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Preparation and Evaluation Novel Nanogel Formulation Containing Silver Nanoparticles of *Bixa orellena* Seed Extract

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ABSTRACT
The goal of the study is to create a novel nanogel formulation using silver nanoparticles from bixaorellana seed extract. Bixaorellana is known to contain a compound called Bixin, which has been utilized for its antifungal, antibacterial, and anti-inflammatory properties. Topical medication delivery is a widely utilized approach for achieving defined and sustained release of drugs at the intended site of action. The present study involves the synthesis of silver nanoparticles using an environmentally harmless and economically efficient method, utilizing the extract derived from the seeds of Bixaorellana.No chemical interaction was detected during the Pre-formulation investigation as verified by FTIR analysis. The nanogel was synthesized utilizing HPMC K15 and carbapol 940 polymers, with special attention given to selecting a polymer that would control the rate of drug release. The gel underwent evaluation using many characteristics like pH, viscosity, spreadability, and extrudability, among others. The results of the in vitro drug release investigation reveal a significant drug release of 82.54% within a 10-hour period when 1 gram of hydroxypropyl methylcellulose (HPMC) is present. Carbapol exhibited a moderate level of drug release. Thus developed nanogel-based innovative formulation may be a promising medication delivery for bixaorellana seed extract-related treatments.
Key words- *Seed extract, Silver nanoparticles, Nanogel, Polymer, In vitro study etc.*

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INTRODUCTION

The utilization of nanotechnology has proven its ability to enhance the efficiency of incorporating herbal-based medications by enhancing the efficacy of drug action, facilitating the controlled release of active components, reducing needed dosage, and boosting the biological activity. Various types of nanomaterials, including polymeric nanoparticles, solid lipid nanoparticles (SLN), lipid crystal (LC) systems, liposomes, and nanoemulsions, have been investigated as potential carrier vehicles for safeguarding herbal medications against degradation caused by external factors [1]. Numerous studies have demonstrated that the utilization of nano-delivery systems can effectively enhance the physiochemical characteristics of herbal medications in accordance with specific requirements.

The term Novel Drug Delivery System (NDDS) encompasses various methods, compositions, technologies, and systems that facilitate the safe and effective transportation of pharmaceutical compounds throughout the human body, hence achieving the intended therapeutic outcomes [2]. The NDDS (Novel Drug Delivery System) is a sophisticated pharmaceutical technology that enhances the efficacy of drugs by optimizing drug release to achieve a sustained therapeutic effect. Additionally, it provides enhanced safety measures and enables targeted drug delivery to specified tissues [3].

The field of science has shown significant interest in the synthesis of silver nanoparticles due to their diverse range of applications. These nanoparticles have shown successful utilization in cancer diagnosis and treatment [4]. Typically, nanoparticles are produced using various chemical and physical techniques, which can be costly and harmful to the environment. These methods involve the use of toxic chemicals which carry potential biological risks [5]. Consequently, the growth of biologically-inspired experimental approaches for nanoparticle synthesis is becoming a crucial aspect of nanotechnology research.

Nanogels refer to nanoparticles that consist of a hydrogel containing a bound hydrophilic polymer, often exhibiting a particle size ranging from 100 to 200 nm. Nanogels are formed by the physical or chemical cross-linking of synthetic polymers or biopolymers. The nanogels include micromolecules or macromolecules within their pores [6-8]. Nanogels exhibit characteristics such as the ability to undergo

swelling and degrading, possess a variable size, exhibit a substantial surface area, and hold a significant amount of water. Nanogels have been employed as carriers for the regulated and sustained release of various physiologically active substances, functioning as medicines [9-11]. Nanogels are seen to exist as three-dimensional structures capable of encapsulating medicines, polymers, and dispersed liquid phases. The beneficial nature of nanogel formulations has been attributed to the availability of diverse polymer systems and the simplicity with which their features can be altered [14].

The primary objective of this work was to develop a novel type of Nanogel that incorporates silver nanoparticles derived from the seed extract of bixaorellana. This study aimed to synthesize a nanosystem through the inclusion of a nanoformulation. Bixin, being the primary constituent found in the extract, has antifungal, antibacterial, and anti-inflammatory properties. The nanogel-based formulation that has been developed demonstrates potential as a drug delivery system for the treatment of different reported activities associated with bixaorellana seed extract.

