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FUNCTIONALISED SELENIUM NANOPARTICLES FOR THE TARGETED DELIVERY OF VENLAFAXINE

Vandana Malviya*[1], Dr. Mehta Parulben D.[2] and Priyanka Namdeo[3]

Lakshmi Narain College of Pharmacy, Raisen Road, Kalchuri Nagar, Bhopal, 462022, India.

***Corresponding Author: Vandana Malviya**

Lakshmi Narain College of Pharmacy, Raisen Road, Kalchuri Nagar, Bhopal, 462022, India.

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ABSTRACT

The prime objective of this work was to formulate selenium nanoparticles, surface decorate them with gallic acid, load venlafaxine in the nanoparticles and evaluate the colon targeting ability of the surface functionalized selenium nanoparticles. Venlafaxine has been widely prescribed drug for management of depression. The surface decoration of the SeN with gallic acid was achieved in alkaline pH using 0.1N NaOH to adjust the pH and drug loading was achieved by continual stirring for long duration. The synthesized SeN and SeN-G were characterized for shape, size, UV absorption, FTIR, entrapment efficiency and *in vitro* release of venlafaxine in presence and absence of rat caecal content. The formation of Se NP is indicated by the UV spectrum showing absorbance at 226.0 nm. The FTIR spectrum revealed the stretching and bending vibrations of O-H, C-H, C-C, N-O, C-N and other groups due to the presence of gallic acid. The particle size of the SeN and SeN-G was found to be 46 and 67 nm respectively and the SEM images displayed smooth particles with spherical structure. The percent entrapment was found to be 63.4% in SeN-G and 63.1% in SeN. In absence of the caecal medium, the release of drug from SeN 61.23% in 24 h whereas SeN released more than 75%. On the other hand, in the presence of colonic media (caecal medium) the release with gallic acid decorated particles was increased to 94.82% in 24 h.

KEYWORDS: Entrapment efficiency, Nanoparticles, Particle size and Venlafaxine.

INTRODUCTION

Oral drug delivery system is the most commonly used route for drug delivery due to its ease of administration, better patient compliance, and flexibility in design and development of formulation.[1] The colon-specific drug delivery systems are also gaining importance for the systemic delivery of proteins and peptide drugs.[2-4] Besides this low hostile environment, the colonic transit time is long (20-30 h) and the colonic tissue is highly responsive to the action of absorption enhancers.[3,4] The longer residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancers make colon a promising site for the delivery of protein and peptides, oral vaccines, insulin, growth hormone, erythropoietin, interferons and interleukins.[5-7]

Colonic delivery can be accomplished by oral or rectal administration. Rectal dosage forms such as suppositories and enemas are not always effective since a high variability in the distribution of these forms is observed and enema solutions can only offer topical treatment to the sigmoid and descending colon9. Therefore, oral administration is preferred, but for this purpose, many physiological barriers have to be overcome.[8,9] Selenium, as one of the fundamental minor components, is affirmed to improve the action or restore the activity of the seleno-catalyst and glutathione peroxidase in prevention of free radical harm to cells and tissues in vivo. Selenium supplements can prevent diseases, such as viral infections, immune system dysfunction, and neural function loss. Metal NPs of Au and Ag, have immense medicinal benefits but are costlier to synthesize, whereas the synthesis of Se nanoparticles (SeNPs) is economical and they can be integrated with other biological agents to enhance their biological properties. Due to their higher surface-to-volume ratio at the nano-level, the surface of the particles is more exposed which leads to an enhanced activity of selenium more profoundly in the nano-regime. SeNPs show promising potential as antioxidants, cancer therapeutic agents, and drug carriers in biological applications.[10]

MATERIAL AND METHODS

Preformulation Studies[11]

Organoleptic Evaluation

The color, odor and appearance of the obtained drug sample were observed with the help of the sensory organs.

Solubility (at room temperature, qualitative)
Solubility was observed in different solvents like water, HCl, ethanol and acetone.

Identification Test
FT-IR spectrum of the sample of venlafaxine was obtained and examined for the presence of characteristic peaks and matched with that of the reference spectra in databases for confirmation of the identity of the drug.

