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Bionanosuspension-A Novel Carrier: It's Development using Novel Isolated Biopolymer and Evaluation of *In-vitro* release of the Model Drug

Sushant Kumar[*1], N.V. Satheesh Madhav[2], Anurag Verma[3],Kamla Pathak[1]

[*1]Faculty of Pharmacy, Pharmacy college Saifai, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, U.P, Pin code: 206130, India
[2]Formulation Research Development, Vital Therapeutics and Formulations, Pvt. Ltd., Telangana, India
[3]College of Pharmacy, Teerthankar Mahaveer University, Moradabad, U.P, Pin code: 244001, India

ABSTRACT

The purpose of this research was to isolate the novel biopolymer from the seeds of Juglans regia. The purpose of isolation from natural seeds was to evaluate the potentiality of biopolymer in delivery of nanosized lamotrigine as an antiepileptic drug. The biopolymer was isolated from the seeds of Juglans regia and characterized for its suitability in preparation of bionanoparticles in the form of bionanosuspension. The biopolymer was isolated by grinding the soaked seeds and then the juice was taken and centrifuged. The solution was treated with acetone and methanol separately and after refrigeration for 24 hours, the free flowing biopolymer was obtained after drying. Lamotrigine was nanosized by screening its nano size particle by UV method. The nanosized lamotrigine was used for preparation of bionanoparticles by sonication method. The isolated biopolymer confirms its polymeric nature in spectral analysis. The prepared bionanoparticles showed the release of lamotrigine in sustained manner over 36 hours. LJ7 showed up to 92.051% drug release in 36 hours. According to the release kinetic study the best fit model was found to be Koresmayer-peppas and the mechanism of drug release was found to be anamolus transport. Thus the obtained results of isolated biopolymer characterization from and other evaluation like % entrapment efficiency, particle size, release study, kinetic studies and stability study revealed that the isolated biopolymer has good potentiality to form bionanoparticles and it can be safely used as an alternative to synthetic and semisynthetic polymers for the preparation of lamotrigine loaded stable bionanoparticles.

Key words: Biopolymer, Bionanoparticles, Bionanosuspension, Lamotrigine, Epilepsy, Nanosizing *Juglans regia* seeds

INTRODUCTION

Biopolymer is an intelligent biomaterial which is biodegradable and biocompatible in nature. Now days the researches on biopolymers have revealed that biopolymer isolated from natural sources may be used as an alternative to standard synthetic and semisynthetic polymers. The isolated biopolymer have a number of novel properties like biodegradability, mucoadhesivity, filmability, retardability and biocompatibility as compared to synthetic polymers like carboxy methylcellulose, hydroxypropyl methyl cellulose.

The biopolymers are economical and environmental friendly. These may be isolated by simple an economical process on large scale. Their novel

Corresponding Author:
k.sushant25[at]gmaildotcom

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characteristics make it intelligent and smart biomaterial as synthetic polymers. The synthetic and semisynthetic polymers sometimes may produce unwanted effects on long term treatment. Since the biopolymers are isolated from the natural sources and because of their inertness and non-toxic effects these may be used as an alternative to synthetic and semisynthetic polymers.

As these biopolymers have good film forming ability, mucoadhesivity, sustainability, retardability, release rate controlling ability these are the excellent biomaterial. These natural biopolymers having significant polymeric properties may be used for designing of the novel drug and targeted drug delivery systems. The researches have proven that this isolated biopolymer have excellent release rate controlling properties. The drug may be loaded in different novel carriers like bionanoparticles formulated by using these novel biopolymers.

The nanoparticles, one of the most smart carrier systems which have attracted the researchers for using as a smart tool for drug targeting to brain in efficient way. NPs having the particle size in nano range may cross the BBB in efficient way. So it can be used as a novel tool for targeting the antiepilepticdrug like lamotrigine.

A number offormulations are there in market for the delivery of lamotrigine form the different conventional formulation like tablets. A number of researches are there which reveals for the delivery of drug from the formulated microcapsules and nanoparticlesby using the synthetic and semi synthetic polymers.