MATERIAL AND METHODS

Extraction

The B. orellana seed was exposed for two days of sun drying before spending 72 hours at 50 °C in a tray dryer. The mechanical grinding of the dried B. orellana seed provided the powdered material needed for the extraction process.

Hot extraction- 30 g dried powdered sample were taken in three soxhlet apparatus containing 200 ml of solvent. The extraction was carried out in a soxhlet apparatus for 12 hr with different solvents like methanol at 60 ^{0}C.

Green synthesis of silver nanoparticles

The experiment was done using solutions of $AgNO_3$ with concentrations of 0.2 mM, 1 mM, and 2 mM. The solutions were stirred at a temperature of 60 ^{o}C for duration of 5 minutes using a hot plate. Subsequently, a volume of 5 ml of Bixaorellana seed extract (BOSE) was incrementally introduced into the mixture. Additionally, same mixture was placed on a magnetic stirrer for durations of 5, 13, and 20 minutes, with a rotational speed of 500 revolutions per minute (rpm). The BOAgNPs that were prepared were obtained through filtration using a clean muslin cloth. subsequently, the filtrate underwent a secondary filtration process using Whatman filter paper and was thereafter held at a temperature of 4 degrees Celsius in preparation for the creation of nanoparticles. The confirmation of the synthesis of $AgNO_3$ has been verified through the observed alteration in color, transitioning from a bright orange hue to a dark orange shade [4,5].

Preparation of nanogel

The gel of the prepared BOAgNPs was formulated by dispersing a gel-forming agent, namely hydroxypropyl methylcellulose (HPMC) K15 carbopol 940, which had been soaked in hot water for a duration of 24 hours. Subsequently, the BOAgNPs were added to the solution while ensuring uniform stirring through the utilization of a high-speed homogenizer operating at speeds ranging from 7000 to 10000 revolutions per minute. The pH of the solution was modified to 7.0 by employing triethanolamine as a means to create the gel. The resulting gel, involving BOAgNPs, was thereafter kept at ambient temperature [15,16]. Table 1 presents a brief summary of the excipients utilized in the formulation.

Table no.1 Composition of excipients used for preparation of nanogels

Ingredients	F1	F2	F3	F4	F5	F6
BOAgNPs (ml)	1.0	1.0	1.0	1.0	1.0	1.0
Carbopol 940 (g)	0.5	1.0	1.5	-	-	-
HPMC K15 (g)	-	-	-	0.5	1.0	1.5
Propylene glycol (ml)	10	10	10	10	10	10
Triethanolamine (ml)	1.0	1.0	1.0	1.0	1.0	1.0
Methyl paraben (g)	0.1	0.1	0.1	0.1	0.1	0.1
Propyl paraben (g)	0.5	0.5	0.5	0.5	0.5	0.5
Water (ml)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation of nanogel

Appearance and Homogeneity

The gel bases were visually examined for clarity, color, and the presence of any particles. The nanogels that were produced were assessed for homogeneity using a visual examination following their placement in the container. They were examined for the appearance and presence of aggregates.

Particle size and polydispersity index

The average particle size was obtained using the Horiba SZ-100 Particle Size Analyzer.The analysis of size was conducted in the aqueous phase, taking into account the hydration effect, which is reflected in the Z value.The PDI, which is a dimensionless parameter, is utilized to quantify the polydispersity of the formulation [15].

pH measurement

The pH of the nanogel formulation was determined by employing a pH meter. In order to carry out this determination, a mass of 1 gram of nanogel was measured and afterwards dispersed in 10 milliliters of distilled water. The sample was allowed to incubate for a duration of 4-5 minutes in order to obtain the precise pH measurement. The data collection process involved obtaining three separate readings.

Drug Content

Drug content was determined by dissolving nanogel in 10 ml of ethanol. The combination underwent centrifugation at a speed of 448 relative centrifugal force (RCF) for a duration of 1 hour. The liquid supernatant was extracted, and subsequent analysis was conducted on the samples utilizing a UV spectrophotometer set at a wavelength of 452 nm.