Melting point determination
Melting point was determined by open capillary method and is uncorrected. A small quantity of powder was placed into fusion tube and placed in the melting point apparatus.

Compatibility analysis
The FTIR spectra of the pure drug and a physical mixture of the drug and the polymers under study were obtained and observed for deletion of the characteristic peaks of the drug.

Partition Coefficient[12]
This study was performed by using butanol as oil phase (30ml) and water as aqueous phase (30ml). The 2 phases were mixed by keeping them in a separating funnel and 5 mg of drug was added in it then 2 phases were separated from each other when it was shaken continuously and then separated from each other by separating funnel. Both phases were taken in a conical flask and then analyzed against their respective blank solution and the partition coefficient was calculated by following formula.

Ko/w = Concentration of drug in butanol/ Concentration of drug in water.

Determination of λmax
Accurately weighed 5 mg of venlafaxine was dissolved in 5 mL of water in a 10 mL volumetric flask. 1 mL of this solution was taken in to a 10 mL volumetric flask and volume made up to the mark with phosphate buffer pH 6.8.[13] The resulting solution was then scanned between 200-400 nm using UV spectrophotometer. The λmax was found to be 225 nm. The solution was stored for 3 days at room temperature and rescanned to observe any changes in wavelength.

Preparation of Calibration Curve in phosphate buffer pH 6.8
Accurately weighed 10 mg of venlafaxine was taken in 10 mL volumetric flask and dissolved in water to the mark resulting in a stock solution of 1000 µg/mL. 1 mL of the above stock solution was taken in another 10 mL volumetric and volume was made up with phosphate buffer pH 6.8 to mark resulting in a solution of 100 µg/mL. Aliquots of 1-6 mL of stock solution were taken into a series of 10 mL volumetric flask and volume was made up to the mark using phosphate buffer pH 6.8 and were analyzed at 225 nm using UV spectrophotometer. A standard curve was constructed against absorbance and concentration.

Preparation of Selenium Nanoparticles (SeN)[14,15]
Solutions of ascorbic acid (100mM) and sodium selenite (25mM) were prepared in distilled water by dissolving the appropriate quantities. The selenium nanoparticles were prepared by reduction of the sodium selenite by ascorbic acid. Briefly, 3 mL of ascorbic acid solution, 3 mL of sodium selenite solution and 0.10 g polyvinyl alcohol (PVA) were taken in a beaker and diluted with 9 mL distilled water. To this solution was added 1 M NaOH solution to make the pH of the solution slightly alkaline. On attaining the alkaline pH, the color of solution started to change from colorless to red. The solution was stirred for 30 min to complete the reduction process. The SeN solution was centrifuged at 10000 rpm for 10 min. The supernatant was discarded (contained excess PVA) and the sediment was re-dispersed in 5 mL distilled water to obtain purified Se NP.

Table 1: Quantity used for synthesis of Se NPs.

Formulation	Ascorbic acid (mL)	Distilled Water (mL)
SeN	3.0	9.0

Surface decoration of SeN with gallic acid
The solution of SeN before centrifugation was surface decorated with gallic acid. To the red colored SeN solution, 0.1N NaOH was added dropwise to adjust the pH to 8.5. To this solution was added dropwise a solution of gallic acid (3 mg) in ethanol (0.5 mL). The mixture was stirred in dark on a magnetic stirrer for 3 h to obtain the gallic acid decorated SeN (SeN-G).

Loading of venlafaxine to SeN-G
Venlafaxine (2 mg) was dissolved in 50 µL of water and then added to the SeN-G solution dropwise with stirring. The mixture was further stirred for 8 h to achieve drug loading in the nanoparticles.

Characterization of SeN
Spectrophotometric characterization
The preparation of SeN was confirmed by measuring the absorption maxima of the SeN solution in reference to selenium nitrite solution from 300-850 nm using UV-Visible spectrophotometer.

FT-IR spectral study
The prepared SeN were subjected to FTIR analysis in order to examine the functional groups present in the preparation. The spectrum was recorded in the region of 400- 4000cm^{-1}.

