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PREPARATION, CHARACTERIZATION AND EVALUATION OF RESVERATROL-LOADED PEGYLATED PLGA NANOPARTICLES

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Keywords:

Resveratrol, Polyethylene glycol, PLGA, Nanoparticles, Cytotoxicity

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ABSTRACT: This study focuses on preparing and evaluating polymeric nanoparticles made of pegylated PLGA. In this study, both double-emulsion solvent evaporation and single-emulsion solvent evaporation were employed to formulate the pegylated PLGA nanoparticles with PVA as the surfactant. For the encapsulation of the hydrophobic drug Resveratrol, formulations were successfully prepared and tested for their particle size, polydispersity index, zeta potential, drug loading and entrapment efficiency. Scanning electron microscopy was used to observe the morphology and surface characteristics of the nanoparticles. The results demonstrated successful fabrication of the Resveratrol loaded pegylated PLGA nanoparticles. PVA was demonstrated in the present study to be a promising surfactant for the encapsulation and delivery of poorly water-soluble compounds as pegylated PLGA nanoparticles with the desired particle size, morphology and drug loading. PLGA nanoparticles encapsulated with Resveratrol had been successfully used to deliver the drug to the target site by pegylated PLGA nanoparticles.

INTRODUCTION: Nanosized polymeric particles have emerged as a pragmatic method in the formulation of hydrophobic drugs. They are characterized by rapid dissolution rates, which enhance bioavailability after oral administration. Due to their simplicity and advantages over other strategies, they have proven to be highly effective in addressing the problems associated with poorly water-soluble and poorly lipid-soluble drugs. A suitable method and a suitable stabilizer are used to prepare colloidal dispersions of nanosized drug particles.

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For the preparation of nanoparticles, Resveratrol was selected as a model drug. The effects of Resveratrol on cancer are numerous [1] as there is an antiproliferative effect of Resveratrol on prostate and breast cancer cell lines [2, 3]. In breast cancer models, Resveratrol suppresses the expression of cell cycle regulatory proteins such as cyclin D1, E and insulin-like growth factor ((IGF-1) 4-7. Its low solubility and stability limit of its potential activity, making it poorly bioavailable and susceptible to metabolism.

Our literature review found few studies exploring how to enhance Resveratrol's effectiveness and overcome its related problems. It is indeed a challenge to target natural bioactive specifically [8-12]. The present research was performed to examine how an amphiphilic polymeric conjugate could be used to create and evaluate nanoformulations that are effective at delivering the poorly soluble model

drug Resveratrol. We are investigating the feasibility of synthesizing nanoparticles using pegylated PLGA conjugates to enhance wetting characteristics and decrease nanoparticle agglomeration while evaluating their drug loading, entrapment, polydispersity index, zeta potential and surface morphology characteristics. To overcome the related issues and increase the thrust of drugs in breast tumours, the current study developed a targeted delivery system for Resveratrol.

The presence of Resveratrol in the food chain, as a dominant bioactive component is unlikely to cause adverse or untoward effects. As a result of its enormous safety margins, it can provide additional preventive and curative benefits.

It uses PLGA and polyethylene glycol (PEG), which are further conjugated to develop a pioneering system for delivering Resveratrol [13-17]. Resveratrol could be delivered to tumour cells via intravenous injection in a sustained manner and protected against rapid degradation.

MATERIALS AND METHODS: PEG and PLGA were purchased from Sigma Aldrich. Alpha Remedies, Ambala provided Resveratrol as a gift sample. Other drugs & chemicals were procured from reputable vendors. Analytical grade chemicals were used for all other experiments.

Drug Excipient Compatibility Studies: There is a possibility that the drug may be degraded as a result of the drug-excipient interaction. In order to produce a stable and effective dosage form, the excipients must be compatible with each other. FTIR spectroscopy was used to investigate possible drug interactions.

Fourier Transform Infrared (FTIR) Spectroscopy: By using Fourier transform infrared (FTIR) spectroscopy (Bruker instrument, Germany), FTIR spectra were obtained for a physical mixture of pure drug with excipients and the lyophilized formulation with the drug from wavelength of 4000 cm^{-1} to 400 cm^{-1}. Interactions were observed in the FTIR spectra.