Spreadability

The determination of spreadability is achieved through the use of equipment recommended by Mutimer. The calculation of spreadability was determined by the utilization of a certain formula.

$$S=M.\ L/T,$$

Where, S=Spreadability,

L=Length of glass slide,

M=weight tied to higher slide,

T=Time taken to separate the slides.

Extrudability

The mixtures were put into flexible aluminum tubes. The tubes were compressed in order to extrude a gel ribbon measuring 0.5 cm within a 10-second timeframe, and the extrudability of the formulations was subsequently assessed.

Entrapment efficiency

The entrapment efficiency of the nanogel was assessed by quantifying the amount of drug present in the nanogel formulation (in milligrams) and comparing it to the initial amount of drug introduced (in milligrams) to the aqueous phase.

Viscosity

The viscosity of the gel formulations was assessed at a temperature of 25°C using a Brookfield viscometer equipped with spindle number S-96, operating at a rotational speed of 1 revolution per minute. The viscosity values were measured in centipoise (cps). The measurement of each formulation was conducted in triplicate, and the average values were calculated [16].

***In-vitro* drug release**

The Frantz Diffusion Cell has been used in the present study, utilising a cellophane membrane. A quantity of 100mg of Nanogel is introduced into the donor compartment, which is subsequently filled with phosphate buffer solution at a pH of 7.4. The membrane was affixed within the compartments of the Frantz Diffusion Cell. The reservoir compartment was filled with a phosphate buffer solution at a pH of 7.4. The experiment was conducted at a temperature of 37± 100 C, with the rotational speed set between 100 and 120 rpm. The duration of the experiment was 24 hours. A volume of 5 ml was extracted from the reservoir compartment using hypodermic syringes at hourly intervals over a period of 10 hours. The spectrophotometric measurement of absorbance was conducted at a wavelength of 452 nm. To maintain a constant volume, the reservoir compartment was replenished with a new volume of 5 ml phosphate buffer solution at a pH of 7.4, as described in reference [18].

Stability studies

The optimized formulation underwent stability testing for a duration of 45 days, following the guidelines set by the International Council for Harmonisation (ICH). The testing was conducted at a controlled temperature of 40º ± 2ºC and a relative humidity (RH) of 75%. The optimized formulation was evaluated for variations in drug content and in-vitro diffusion characteristics using the previously described methodology.

RESULT AND DISCUSSION

Evaluation of nanogel

Appearance & Homogeneity

All F1 to F6 formulations show clear orange colored appearance, all the formulations were homogenous and free of grittiness.

Particle size and polydispersity index

The modified formulation OF BOAgNPs was put forward for the preparation of the nanogel formulations. After the preparation of all batches, the nanogel particle size was assessed using the HORIBA SZ-100 particle size analyzer. Additionally, the Polydispersity index was computed. The results obtained are recorded in Table 2.

Table no. 2 Results of Particle size and PDI of Nanogel batches

Run/Batch	Particle size (nm)	polydispersity index
F1	88.5	0.401±0.024
F2	88.0	0.412±0.002
F3	87.6	0.435±0.013
F4	89.2	0.425±0.007
F5	93.1	0.405±0.006
F6	86.5	0.418±0.008

Polymer compatibility study by FTIR

The IR spectra of Carbapol 940 with BOSAgNPs (Figure 1) shows 3341 (O-H stretching), 1636 (C=C stretching), 1451 (C-H stretching), 1230 (C-O stretching) vibrations.