Bionanoparticles which are excellent and smart nanoparticulate systems which may be prepared by using these isolated biopolymer form different natural sources. These bionanoparticles have significant stability, drug loading efficiency and drug release rate controlling capability. So the bionanoparticles in the form of bionanosuspension [1] dispersed system may be used for delivery of nanosized lamotrigine in sustained manner. The lamotrigine is most significant drug in treatment of epilepsy.

Epilepsy [2] is a neurological disorder in which the brain condition becomes abnormal and shows the repeated, uncontrolled, and sudden changes in brain. In epilepsy [3] there are abnormal changes in electrical activity of brain. The epileptic episodes are called as convulsions. There are two types of seizures one is generalized seizure and other is partial seizure. The generalized seizure occurs in whole brain and the partial seizure occurs in any one part of the brain. The partial seizure can be converted in the generalized seizure. There are a number of factors and conditions which may cause the epilepsy after affecting the brain activity in abnormal way.

In this research work bionanosuspension having the bionanoparticles loaded with nanosized lamotrigine has been prepared by using the novel biomaterial from seeds of *Juglans regia*. The biopolymer was isolated from the seeds of *Juglans regia*. The isolated biopolymers [4] showed the significant result in physico-chemical characterization. It also showed the release of nanosized lamotrigine in sustained manner form the formulated bionanoparticles [5,6] in the form of bionanosuspension. In this way the isolated biopolymer for the natural source like seeds of *Juglans regia*. So isolated biopolymer [7] form *Juglans regia* may be used as an alternative of available synthetic and semi synthetic polymers. This isolated biopolymer is biodegradable and biocompatible.

MATERIAL AND METHODS

Materials

Lamotrigine was obtained as a gift sample from Affy pharma private limited, Baddi. The *Juglans regia* seed was purchased from the market of Lucknow. All other chemicals used were of analytical grade.

Isolation of Biopolymer

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The *Juglans regia* seeds were purchased from the local market of Lucknow. 200 gram of seed was weighed and soaked in double distilled water overnight. The swollen seeds were taken and their outer covering was removed. The uncovered seed was grinded in grinder as a paste. If necessary, small quantity of distilled water may be added during the grinding. This paste was filtered through the muslin cloth. The collected filtrate was centrifuge at 5000 rpm for 10 minutes. After centrifugation the supernatant was taken. Centrifugation was done to remove any residue. Then half of the supernatant was treated with acetone in 1:1, 1:2 and 1:3 ratios. Another half of supernatant was treated with the methanol in the same ratios as acetone. Then these were placed in refrigerator for overnight. Then after treatment these were centrifuged at 5000 rpm for 30 minutes. The supernatant was discarded and the biomaterial as a sediment collected and air dried. If any moisture is there can be dried in desiccators for 48 hours. If the biomaterial consists of any oil, can be removed by washing with acetone or chloroform. The obtained biomaterial was passed through sieve number 200 and stored for further use.

Characterization of Isolated Biopolymer

The physico-chemical [8] properties of isolated biopolymer were characterized [9] for color, odor, taste and solubility. The chemical tests for presence of carbohydrate, starch and proteins were also performed. The isolated biopolymer was also characterized for SEM analysis, DSC testing, IR spectroscopy, mass spectroscopy and NMR spectroscopy.

Nanosizing of Lamotrigine

500 mg of lamotrigine was taken and dissolved in 25 ml of methanol. The clear solution was sonicated for 15 cycles continuously. During sonication 25 ml of purified water was added slowly drop by drop till precipitation was observed. The obtained precipitate was allowed for centrifugation. After each sonication cycle, the absorbance, % transmittance (%T) and % blockage (100-%transmittance) was measured. The residue was recovered and then dried to collect the nanosized lamotrigine in nanoparticles range. This nanosized lamotrigine obtained by this standard solvent evaporation method, was evaluated for different parameters. The dried nanosized lamotrigine was packed and stored for further use. The lamotrigine was also nanosized by novel sonication method. Here 500 mg of lamotrigine was taken and mixed with dextrose and 25 ml double distilled water. This dispersed solution was sonicated for 15 cycles continuously. During sonication 25 ml of purified water as added slowly drop by drop till precipitation was observed. The obtained precipitate was allowed for centrifugation. After each sonication cycle the sample was allowed for absorbance and % transmittance (%T) and % blockage (100-%transmittance) measurement. The residue was recovered and then dried to collect the nanosized lamotrigine.