Preparation of Pegylated PLGA Conjugate: Pegylated PLGA conjugates were successfully synthesized and characterized in the laboratory [18]. FTIR and NMR spectroscopy have been used extensively in laboratory to analyze and characterize the conjugate.

Preparation of Nanoparticles by Double Emulsion Solvent Evaporation (DESE) using PVA as Stabilizer: PVA was used as a surfactant in the DESE method to prepare Resveratrol-loaded nanoparticles from pegylated PLGA polymer and designated as S1. In 2.5 ml of dichloromethane, 10 mg of Resveratrol was dissolved and allowed to solubilize. Approximately 20 mg of polymers (pegylated PLGA) were dissolved in a drug-dichloromethane solution after 20-30 minutes (drug: polymer ratio of 1:2). In order to prepare the first primary emulsion, 2.5 ml of 1.5 % w/v PVA was added dropwise and homogenized at high speed 3,000 rpm for 20-30 minutes until the emulsion became rich and creamy. Using the creamy foam consistency of the primary emulsion as a guide, 25 ml of 0.5 % w/v PVA was homogenized at 18,000 rpm for 20-30 minutes to form the secondary emulsion. A magnetic stirrer was used overnight to evaporate the organic solvent from the secondary emulsion and after it was sonicated for 45 minutes. The double emulsion was centrifuged at 5,000 rpm for 5 minutes to discard the large particles formed. Afterwards, the supernatant was centrifuged for 30 minutes at 7,000 rpm to obtain the nanoparticles, which were then washed three times with distilled water to remove the surfactant and finally freeze-dried. The same concentrations of PVA were used in both primary and secondary emulsions of formulation S2 based on pegylated PLGA. The volume of PVA increased to 5 ml in the primary emulsion and 50 ml in the secondary emulsion [19, 20].

Preparation of Nanoparticles by Single Emulsion Solvent Evaporation (SESE) using PVA as Stabilizer: In 2.5 ml of dichloromethane, 10 mg of Resveratrol was dissolved. An addition of 20 mg polymer (pegylated PLGA) was made to the drug: polymer ratio of 1:2. To form an emulsion, 50 ml of2.5 % w/v PVA was added dropwise to the resulting drug-polymer solution and homogenized at 15000 rpm for 10-15 minutes. A creamy emulsion is formed. For the removal of the organic solvent dichloromethane, the resulting solution was sonicated for 45 minutes, followed by gentle magnetic stirring for 12-14 hours.

After centrifugation at 15000 rpm for 30 minutes, the nanoparticles were washed repeatedly three times with distilled water to remove the surfactant, then freeze-dried. S3 is the formulation designation. Formulation S4 was prepared by using 1.5 % w/v of 50 ml of PVA[19, 20].

Characterization of Pegylated PLGA Nanoparticles:

Percentage Yield of Nanoparticles: This formula calculates the percentage yield of the formulations after nanoparticles have been prepared by both DESE and SESE methods [21, 22]:

Percentage Yield = (Weight of nanoparticles obtained) / (Weight of drug and polymer used for nanoparticles preparation) x 100

Drug Loading and Entrapment Efficiency Determination: Two grams of Resveratrol nanoparticles were accurately weighed and put into a centrifuge tube with two mL of dichloromethane to determine drug loading and entrapment efficiency. A shaker was used to shake it continuously for 3–4 hours at 37°C. A centrifuge was used to separate the dispersed phase from the continuous phase. A UV- spectrophotometric measurement at 306 nm was then conducted on the supernatant to determine the amount of drug released. Here are the equations used to calculate drug loading and entrapment efficiency percentages [21-23]:

Drug loading efficiency (%) = (Amount of drug present in nanoparticles) / (Amount of drug loaded nanoparticles) x 100

Entrapment efficiency (%) = (Amount of drug present in nanoparticles) / (Intial amount of drug added) x100

Particle Size Analysis: The particles and the distributions of the sizes of the nanoparticles were measured using an instrument called the Malvern Nano ZS90, which is equipped with a solid-state laser and uses dynamic light scattering (DLS). Before measuring, required amount of dried nanoparticles from each formulation were suspended in double distilled water and sonicated. After the homogeneous suspension was formed, the average hydrodynamic particle size, size distribution and polydispersity index were determined.

Zeta Potential Measurement (ZP): A calculated amount of dried nanoparticles from each formulation were sonicated for a suitable period before measuring their zeta potential with the Malvern NANO ZS90. The ZP characterizes particle surface charge and provides long-term stability information.