The results revealed no chemical changes in the IR peaks of BOSAgNPs, when mixed with polymer Carbapol 940. These observations indicated the compatibility of Carbapol 940 with BOSAgNPs. The FTIR spectrum of Carbapol 940 with BOSAgNPs shown in figure no.1 IRspectra indicated no well-defined interaction between the drug and polymer**.**

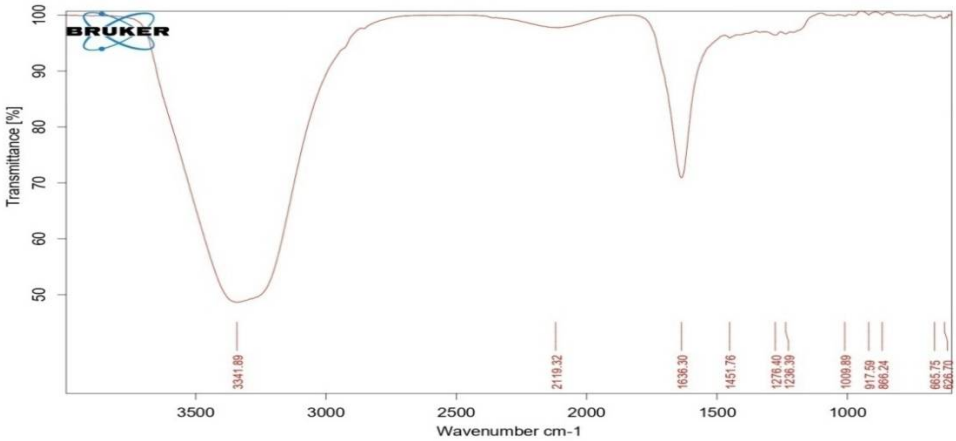

Figure no. 1 IR spectrum ofBOSAgNPs with carbapol 940

The IR spectra of HPMC K15 with BOSAgNPs (Figure 2) shows 3344 (O-H stretching), 1635 (C=C stretching), 1054 (C-O stretching) vibrations.

The results revealed no chemical changes in the IR peaks of BOSAgNPs, when mixed with polymer HPMC K15. These observations indicated the compatibility of HPMC K15 with BOSAgNPs. The FTIR spectrum of HPMC K15 with BOSAgNPs shown in figure no. 2 IR spectra indicated no well-defined interaction between the drug and polymer**.**

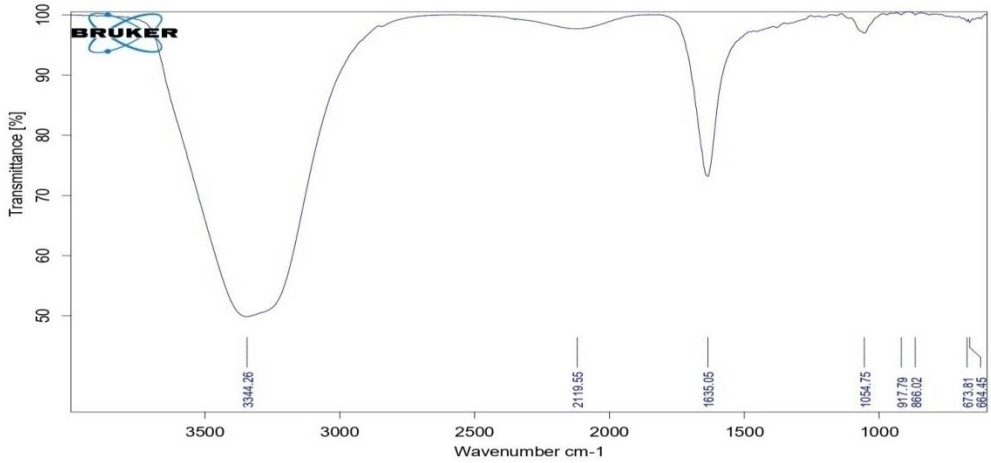

Figure no. 2 IR spectrum of BOSAgNPs with HPMC K15

pH measurement

The pH values of all the developed formulations were between 6.45 and 7.10, as seen in Table 3. These values are significant in terms of minimizing the potential for skin irritation upon application.

Drug Content

The nanogel that was produced was assessed for its drug content properties. The drug content exhibited a range of 71.30±0.43% to 92.43±0.49%. The results obtained from formulation F5 indicate that it exhibits the highest drug content, with a value of 92.43%. The findings have been shown in Table 3.

Spreadability

The nanogel that was produced has been evaluated in terms of its spreadability parameter. The spreadability of all bathes was seen within a certain range, however, formulation F5 exhibited superior spreadability compared to the other formulations. The findings have been shown in Table 3.