Particle Size determination
The particle size of SeN was analyzed by differential light scattering (DLS) principle using a particle size analyzer. A dilute suspension of the SeN was prepared in distilled water and particle size and distribution were recorded.

Surface characterization
The surface morphology of the prepared SeN was studied using scanning electron microscopy (SEM).

Entrapment Efficiency
The SeN were centrifuged for 30 min at 15000 rpm and the pellet obtained was collected by decantation of the supernatant. The pellet was dissolved in water and the quantity of venlafaxine in the pellets was quantified by measuring the absorbance at 225 nm using UV spectrophotometer.

***In vitro* release study**
In vitro dissolution studies for the SeN and SeN-G formulations were performed by using basket type dissolution test apparatus using phosphate buffer pH 7.4 as the dissolution medium. The formulation was placed in a dialysis bag and immersed in thebasket and the dissolution study was carried out for 12 h. At predetermined intervals, 1 mL of the dissolution media was pipetted out and was diluted to 10 mL using PBS pH 7.4. Absorbance of the solution was recorded at 225 nm using UV visible spectrophotometer.

***In vitro* release studies in presence of rat caecal content**
Preparation of rat caecal content
Wistar rats weighing 150-200 g were used to obtain the caecal content. The rat were administered with 4 mL of 1% w/v of dispersion of chitosan in water for 7 days. Thirty minutes prior to the start of study, 3 rats were killed by spinal traction, the abdomen was dissected open and immediately transferred to pH 6.8 phosphate buffer. The caecal bag was opened and its content was weighed, homogenized, and suspended in phosphate buffer pH 6.8 to obtain a concentration of 4% w/v of caecal content.

***In vitro* dissolution studies**
The drug release for all the formulations was carried out in phosphate buffer pH 7.4 with rat caecal content (4%w/v). At fixed time intervals, 1 mL of the dissolution media was pipetted out and its volume was made up to 10 mL using PBS pH 7.4. Absorbance of the solution was observed at 225 nm using UV spectrophotometer. [16]

RESULTS AND DISCUSSION

The prime objective of this work was to formulate selenium nanoparticles, surface decorate them with gallic acid, load venlafaxine in the nanoparticles and evaluate the colon targeting ability of the surface functionalized selenium nanoparticles. The work was accomplished using the reported methods with modification wherever required and the observations and results are presented in this chapter.

Preformulation Studies
Organoleptic properties
Table 02: Organoleptic properties of Venlafaxine.

Test	Specification	Observation
Color	White to Off white	White
Odor	Odorless	Odorless
Appearance	Crystalline Powder	Crystalline powder

Solubility analysis
The solubility was qualitatively studied in organic and aqueous solvent. Soluble in water and methanol. Slightly soluble in Ethanol. Insoluble soluble in Acetone.

Melting point
The melting point of venlafaxine was determined by capillary method, melting point of venlafaxine was found to be 217-218°C. Melting point compared with USP standards that showed that drug is pure.

Loss on Drying
Loss on drying of venlafaxine was 0.30 % determined by heating the drug to constant weight in hot air oven

Calibration curve of venlafaxine
Calibration curve of venlafaxine was determined by plotting absorbance versus concentration (µg/ml) at 225 nm.

The linear regression analysis for the calibration curve was Abs = 0.057(concentration) – 0.004 with a regression coefficient of 0.999.

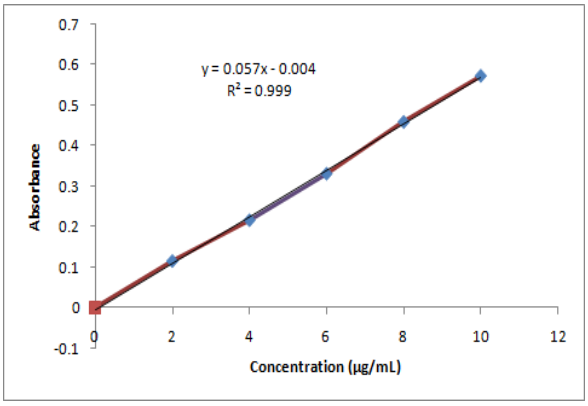

Figure 01: Calibration curve of venlafaxine.

