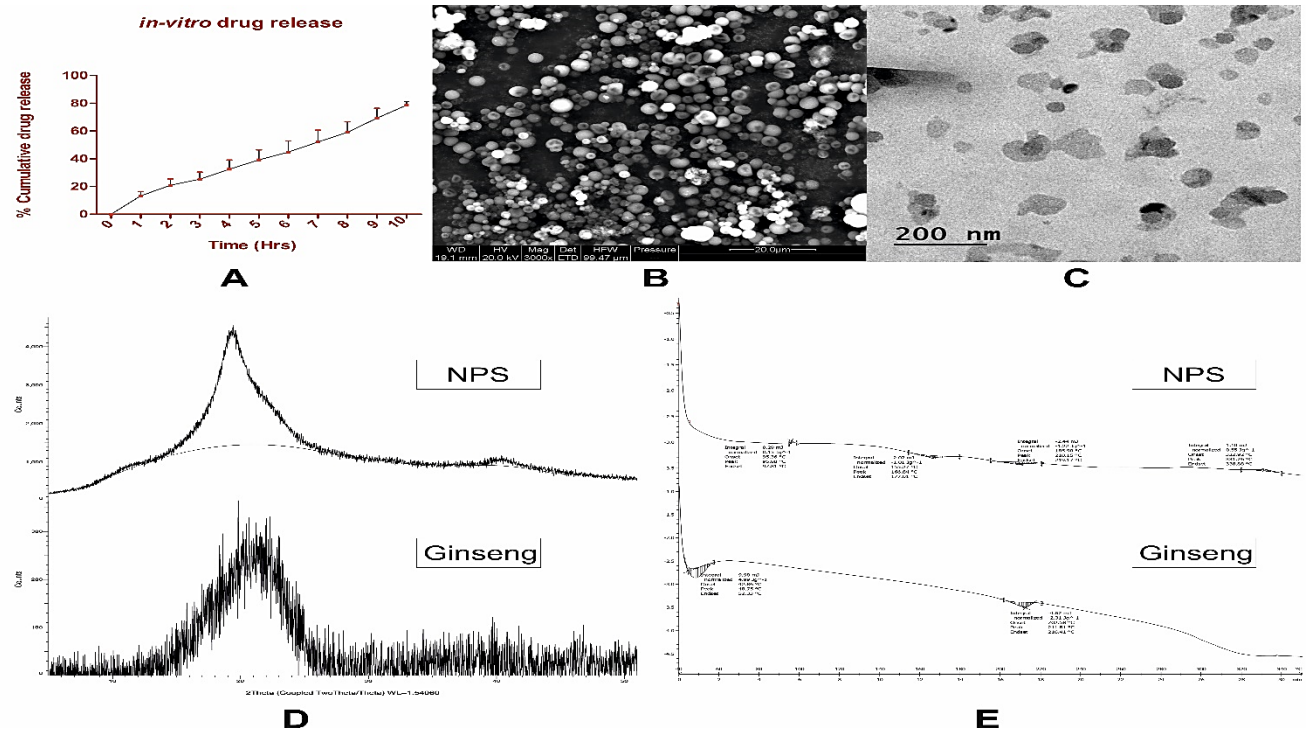

Figure 4: A) *In vitro* drug release, B) SEM analysis, C) TEM analysis, D) Comparative XRD diffractogram and E) Comparative DSC thermogram of drug and nanoparticles.