Extrudability

The nanogel that had been produced was assessed for its extrudability parameter. The extrudability measurements for all batches fell within the range of 0.6 to 0.2 cm, with the exception of formulation F5, which exhibited a value of 0.5 cm. The ability to be extruded within a 10-second timeframe from a collapsible tube. The findings have been shown in Table 3.

Table no. 3 Results of extrudability for all formulation

Batch/Formulation	pH	Drug Content (%)	Spreadability (cm)	Extrudability(cm)
F1	6.45 (±0.08)	82.30 (±0.28)	5.1 (±0.18)	0.4
F2	6.51 (±0.05)	78.54 (±0.25)	4.9 (±0.25)	0.5
F3	6.95 (±0.03)	71.30 (±0.63)	4.6 (±0.23)	0.6
F4	6.48 (±0.04)	88.74 (±0.14)	4.6 (±0.14)	0.4
F5	7.10 (±0.02)	92.43 (±0.32)	5.3 (±0.12)	0.5
F6	6.51 (±0.08)	90.10 (±0.48)	5.1 (±0.18)	0.3

Viscosity

The viscosity of the produced nanogel was determined using a Brookfield viscometer. The viscosity of the nanogel was measured at rotational speeds of 100 and 200 revolutions per minute (RPM) for all formulations. In order to maintain a constant viscosity, the torque was set at 95%. The F5 formulation batch has superior viscosity in comparison to the other batches. The viscosity against revolutions per minute (rpm) plots for the formulations demonstrate a reduction in viscosity as the shear rate (rpm) is raised, indicating that the gel exhibits pseudo plastic flow. The viscosity of formulations was significantly influenced by the concentration of HPMC K15 M. The viscosity of the nanogel formulation is provided in Table 4.

Table no. 4 Viscosity of nanogel formulations

Batch/Formulation	Torque	RPM	Viscosity (cps)
F1	95%	100	3560
		200	4900
F2	96%	100	3958
		200	4852
F3	94%	100	4396
		200	5430
F4	95%	100	5011
		200	5360
F5	96%	100	5687
		200	6515
F6	95%	100	5485
		200	6125

***In-vitro* drug release**

The drug release studies of the nanogel was conducted using a Franz diffusion cell in an in vitro setting. The experiment was conducted at a temperature of 37 ± 2°C. The receptor compartment of the diffusion cell was filled with a 30 mL solution of phosphate buffer (pH 7.4). The solution was continuously agitated using a magnetic stirrer set at a speed of 100 to 120 revolutions per minute. A cellophane membrane was utilized as a release barrier between the receptor and donor compartments. Periodically, a 5ml sample was extracted from the diffusion cell using the sampling port at hourly intervals. An equivalent volume of phosphate buffer solution (pH 7.4) was promptly substituted. The sample that was gathered was subjected

to analysis by the utilization of UV spectroscopy. The drug release profile from the nanogel is presented in Table 5.

Table no. 5 Drug release profile from nanogel formulations

Time (Hr)	% Cumulative drug release					
	F1	F2	F3	F4	F5	F6
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	10±0.02	12.75±0.02	15.25±0.01	8.75±0.04	15.32±0.03	13.5±0.01
2	16.25±0.01	14±0.03	21.25±0.08	11.50±0.03	23.56±0.02	19.87±0.02
3	19.89±0.04	15±0.05	26.75±0.04	15.50±0.02	31.20±0.04	27.54±0.01
4	23.6±0.02	21.25±0.04	31.50±0.03	21.75±0.04	39.87±0.02	35.24±0.03
5	31.51±0.03	25.5±0.01	37.50±0.02	29±0.02	46.50±0.01	43.52±0.01
6	35.4±0.03	29±0.03	45.75±0.01	33.75±0.01	53.87±0.03	50.1±0.04
7	41.74±0.01	33.75±0.02	50.50±0.03	37.5±0.03	60.01±0.01	58.4±0.01
8	48.54±0.03	34.75±0.01	57.25±0.01	42.25±0.02	67.27±0.02	66.74±0.03
9	53.6±0.02	36.5±0.03	60.50±0.02	48±0.03	74.59±0.01	72.4±0.02
10	57.4±0.02	41.58±0.03	68.41±0.02	56.40±0.03	82.54±0.04	79.4±0.01

Based on the statistics mentioned above, it was observed that all batches exhibited a cumulative drug release of around 50%. However, batch F5 exhibits a significant drug release of 82.54% after 10 hours. The HPMC polymer at a dosage of 1 gram exhibits favorable dissolving outcomes. The polymer serves as a rate controlling agent and demonstrates favorable outcomes in the formulation. The figure labeled as Figure 3 displays a graph of the percentage of drug release.