Drug-polymer compatibility study

The FTIR spectra of the pure drug and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm-1). Deletion of the peaks of the pure drug in the mixture spectra is usually taken as an indication of incompatibility of the drug and excipients. On comparison of the FTIR spectra of the drug and the mixture it was observed that no peak was deleted and only the intensities of the existing peaks changed which might be due to the coupling of absorption frequencies. This provides evidence of compatibility between the drug and the matrix forming polymers.

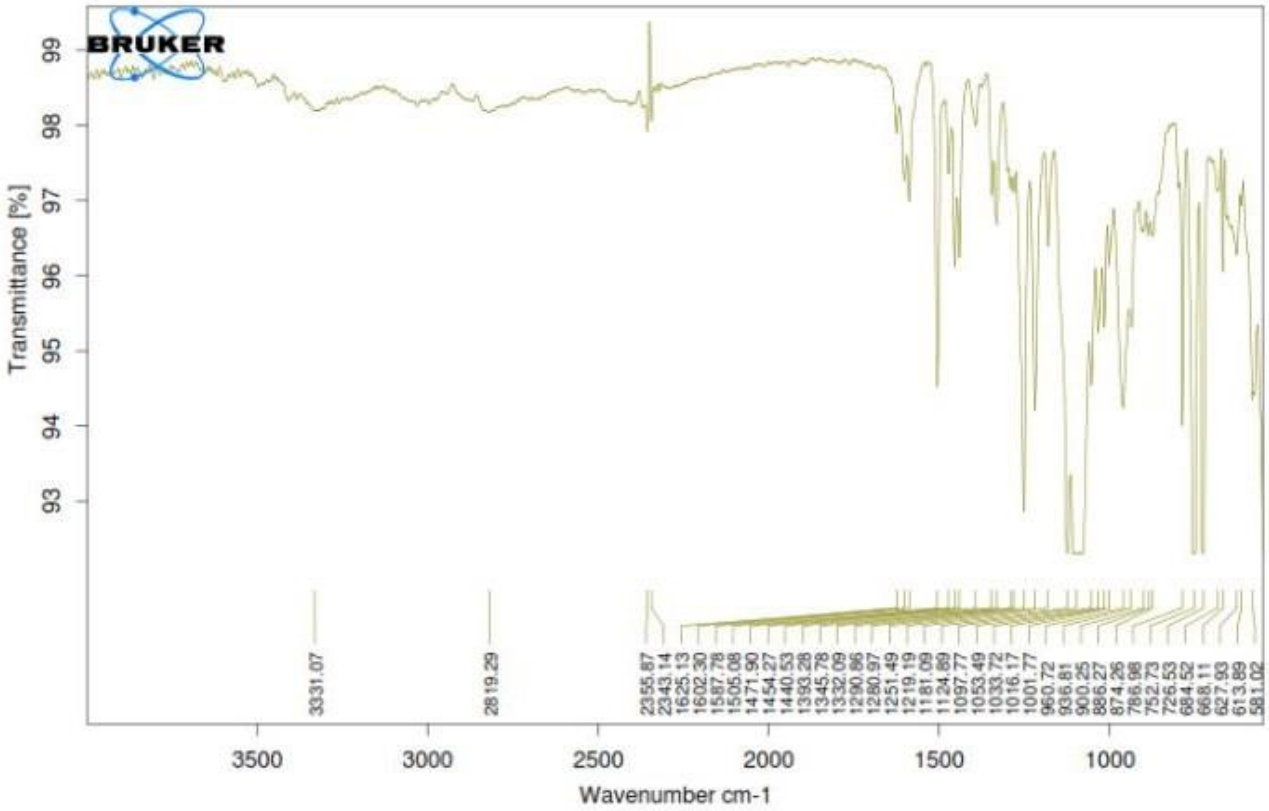

Figure 02: FTIR spectra of venlafaxine.