Scanning Electron Microscopy (SEM): A scanning electron microscope (Hitachi SEM-S-3600N) was used to examine the shape and surface morphology of the nanoparticles. A suitable sample of nanoparticles was mounted on metal stubs using double-sided adhesive carbon tape and a razor blade. Gold was sputter-coated onto the samples for secondary electron emissive SEM and morphology was observed under argon.

***In-vitro* Drug Release Study of the Nanoparticles:** Several research reports have shown that nanoparticle delivery systems also require extra or more work before a suitable (dissolution) method can be recommended, as mentioned in many of these studies.

Dissolution or *in-vitro* release studies are important in drug product development, as recommended by the CDER's nanotechnology risk assessment working group. A sample and separate method, a continuous flow method and a dialysis membrane method are suited for the *in-vitro* release studies of nanoparticles or nanosized dosage forms. Using a sample and a separate method, we conducted an *in-vitro* release study of the formulated polymeric nanoparticles. To dissolve and separate the release drug from the nanoparticles, magnetic shaking and orbital shaking were used [24, 25].

Analytical Method: Using centrifuged tubes containing 2mg of nanoparticles, phosphate buffer pH 7.4 was used to dissolve the nanoparticles. The samples were incubated at 37°C and shaken regularly at 120 rotations/minute using an orbital shaker. At scheduled intervals, 0.5 ml of the supernatant was taken and tested for drug release at 306 nm using UV-visible spectrophotometry and withdrawal volume is replaced by buffer of same pH. The experiments were performed with three replicates with same conditions to meet the statistical requirements [26-28].

Cytotoxicity Evaluation *via* MTT Assay: As described here, MTT assay was used to determine

the cytotoxicity of NPs on breast cancer cells (MCF7) [29-31].

RESULTS AND DISCUSSION:

Drug-excipient Compatibility Studies: By comparing the FTIR spectrum of pegylated PLGA, Resveratrol and PVA with that of a physical mixture of pegylated PLGA-Resveratrol-PVA, it is evident there is no incompatibility between the excipients, suggesting its perfect stability.