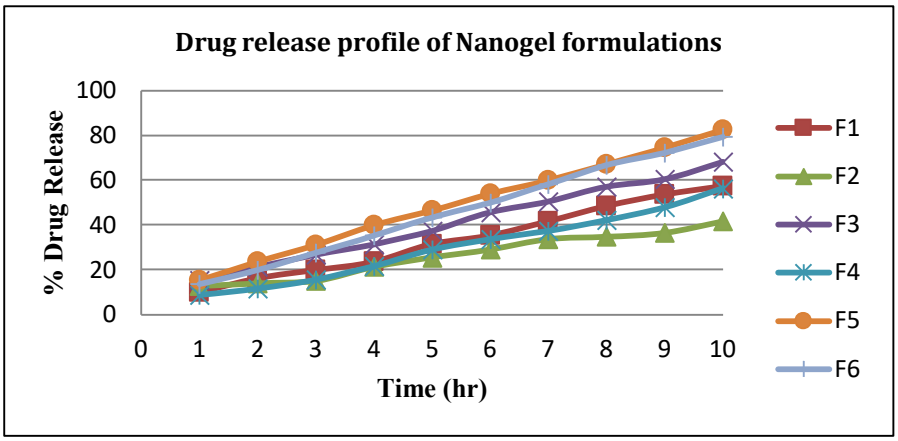

Figure no. 3*Invitro* drug release profile of nanogel preparations

Stability studies

The stability investigations of the formulation that exhibited the highest dissolving rate were subsequently conducted. The assessment of the visual, physical, and chemical stability of the optimized batch was conducted in accordance with the International Council for Harmonisation (ICH) recommendations at a temperature of 40 ± 2°C and a relative humidity of 75 ± 5%. The nanogel from the improved batch was encapsulated with aluminum strips and afterwards subjected to a storage period of 45 days. The physical appearance and drug entrapment efficiency of the samples were assessed after a period of 45 days. The formulations exhibited stability for a duration of three months when stored at room temperature. There were no alterations seen in the medication content, clarity, pH, and viscosity.The stability analysis of the optimized F5 formulation is concisely described in Table 6.

Table no. 6 Data of stability study

Sr. no.	Observation	Before stability testing	After stability study
1	Clarity	Clear	Clear
2	Appearance/Homogeneity	Homogenous	Homogenous
3	pH	7.10	7.10
4	Viscosity	5687 cps at 100 rpm	5650 cps at 100 rpm
5	Drug Content	92.43 %	92.41%
6	Drug release	82.54 % at 10 hr	82.36 % at 10 hr

CONCLUSION

The results of the in vitro drug release investigation demonstrate that, in the presence of 1 gm of hydroxypropyl methylcellulose (HPMC), there was a drug release of 82.54% after 10 hours. Carbapol exhibited a moderate level of drug release. The viscosity of the nanogel increases as the concentration of HPMC polymer is raised. The concentration of Hydroxypropyl methylcellulose (HPMC) is regarded as a measure for influencing viscosity. The findings from the stability studies indicate that there were no observed alterations in entrapment efficiency, drug content, and drug release over a period of three months.The integration of nanosystems into herbal medicines has the potential to decrease adverse effects and enhance therapeutic efficacy. The utilization of nanosystems in nanoformulations has led to an enhanced capacity of molecules to access smaller capillary vessels through both transcellular and paracellular pathways. The formulated preparation can be employed for diverse therapeutic interventions targeting the issues reported in the existing literature. In the age of nanotechnology, the in vivo investigation of the aforementioned formulation may prove to be a fruitful discovery.

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