Biosynthesis of Selenium nanoparticles

The biosynthesis of Se NP was carried out by reducing sodium selenite in presence of ascorbic acid. The formation of SeN was rapid with ascorbic acid. The change in color was evident from light yellow to red resulting with the reduction of the selenium salt (Figure 6.4). Synthesis of SeN was carried out in parallel by the reduction of sodium selenite using ascorbic acid. PVA was used as the stabilizing agent in the synthesis of SeNs. The PVA molecules helps in preventing agglomeration of the nanoparticles and help in controlling the particles size.[78] Previously researchers have also indicated the use of bovine serum albumin or polysorbate 80 for stabilizing the SeN.[40] Sodium selenite, sodium selenosulfate or selenious acid are examples of the precursors in the chemical synthesis of SeN.

Characterization of Se NP

UV absorption and Infrared spectral study

The formation of Se NP is indicated by the UV and IR spectrum showing absorbance at 226.0 nm (Figure 3). Previously few authors have reported that the suspension of the SeNs of 20 nm diameter had a yellowish-orange appearance and showed the absorption maximum below 250 nm.

The Fourier Transform Infrared spectrometer (FTIR) spectrum of the synthesized Se NP reveals broad vibration peak at 3423 cm^{-1} corresponding to O–H stretch of alcohols or phenol groups. Vibration peaks at 3125, 3019, 2983 and 2827 cm^{-1} represent the C–H stretch corresponding to alkynes. Occurrence of peak at 2341 cm^{-1} corresponds nitro compounds (N–O asymmetric stretch) present in the compound. The strong band at 1522 cm^{-1} corresponds to the aromatic ring (C–C and C–H stretching).

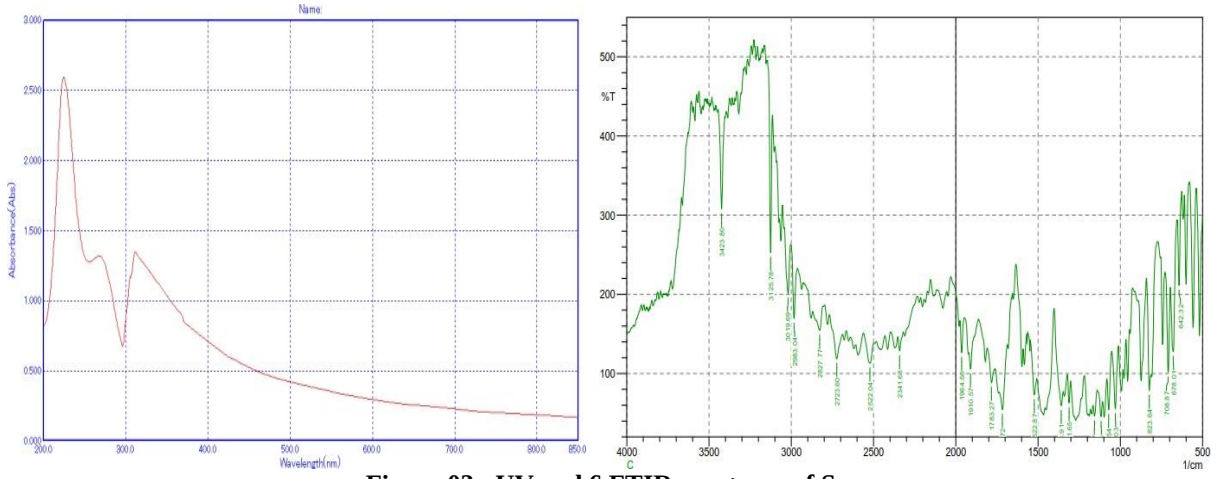

Figure 03: UV and 6 FTIR spectrum of Se.

Particle Size and distribution

The particle size was determined using a Malvern particle size analyzer. The particle size of the SeN and SeN-G was measured and an increase in size was observed on surface functionalization of the nanoparticles.

Table 03: Particle size of synthesized SeN and SeN-G.

Formulation	Particle size (d.nm)	PDI
SeN	46	0.581
SeN-G	67	0.765

Entrapment Efficiency

The percent entrapment was found to be 63.4% in SeN-G and 63.1% in SeN.

***In vitro* drug release study in absence and present of rat caecal content**

The *in vitro* release study was done for SeN and SeN-G to assess the time duration up to which the drug is released by the nanoparticles and to prove a sustained release (Table 4 and 5). The % cumulative release was plotted against time to obtain the release kinetics equation for the formulations (Figure 4).