Drug-Excipient Interaction Study

The drug-biopolymer interaction study was performed by the UV spectroscopy method. The lamotrigine -biopolymer mixture was prepared in ratio of 1:1, 1:3 and 3:1 by wet and dry mixing. After mixing the drug and polymer mixtures were stored at 50℃ for three days in wet method and then the mixture was diluted with solvent and scanned for the absorption maxima (λmax). In dry method the three different ration of drug-biopolymer was prepared in their physical form and then after storage at room temperature this was diluted with 2 ml of methanol and then scanned by UV spectrophotometer for any change in λmax.

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Formulation of Lamotrigine Loaded Bionanosuspension

The formulations of bionanosuspension were prepared by using different drug-biopolymer ratio and drug-standard polymer ratio as given in the Table 1. The bionanosuspension was prepared by sonication of the mixture of drug and biopolymer along with other excipients like polyvinyl alcohol as suspending agent, sodium benzoate as the preservative, purified water and dextrose as nanosizent. The lamotrigine, *Juglans regia* biopolymer and other excipients were accurately weighed and triturated with addition of the double distilled water. This mixture was sonicated for 3 cycles. Then 0.5 ml of 0.5 % polyvinyl alcohol was added during sonication. The volume was made up to 10 ml with double distilled water having sodium benzoate (0.1-0.5%). Add dextrose if necessary as nanosizing agent and allowed for sonication for 15 cycles. After sonication the bionanosuspension was refrigerated for two days. If no settlement is there then it means the formulation is optimized. If settlement is there the 0.5 ml of 0.5 % polyvinyl alcohol was again added and allowed for sonication for 10 cycles and refrigerated for 48 hours. The different formulations were prepared and after optimization according to stability the formulations LJ1-LJ8 were prepared. After formulation their stability was tested and then evaluated for different parameters including release study.

Table 1: Formulation table of Lamotrigine loaded bionanosuspension using *Juglans regia* Biopolymer

Formulations	LJ1	LJ2	LJ3	LJ4	LJ5	LJ6	LJ7	LJ8
Drug : Biopolymer ratio	1:02	1:03	1:04	1:05	1:08	1:10	1:12	1:15
Lamotrigine (mg)	10	10	10	10	10	10	10	10
Juglans regia (Biopolymer) (mg)	20	30	40	50	80	100	120	150
Polyvinyl alcohol(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium benzoate (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Double distilled Water (ml)	10	10	10	10	10	10	10	10

Characterization of Lamotrigine Loaded Bionanosuspension

Dispersiblity Study of Bionanosuspension:

20 mg of the formulated nanoparticles was taken and dispersed in 20 ml of the distilled water in a test tube. The time for settling of the dispersed nanoparticles in the bottom was noted and then again the nanoparticles was redispersed and noticed for the redispersion. After shaking any lump or aggregates or any precipitation formation was observed.

pH Study of Bionanosuspension:

The ph of formulated bionanosuspension was evaluated with digital pH meter. The study was done in triplicate and the mean was taken and checked that the pH of the nanosuspension is in required range or not.

% Entrapment Efficacy of Loaded Bionanosuspension:

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The freshly formulated bionanosuspension was taken and centrifuged at 2000 rpm in ultracentrifuge. After centrifugation the supernatant was taken and diluted up to 10 µg/ml and the amount of drug unincorporated was measured by determining the absorbance under UV spectroscopy at 307 nm.The amount of the drug loaded in nanoparticles was calculated by subtracting the amount of free drug in supernatant from the initial amount of drug taken in formulation. This determination was done in triplicate and average was calculated by using the following formula:

$$\% \text{ Entrapment efficacy} = \frac{\text{Amount of the drug loaded in nanoparticles}}{\text{Initial amount of the drug taken in formulation}} \times 100$$

Particle Size screening of the Nanoparticles in Bionanosuspension by UV Method

The bionanosuspension was evaluated by measuring the % transmittance of the bionanosuspension. The % transmittance was measured as a function of the particle size in nano range done by sonication method. The % transmittance depends on the particle size range at the particular range that defines the size particles are below range and size of the particles beyond the range required. The % transmittance was determined before and after the sonication cycle. The % transmittance at different wavelength indicates that when the light is passed through the particles means the particle size is below that wavelength which indicates that % of the particles is below 400 nm in the mixture and the % blockade shows that the % of particles is above 400 nm. The % transmittance was measured by using the UV spectrophotometer. After each sonication cycle the % transmittance was found to be increased due to reduction of the particles to nano range. The effect of sonication on % transmittance was observed after sonication and measuring the % transmittance after each sonication cycle.