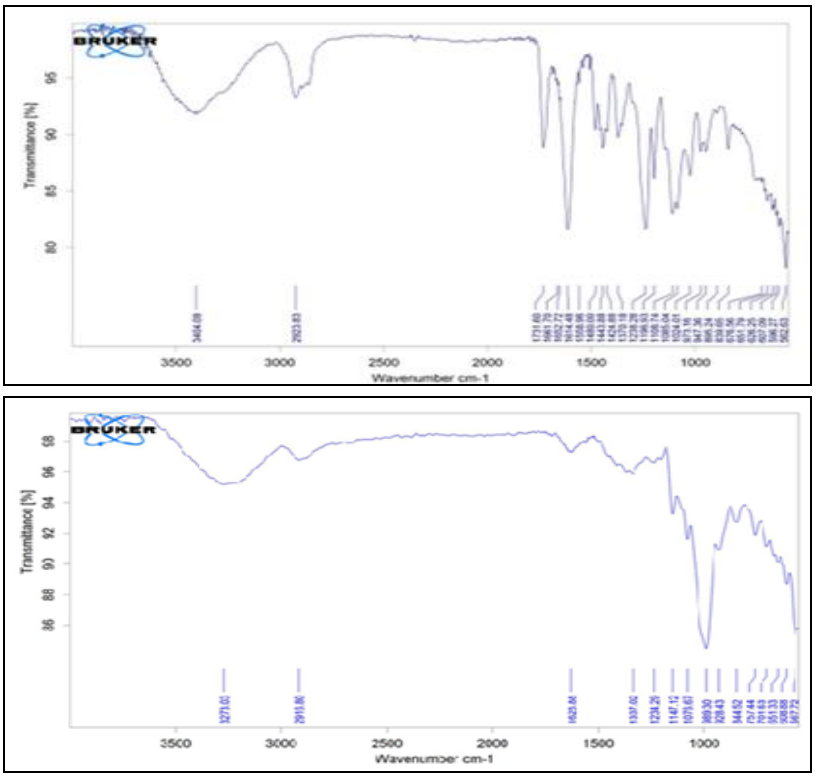

FIG. 1: FTIR SPECTRUM OF (A) PVA AND (B) RESVERATROL

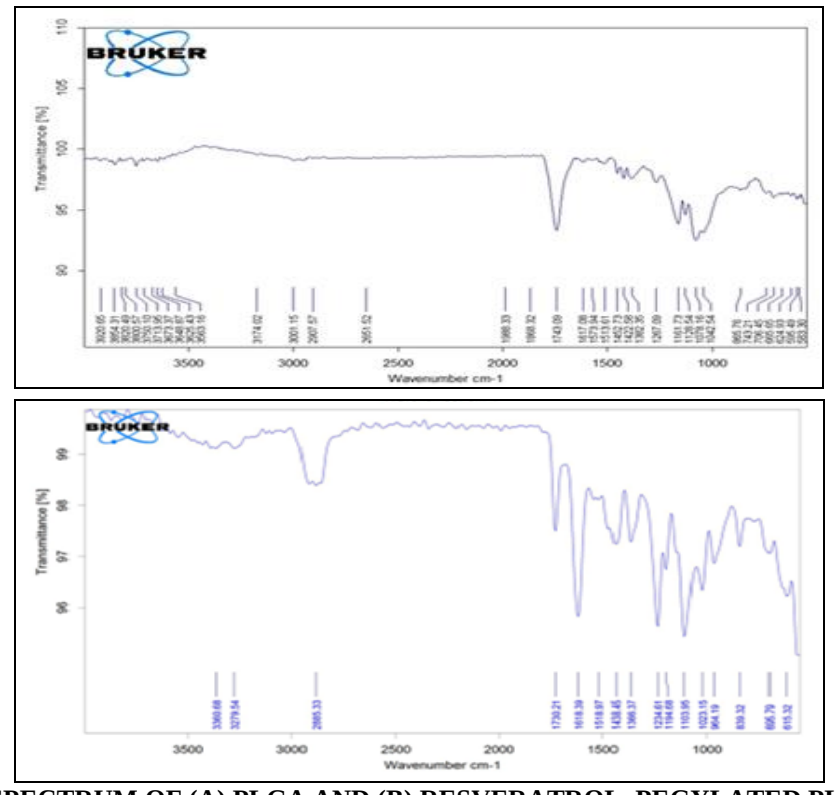

FIG. 2: FTIR SPECTRUM OF (A) PLGA AND (B) RESVERATROL, PEGYLATED PLGA AND PVA

Preparation of Nanoparticles: Table 1 shows the formulation of NPs containing resveratrol using both the double emulsion solvent evaporation (DESE) and single emulsion solvent evaporation (SESE) methods. It is possible to obtain formulations with the desired size, encapsulation and surface properties by either of the methods. In emulsion technique, it is important to complete emulsification of both organic and aqueous phases. There are different stabilizers used in literature, but PVA is the most common and most suitable.

TABLE 1: COMPOSITION OF NANOPARTICLES S1-S4

Formulation code	Resveratrol (mg)	Polymer Used	Amount of Polymer (mg)	Method used	Stabilizer PVA (%w/v) & Volume (ml)	
					Primary	Secondary
S1	10	Pegylated PLGA 85:15	20	DESE	1.5& 2.5	0.5 &25
S2	10	Pegylated PLGA 85:15	20	DESE	1.5& 5	0.5 &50
S3	10	Pegylated PLGA 85:15	20	SESE	2.5&50	---
S4	10	Pegylated PLGA 85:15	20	SESE	1.5&50	---

As can be seen in **Table 2**, both techniques yielded sufficient particles, which indicates a better way to formulate them.

TABLE 2: PERCENTAGE YIELD OF THE NANOPARTICLES

Formulation Code	Yield (%)
S1	74.32
S2	73.56
S3	72.78
S4	73.87

Characterization of Nanoparticles: SEM images revealed smooth surface NPs **Fig. 3.** As shown in **Table 3**, the particles loaded with Resveratrol were nano sized and homogeneously distributed based on the polydispersity index. A zeta potential (ZP) analysis was performed on nanoparticles loaded with Resveratrol to determine their surface charge.

A nanoparticle's zeta potential can also affect its biodistribution and pharmacokinetics. The reticuloendothelial system is more likely to absorb negatively charged nanoemulsions than neutral or positively charged nanoemulsions.