Table 04: *In vitro* release of Venlafaxine in absence of rat caecal content.

Time (h)	Cumulative Release (%)	
	SeN	SeNG
0	0	0
1	5.81	6.84
2	13.29	17.88
4	18.11	24.39
6	23.26	31.36
8	29.37	37.23
10	36.53	43.63
12	43.18	48.73
24	61.23	75.19

Table 05: *In vitro* release profile of formulations in presence of rat caecal content.

Time (h)	Cumulative Release (%)	
	SeN	SeNG
0	0	0
1	5.79	5.91
2	18.42	21.89
4	23.83	29.58
6	28.81	32.58
8	34.54	39.97

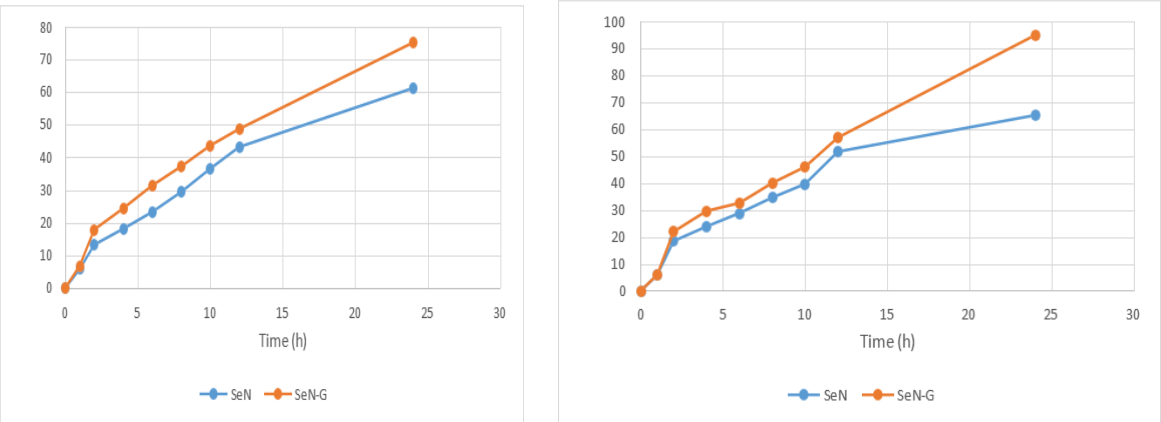

Figure 04: Percent release of venlafaxine in absence and presence of rat caecal content.

The *in vitro* release was assessed in absence as well as presence of rat caecal content. In absence of the caecal medium, the release of drug from SeN 61.23% in 24 h whereas SeN released more than 75%. On the other hand, in the presence of colonic media (caecal medium) the release with gallic acid decorated particles was increased to 94.82% in 24 h. It was also observed that surface decoration of gallic acid on the SeN was able to increase the drug release from the formulations suggesting the assistive role of the gallic acid in degradation of nanoparticle core in the colonic microflora.

CONCLUSION

Venlafaxine has been widely prescribed drug for management of depression. The retention of drug in the colon has been widely investigated for improving the bioavailability of drugs and selenium nanoparticles have been found improve targeting to various organs including colon. The formation of Se NP is indicated by the UV spectrum showing absorbance at 226.0 nm. The particle size of the SeN and SeN-G was found to be 46 and 67 nm respectively and the SEM images displayed smooth particles with spherical structure. The percent entrapment was found to be 63.4% in SeN-G and 63.1% in SeN.

In absence of the caecal medium, the release of drug from SeN 61.23% in 24 h whereas SeN released more than 75%. On the other hand, in the presence of colonic media (caecal medium) the release with gallic acid decorated particles was increased to 94.82% in 24 h. In this study, SeNs was rapidly synthesized using ascorbic acid as the reducing agent. The synthesized SeN was surface functionalized with gallic acid and finally venlafaxine was loaded in the SeN. Rapidly synthesized SeN-G demonstrated significant improvement in the release of venlafaxine in presence of rat caecal content suggesting an improved colonic targeting.

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