Particle Size Analysis

The particle size of the bionanosuspension was studied by characterizing with the Malvern zetasizer. The particle size distribution by intensity was confirmed by using the zetasizer.

***In-vitro* Release Study of Bionanosuspension**

The *in-vitro* release study was performed for the all formulation. *In-vitro* release study was performed by novel static method by using modified M.S.(Madhav-Shanker) Diffusion apparatus. It consists of two compartment one donor and one receiver compartment. The formulation for release study was taken in donor compartment (1 ml) and the end of the donor is tied with the egg biomembrane. This donor compartment was immersed in the receiver compartment having 13 ml of pH 7.4 phosphate buffer solution. Sampling was done at different regular time interval for 36 hours. The samples were withdrawn completely and replaced with the fresh phosphate buffer solutions after every sampling. The samples were analyzed by UV Spectrophotometer for determining the released amount of the drug. The graph was plotted between the % CDR and time. The other parameters like r2, t50 and t80% were calculated for evaluation of release study from different formulations and selection of best formulation.

Stability Study

The stability study was performed as per ICH guidelines. The formulations were stored at different temperatures like at 25℃ ± 2 ℃, 60% ± 5% RH and 40℃ ± 2℃, 75% ± 5% RH for three month in

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humidity chamber. The samples under evaluation were observed for the drug content, pH changes and also any changes in color, odor and taste, its entrapment efficacy and *in-vitro* release study.

RESULT AND DISCUSSION

Isolation of Biopolymer

The *Juglans regia* biopolymer was found to be whitish-cream in color with % yield of 8 ± 1.2%. The color changing point was found to be 275℃ ± 4 ℃.

Characterization of Isolated Biopolymer of *Juglans regia*

The isolated biopolymer [10] was found to be whitish-cream color in appearance. The biopolymer was found to be odorless with characteristic taste. It was found to be sparingly soluble in water. It showed the positive test for carbohydrate and protein. The findings of characterization of isolated biopolymer *Juglans regia* is shown in Table 2.

Table 2: Characterization of Isolated Biopolymer of *Juglans regia*

Parameters evaluated	Observation
Color	White-cream
Odor	Characteristic
Taste	Characteristic
Melting Point	275℃ ± 4 ℃
Solubility	Soluble in water,
	Sparingly Soluble in acetone and methanol
Carbohydrate	Present
Protein	Present

SEM Analysis of Biopolymer

The isolated biopolymer was analyzed by scanning electron microscopy for surface characterization. The SEM analysis shows the rough and flaky structure of the biopolymer. Granular structure was also observed in SEM image. This confirms its polymeric nature of the biopolymer having smooth and amorphous nature. The SEM image of isolated biopolymer is shown in Figure 1.

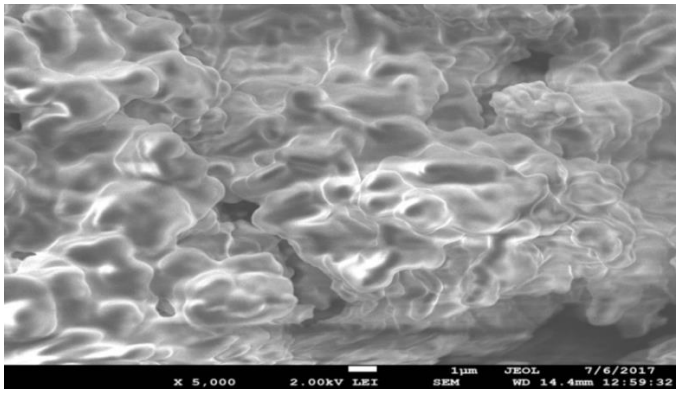

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Figure 1: SEM of Isolated Biopolymer from *Juglans regia* at 5000X