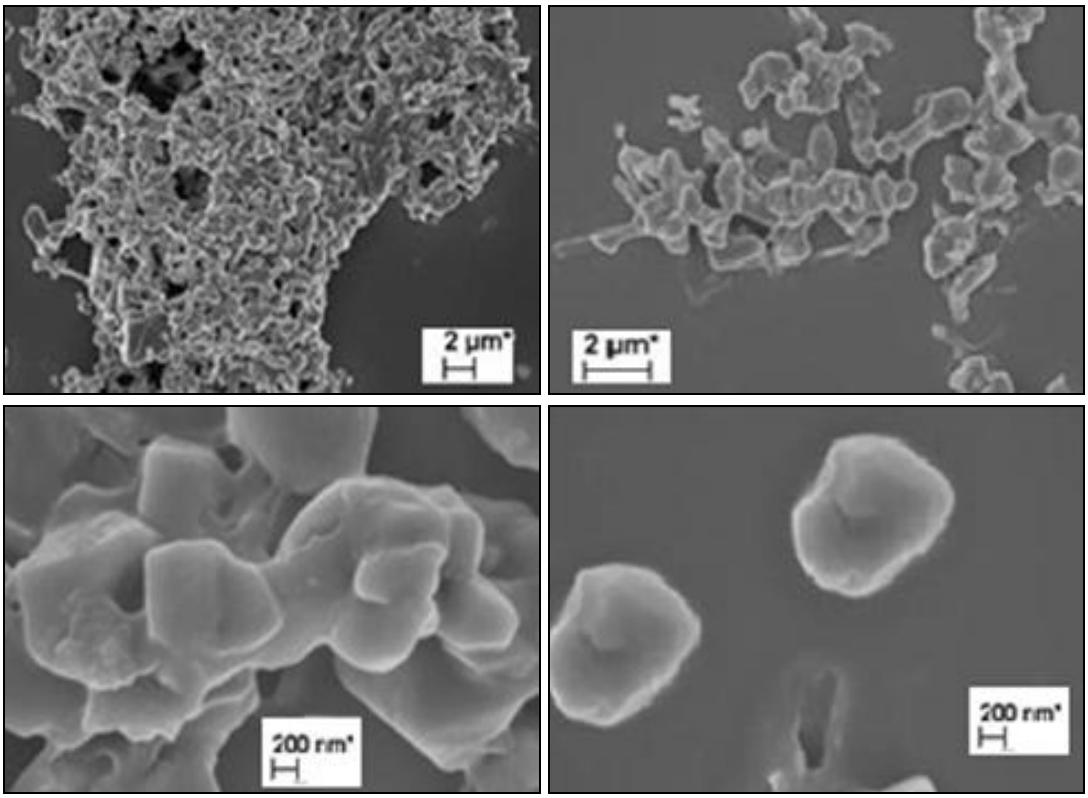

FIG. 3: SEM IMAGES OF PREPARED NANOPARTICLES

TABLE 3: CHARACTERISTICS OF RESVERATROL-LOADED POLYMERIC NANOPARTICLES USING PVAAS SURFACTANT

Formulation code	Particle size (nm)	Polydispersity index (PDI)	Zeta potential (mV)	Drug loading (%)	Entrapment efficiency (%)
				(Mean ± SD)*	
S1	156.0	0.442	-24.6	35.82±0.17	63.45±0.19
S2	230.0	0.421	-29.3	36.44± 0.46	65.86±0.17
S3	139.0	0.421	-32.9	36.06±0.16	66.44±0.16
S4	199.9	0.393	-36.4	37.14±0.17	69.35±0.25

Nanoparticles have a zeta potential or surface charge, which determines the loading efficiency and rate of desorption of drugs in nanoparticles, as well as the types of binding between drugs and nanoparticles. This can also be used to determine if active ingredients/drugs are encapsulated at the centre or adsorb on the surface of nanoparticles. Furthermore, a number of studies have shown that negatively charged nanoparticles clear the bloodstream faster from the bloodstream than positively charged nanoparticles after intravenous administration and remain in the bloodstream for longer periods of time than positively charged nanoparticles. Studies suggest that nanoparticles with negative zeta potentials or cationic charges have increased cytotoxicity. The reason for this may be due to the fact that nanoparticles interact more readily with oppositely charged cell membranes, causing a destabilizing and destructive effect on the membranes as a result [32-35]. The ZP values of all the formulations also indicated the stability of polymeric nanoparticles. Hence, it could be concluded that nanoparticles of pegylated PLGA prepared using PVA as surfacting agent could be a successful delivery system for encapsulating hydrophobic drugs like Resveratrol.