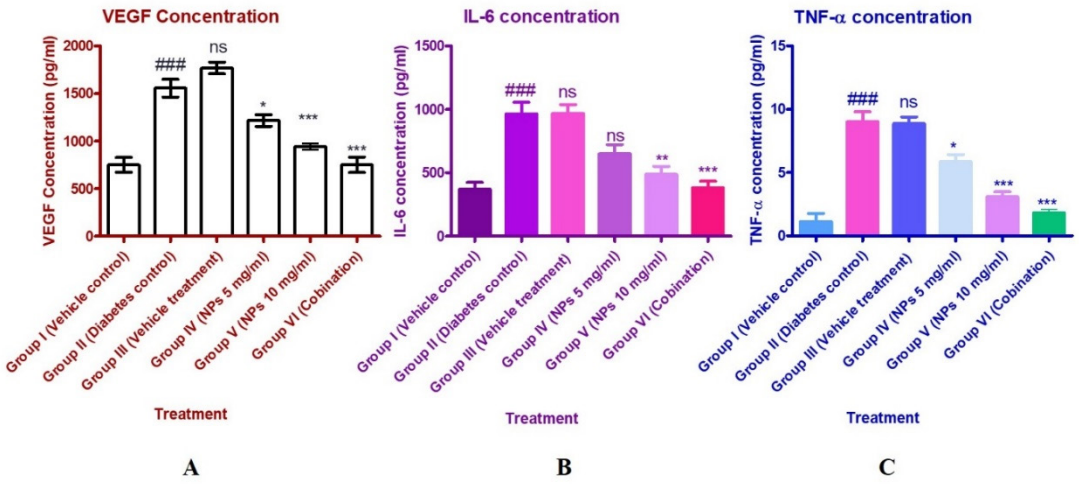

Figure 5: Effect of formulation on the Wistar Rats A) the VEGF, B) TNF- and C) IL-6 levels. Note (adopted statistical method): Data expressed as Mean±Sem and analysed by One-way Analysis of Variance followed by Bonferroni's multiple comparison post-test. ###p<0.001 as compared to normal group and ***p<0.001, **p<0.001 and *p<0.05 as compared to diabetes.

TNF- and IL-6 levels which further supports the involvement of ginseng in the control of DR.[22,23] However; the combination of ginseng and curcumin showed comparatively better control over the VEGF, TNF- and IL-6 levels which are almost equal to the normal group. Obtained results are at the low concentration of both drug which further confirms the synergistic effect of prepared combination.

CONCLUSION

The effectiveness of combinational therapy (curcumin-PLGA and ginseng-PLGA nanoparticles) in the treatment of diabetic retinopathy is demonstrated by the proposed research. Till date the involvement of ginseng in DR is shown through the cell line study and after oral or Parenteral administration. Our findings are on Wistar Rats which may act as the further stronger support for the possible involvement of Ginseng for cure of retinopathy. Proposed formulation can be administered topically which will be free from the invasive and painful process. Moreover; we also observed the synergistic effect through the combination of curcumin and ginseng nanoparticles which opens the new area for further research in context with the topical management of diabetic retinopathy. However; all these findings are preclinical based which need further clinical investigation. Better correlation can be obtained in the future with simultaneous oral supplements containing antioxidants to boost the effect.

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ABBREVIATIONS

DR: Diabetic retinopathy; **PLGA:** Poly (lactic-co-glycolic acid); **HPH:** High pressure homogenizer; **PVA:** Poly-vinyl-alcohol; **XRD:** X-ray Diffraction; **DSC:** Differential Scanning Calorimetry; **SEM:** Scanning Electron Microscope; **TEM:** Transmission Electron Microscopy; **PDI:** Polydispersity index; **%EE:** percentage entrapment efficiency; **STZ:** Streptozotocin; **VEGF:** Vascular Endothelial Growth Factor; **TNF:** Tumor Necrosis Factor; **IL:** Interleukin.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

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AUTHORS CONTRIBUTIONS

Dr. Umesh Laddha: conceptualization, methodology, analysis of data, writing of original paper; Dr. Kailas Moravkar and Dr. Sanjay J. Kshirsagar: supervision; Dr. Yatin U. Gadkari and Mr. Sachin Gaikwad: methodology and writing of original paper; Dr. Neelam Dashputre: Preclinical testing.

ETHICAL STATEMENT

The study involves the preclinical investigation on Wistar rats as per approved protocol by CPCSEA, New Delhi (MET-IOP-IAEC/Oct.2023/08).

SUMMARY

Nanoparticles of ginseng was prepared by using PLGA 50:50 polymer.

Optimization was carried out by using 3^2-factorial design. The HPH pressure and PLGA concentration was selected as the independent variables and the Particle size, PDI and % entrapment were selected as the response. The particle size, PDI, and %EE for were found to be 167.5-350.8 nm, 0.264-0.699, and 69-95.6%, respectively. The batch F8 (HPH pressure 20 kPsi and PLGA 100 mg) with particle size 168.1 nm, PDI 0.264 and 92.3% entrapment efficiency was selected as the optimized batch and further spray dried.

Zeta potential of optimized formulation was found to -21.5 mV.

Optimized batch showed 78.58±1.54% cumulative drug release at the end of 10 hr with Hixon-Crowel cube root model for drug release kinetics.

The XRD, DSC, FTIR, TEM analysis confirmed the entrapment of drug in polymeric strand. SEM analysis showed the presence of spherical particles which are free from any fractures which make prepared nanoparticles suitable for ocular administration.

In vivo study on Wistar rats showed the dose dependent potential of prepared nanoparticles to control the level of VEGF, TNF-α and IL-6 which plays crucial role in the progress of diabetic retinopathy. The combination of curcumin and ginseng nanoparticles showed synergistic control over the VEGF, TNF- and IL-6 and results are comparative to the normal group.

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