Different Spectral Analysis and Their Findings

I.R. Spectral analysis of isolated biopolymer

The I.R. Spectral analysis of biopolymer shows the presence of different functional groups like hydroxyl (3395.29 cm^{-1}), alkynes (668.01 cm^{-1}), carboxylic acid (1386.63 cm^{-1}) which confirms its polymeric characteristics. The other groups like amide at 1638.82 cm^{-1}, alkanes and alkens at 2926 cm^{-1}, tertiary alcohol at 1100 cm^{-1}, were found to be present in the IR spectra. Presence of these functional groups is responsible for the retardibility in drug release like other standard polymer. IR spectra is shown in Figure 2.

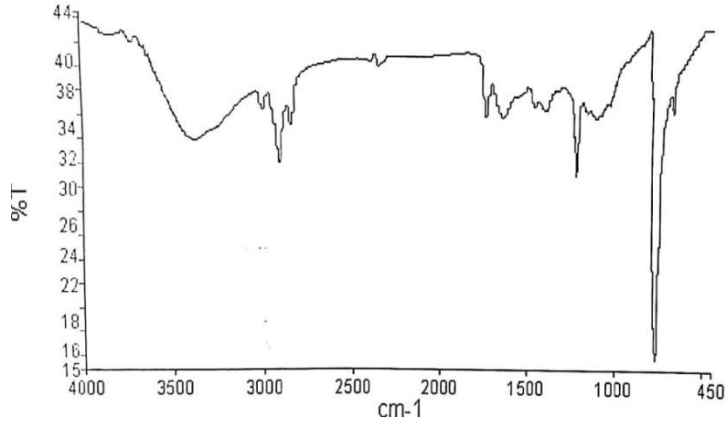

Figure 2: FT IR Spectra of Biopolymer from *Juglans regia*

Differential scanning colorimetry (DSC) Study of isolated biopolymer

The DSC thermogram of *Juglans regia* shows peaks at 83.27Cel and 128.3Cel. The area was found to be 18.24 mj/mg and 0.55 mj/mg respectively. The obtained result reveals its polymeric nature. DSC thermogram is shown in Figure 3.

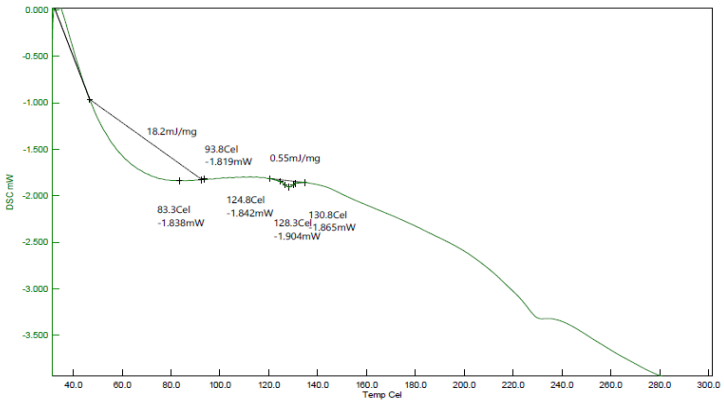

Figure 3: DSC of Biopolymer from *Juglans regia*

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Mass spectroscopy of isolated biopolymer

Mass spectra reveal that the isolated biopolymer is polymeric in nature due to presence of large molecular weight structure. It indicates the presence of protein. HRMS spectra of isolated biopolymer showed the parent peak at m/j 579.29 which confirms its large molecular weight structure like polymer. The high resolution mass spectra is shown in Figure 4.