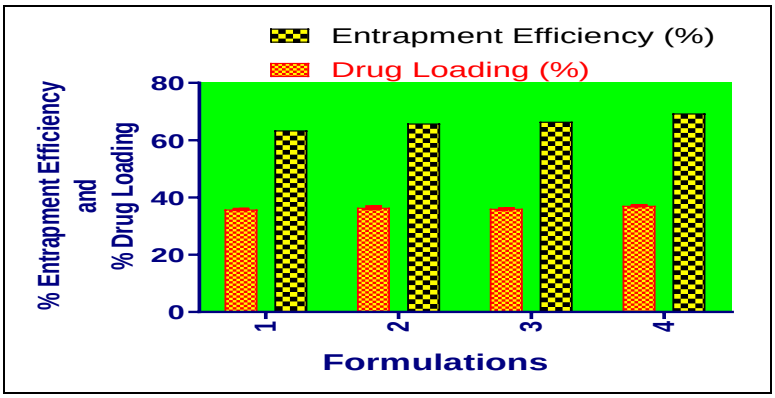

FIG. 4: ENTRAPMENT EFFICIENCY AND DRUG LOADING OF FORMULATIONS S1-S4

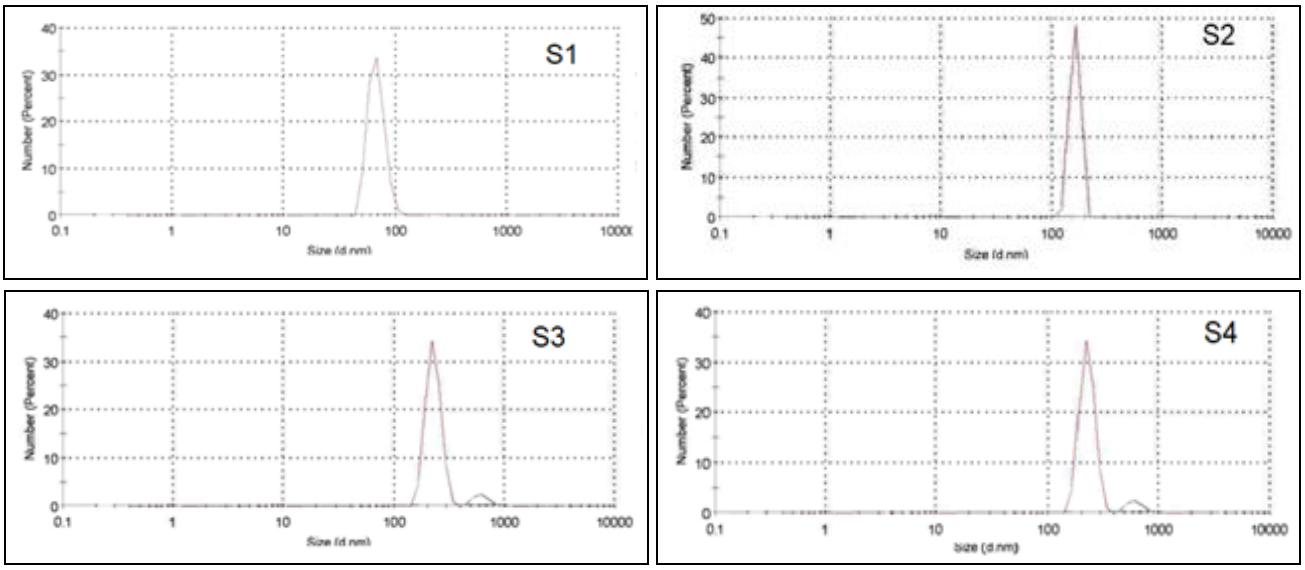

FIG. 5: PARTICLE SIZE DISTRIBUTION CURVE OF S1, S2, S3 AND S4

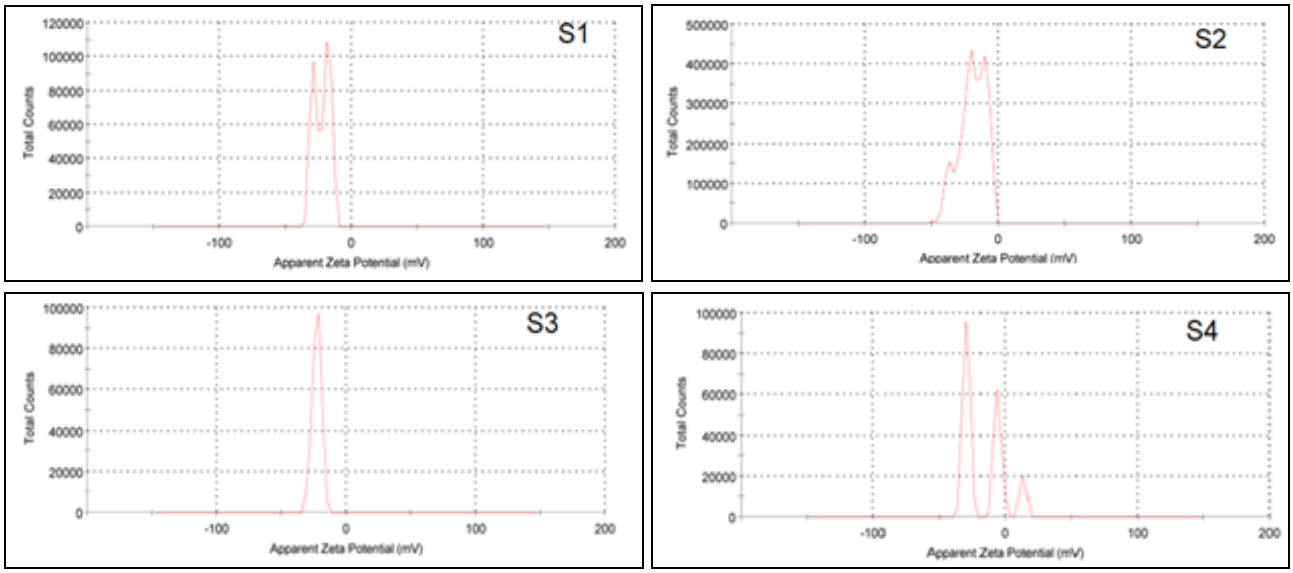

FIG. 6: ZETA POTENTIAL OF S1, S2, S3 AND S4

***In-vitro* Drug Release from Resveratrol Loaded Polymeric Nanoparticles:** The release studies were carried out for selected Resveratrol loaded polymeric nanoparticles (S1-S4) in phosphate buffer (pH 7.4) by orbital shaker method. 2mg of the sample in 2ml of phosphate buffer pH 7.4 in centrifuged tube were incubated at 37°C in an orbital shaker and were shaken regularly at 90 rpm. It was centrifuged at 10000 rpm for 20 minutes and 0.5 ml of supernatant was sampled and analyzed for drug release. The cumulative percentage drugs released were calculated and are presented in **Table 4.** From the result of 168 hours of drug release it was observed that the formulation (S3) showed 92.11% of cumulative percentage drug release which is higher than other formulations.

TABLE 4: *IN-VITRO* DRUG RELEASE DATA OF FORMULATIONS S1-S4

Time (hr)	Cumulative percentage drug release (Mean ± SD) *			
	S1	S2	S3	S4
0	0	0	0	0
1	13.82±0.09	15.36±0.14	16.92±0.11	12.29±0.19
3	19.82±0.19	18.38±0.11	19.96±0.09	18.38±0.09
6	23.72±0.16	24.37±0.11	26.91±0.14	23.39±0.06
9	33.14±0.05	30.89±0.15	34.98±0.17	32.35±0.08
12	40.05±0.16	41.41±0.09	43.39±0.18	37.98±0.13
24	50.69±0.10	53.74±0.09	55.95±0.17	53.46±0.08
36	53.62±0.14	56.24±0.11	57.48±0.18	55.18±0.14
48	58.34±0.19	59.14±0.16	60.42±0.12	58.74±0.09
72	63.10±0.12	65.22±0.11	66.99±0.09	65.89±0.11
96	66.17±0.07	68.33±0.08	69.71±0.13	68.88±0.09
120	68.82±0.10	71.11±0.09	76.28±0.15	73.23±0.17
144	72.72±0.13	81.11±0.19	84.42±0.18	78.23±0.16
168	84.22±0.12	85.67±0.16	90.22±0.12	83.75±0.18