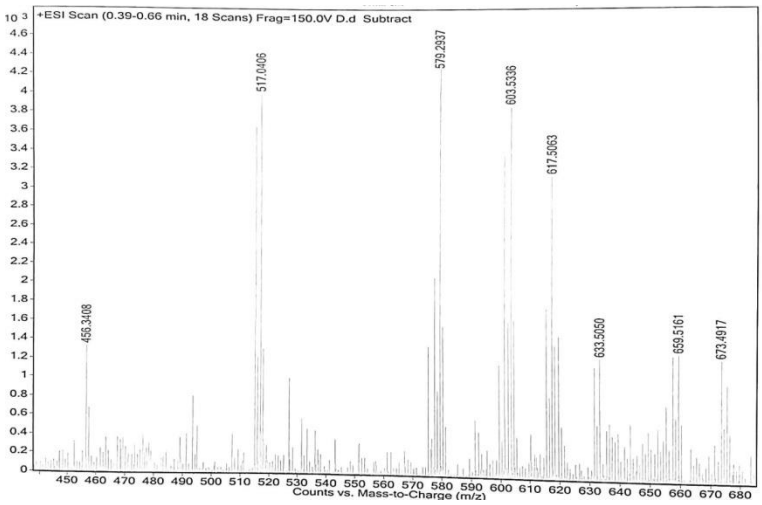

Figure 4: High Resolution Mass Spectrum of Isolated Biopolymer from *Juglans regia*

NMR spectroscopy of isolated biopolymer

The NMR spectra show the presence of different peaks like multiplet at 0.84-0.90 ppm which reveals the presence of primary alkyl group, at 1.25 ppm confirms the presence of methylene group, at 1.26 ppm shows the presence of hydroxyl group, at 2.3 ppm confirms about the presence of ester group, at 4.2 reveals about aliphatic methylene proton and at 7.261 reveals the presence of aromatic group.The presence these groups confirms its polymeric nature. The NMR spectra are shown in Figure 5.

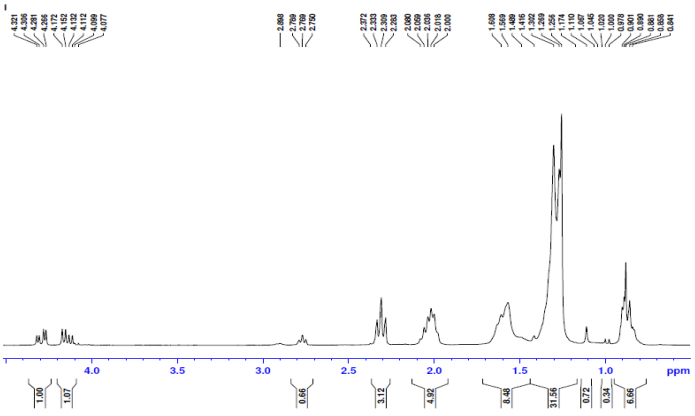

Figure 5: NMR Spectra of Biopolymer from *Juglans regia*

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Nanosizing of Lamotrigine

During the nanosizing of lamotrigine after each sonication cycle the sample was observed for % transmittance that confirm that as the number of cycle increases the % transmittance was increased. This was due to decrease in particle size and particles are now are in nanorange. Thus % transmittance shows the % of particles below 400 nm in bionanosuspension and % blockade give an idea about the % of particles which are above 400 nm. Thus the UV method has given an idea about particles in nanorange.

Drug-Excipient Interaction Study

There was no any change in *λ*max before (307 nm) and after the test (307 nm) in drug excipient study. The *λ*max was found to be same of the drug-biopolymer [11] mixture as that of pure drug. It means it confirms that there was no any interaction between drug and biopolymer and other excipients also. It was observed and confirmed that excipients is not interacting and not producing any changes in drug properties so the isolated biopolymer can be used for the preparation of bionanosuspension.

Formulation of Lamotrigine Loaded Bionanosuspension

The different formulations of bionanoparticles by using different ratio of biopolymer from *Juglans regia* and lamotrigine were prepared. Then after formulation of bionanosuspension was evaluated for different parameters and their finding are described below.

Dispersiblity Study of Bionanosuspension:

The dispersibility of the formulated bionanoparticles was found to be excellent. The redispersion was also found to be good. All nanoparticles were in dispersed state during dispersion. No aggregation or lump formation was observed.

pH study of Bionanosuspension:

The pH of the bionanosuspension was found to be in range of pH 7.1 to pH 7.5. This means the formulations were in desired pH range that is suitable for the stability of the bionanosuspension. The pH of different bionanosuspension formulation observed is given in Table 3.