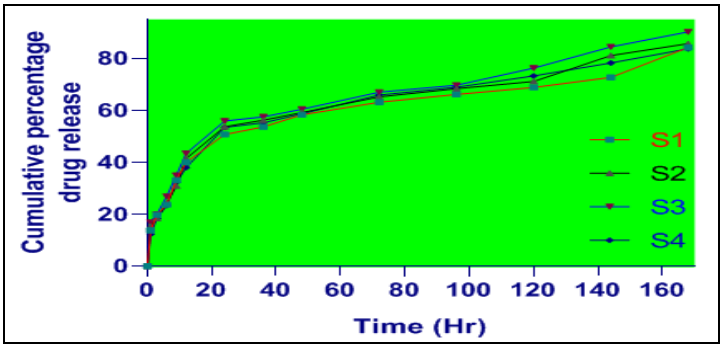

FIG. 7: *IN-VITRO* RELEASE PROFILE OF FORMULATIONS S1-S4 IN OPTIMIZED CONDITION

Cytotoxicity *via* MTT Assay: In MCF7 cells, MTT cytotoxicity assays were performed on all nanoparticles in order to check their cytotoxicity, with a blank nanoparticle serving as a control. Pegylated PLGA and PLGA NPs exhibited a greater cytotoxicity than the free drug. Thus, free Resveratrol at 2.5 M concentrations was found to possess 66.59 % cell viability, while PLGA NPs and Pegylated PLGA NPs recorded 26.84 % and 42.19 %, respectively **Fig. 8**. In the study of several batches of blank nanoparticles, it was evident that there was no cytotoxicity induction on MCF7 cells based on the results of treating several batches of these blank nanoparticles.

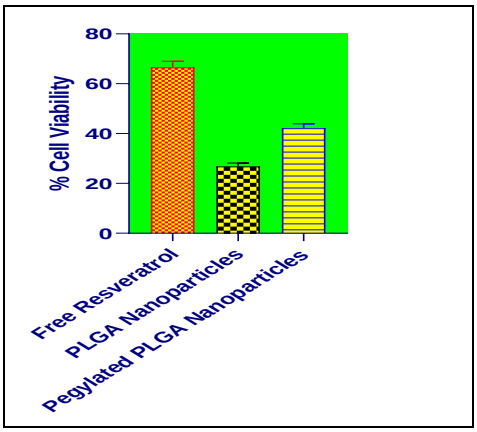

FIG. 8: PERCENTAGE CELL VIABILITY FOR FREE RESVERATROL, PLGA NANOPARTICLES, PEGYLATED PLGA NANOPARTICLES

CONCLUSION: By using PVA as a surfactant, the nanoparticles loaded with Resveratrol were designed and evaluated effectively. As demonstrated in this study, PVA is a promising surfactant for encapsulating and delivering poorly water-soluble compounds as pegylated PLGA nanoparticles with desired particle size, morphology and drug loading. By using pegylated PLGA nanoparticles encapsulated with Resveratrol, the drug was successfully delivered to the target site. PLGA pegylated polymers were synthesized based on the study results to target the desired sites. Several characteristics have been observed in nanoparticles prepared by double emulsion solvent evaporation including size, surface morphology, drug loading and encapsulation. The particle size observed for the formulations S1-S4 was 156.0 nm, 230.0 nm, 139.0 nm and 199.9 nm respectively. Entrapment efficiency (%) for the formulations S1-S4 were found to be 63.45±0.19, 65.86±0.17, 66.44±0.16 and 69.35±0.25, respectively. The drug loading (%) of formulations S1-S4 were found to be 35.82±0.17, 36.44± 0.46, 36.06±0.16 and 37.14±0.17 respectively. Moreover, the optimized nano-formulation demonstrated significant cytotoxic effect. The free Resveratrol at 2.5 M concentrations was found to possess 66.59 % cell viability, while PLGA NPs and Pegylated PLGA NPs recorded 26.84 % and 42.19 % cell viability respectively.

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CONFLICT OF INTEREST: The authors declare that there is not any conflict of interest.

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