Table 3: Different Formulations with Observed their Values

Formulations	Observed pH
LJ1	7.1 ± 0.16
LJ2	7.2 ± 0.26
LJ3	7.4 ± 0.42
LJ4	7.2 ± 0.38
LJ5	7.3 ± 0.23
LJ6	7.5 ± 0.32
LJ7	7.4 ± 0.11
LJ8	7.4 ± 0.19

% Entrapment efficacy of loaded bionanoparticles

The entrapment efficacy of the formulated bionanosuspension was found to be 69.88 % to 83.84%. Thus the formulated bionanosuspension showed the maximum entrapment efficacy up to 83.84%.

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Particle size screening of the Nanoparticles in Bionanosuspension by UV method

Here UV method has been used for screening the nanoparticles size in bionanosuspension. As the sonication cycle was increased the % transmittance was found to be increased because the particle size after sonication has come in nanorange. The % transmittance indicated about the % of particles below 400 nm and the % blockade showed the % of particles above the 400 nm when screened by UV spectrophotometry method. Thus UV method can be used as a screening method for the evaluation of nanoparticles size in bionanosuspension. The Nanosizing of Lamotrigine and its characterization by UV method in Figure 6.

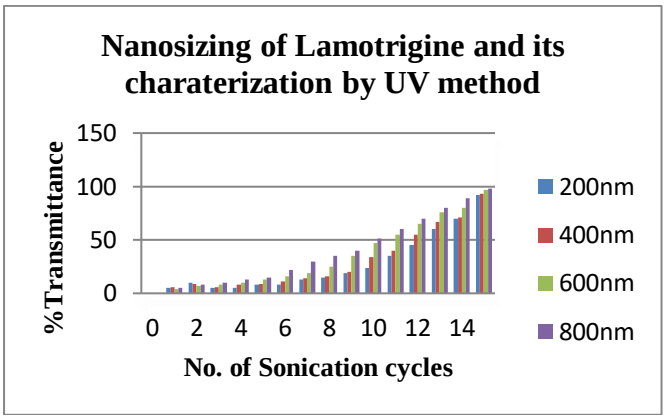

Figure 6: Nanosizing of Lamotrigine and its characterization by UV method

Particle Size Analysis

The nanoparticles size in bionanosuspension was found to be 542.4 nm after evaluation with Malvern Zetasizer. Thus the obtained size with the zeta potential of -15.0 mV confirms that the nanoparticles are in nanoranges which are responsible for the stability of nanosuspension. It also confirms that the stable bionanosuspension loaded with lamotrigine was prepared by using smart isolated *Juglans regia* biopolymers. The result revels that it can be safely used for delivery of lamotrigine in treatment of epilepsy. The particle size distribution in bionanosuspension and Zeta potential distribution of bionanosuspension are shown in Figure 7 and 8 respectively.

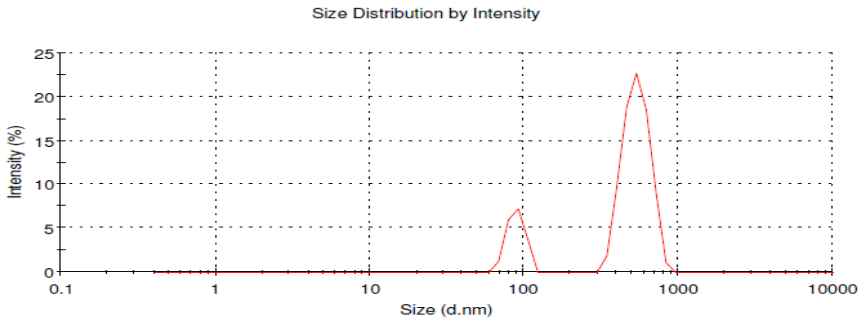

Figure 7: Particle Size Distribution in Bionanosuspension

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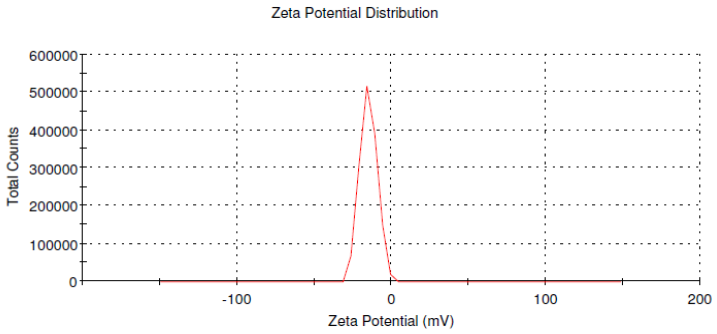

Figure 8: Zeta Potential Distribution of Bionanosuspension

***In-vitro* release study of bio-nanosuspension**

The *in-vitro* release study was done by using M.S. diffusion apparatus. The release kinetic study was done by using the BIT-software and t50% and t80%, r2 were calculated. All the formulation showed more than 90.83% drug release (Figure 9). The *in-vitro* release study of different formulations showed the % drug release from 91.67% to 98.14%. The different formulations were evaluated for the *in-vitro* release study and release kinetic was studied. The formulation LJ7 was found to be the best formulation having t50% of 17 hours and t80% of 30 hours with r2 value of 0.9932. The best formulation LJ7 showed up to 92.051% drug release over 36 hours. According to the release kinetic study the best fit model was found to be Koresmayer-Peppas and the mechanism of drug release was found to be anomalous transport. The result obtained from in-vitro release study and analysis of the release kinetic of the all formulations indicates the sustained release of the lamotrigine from the bionanosuspension.

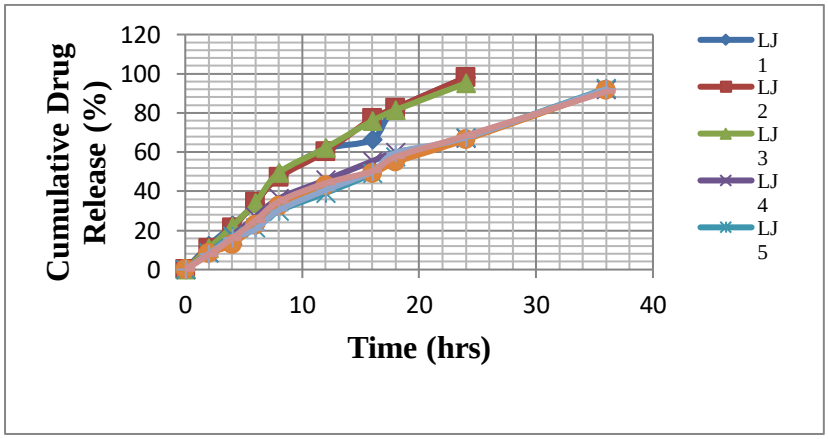

Figure9: *In-vitro* release drug profile of different *Juglans regia* bionanosuspension

Stability Study

The optimized formulation showed no any change in λmax, entrapment efficacy and in drug release. So there was no drug loss during the study period. The other evaluation parameters also showed the satisfactory result. The best optimized formulation was found to be stable during the study period. There was no change in color, odor, pH and physical appearance. During the stability study period all the results obtained from different parameters were satisfactory and the formulation LJ7 was found to be

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the best optimized stable formulation. During the study obtained results confirmed that the formulation was physically and chemically stable because of inbuilt biostabilizing property of the biopolymer.

CONCLUSION

This research work reveals that the isolated biopolymer from the seed of *Juglans regia* showed good polymeric properties. It can be suitably used for the preparation of bionanoparticles in the form of bionanosuspension. The formulated bionanosuspension using this biopolymer showed the good entrapment efficacy. This biopolymer has novel in-built properties like filmability, retardability and release rate controlling capability. It may be used for preparing suitable bionanosuspension. *In-vitro* release and release kinetic study reveals that the isolated *Juglans regia* biopolymers consist of the desired bioretardant and biostabilizing novel properties. The bionanosuspension (LJ7) prepared by using the biopolymer from *Juglans regia* showed the significant entrapment efficacy and sustained release of lamotrigine for more than 36 hours. So biopolymer from *Juglans regia* can be safely used for the formulation of stable bionanosuspension. The isolated *Juglans regia* biopolymer was found to be novel, non-toxic, non-reactive, biocompatible, inert and biodegradable [12]. So the biopolymer can be safely used as the novel biomaterial [13] in delivery of nanosized lamotrigine.

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