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Biopolymer: A Novel Bioexcipient

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Abstract

Polymers are the key material in design of drug delivery systems. These have been shown as the spine for drug development process. These accept an essential part in rising of novel drug delivery systems to crush different intricacies in drug delivery. These are used for controlling the appearance of the drug in needed manner. The hydrophilic and lipophilic polymers are the most ideal choice for getting the ideal conveyance in controlled, manner at the target sites. Isolated of this, these fabricated and semisynthetic polymers are made by different chemical reactions and purification measures. Since these are prepared by different unit operations which are costly. By and by days different investigates are being examined for avoiding the characteristic, physiological and reasonable issues related with the synthetic and semisynthetic polymers. So an alternative rather than synthetic and semisynthetic polymers are being investigated having interest, probability, and any leftover benefits with least troublesome ramifications for environment and physiology of the people. One of the alternatives as opposed to designed and semisynthetic polymers is biopolymers which have pulled in the thought of researchers by using an economical procedures. Biopolymers are novel, adroit and sharp polymers which have been confined from various basic sources. Biopolymers isolated from natural sources might be utilized as novel excipients having a polymeric nature. These isolated biopolymers have superb bioretardant, bio stabilizer, and mucoadhesive properties. These have the brilliant film-framing capacity and biocompatibility properties. The isolated bio-polymers have great drug release rate controlling capacities. Since these are biodegradable and might be utilized as an option in contrast to standard manufactured synthetic and semisynthetic polymers. The isolated biopolymer shows critical biodegradable, mucoadhesive, filmability, and retardability properties which are like properties of standard polymers, may be the alternative in design of novel drug delivery system design.

Keywords: Natural sources, Biomaterials, Biodegradable, Biocompatible, bioretardant, bioadhesive, biostabilizer

1. Introduction

Biocomposites are natural fiber-reinforced biopolymers. Researchers are developing these materials as an alternative to standard materials which will be nonrenewable, recalcitrant, or manufactured by pollution emitting processes. Biocomposites consist of a large variety of organic and inorganic compounds such as natural polymers, synthetic polymers, polysaccharides, sugars proteins, metals, and nanocarbon. While industrial-scale production of biocomposites is becoming

more viable, the sturdiness of those natural materials limits application in many environments. Biocomposites have been described as sustainable materials because of their biodegradability, low ecotoxicity.

2. Biopolymers

Biopolymers [1] isolated from natural sources may be used as novel excipients having a polymeric nature. These isolated biopolymers have excellent bioretardant, bio stabilizer, and mucoadhesive properties. It has the excellent film-forming ability, and bio-stability properties [2]. The isolated bio-polymers have excellent drug release rate controlling abilities. Since these are natural and edible, they are biodegradable and may be used as an alternative to standard synthetic and semi-synthetic polymers [3]. The isolated biopolymer shows significant biodegradable, mucoadhesive, filmability, and retardability properties which are similar to properties of synthetic standard polymers [4]. They have most of the novel properties which can be safely used for drug delivery. The biopolymers are isolated from natural sources [5] which are economical. The synthetic polymers are prepared by using the different chemical treatment which has many harmful effects. The biopolymers have unique novel properties [6]. The biopolymers may be used for controlling the drug release in a sustained way, controlled way, extended way, prolonged way and thus are used as drug carrier bioexcipients [7]. Since they are having a natural origin and biodegradable in nature can be sued for minimizing the unwanted effects with synthetic polymers [8–10].

3. Advantages of novel biopolymer

1. Biodegradable
2. Biocompatible
3. Excellent bioretardant property
4. Biostabilizer
5. Excellent bioretardant
6. Natural
7. Economical
8. Environmental friendly
9. Excellent filmability
10. Excellent filmability

3.1 Bionanoparticles as novel nanoparticulate system

Bionanoparticles are the nanoparticles that are prepared by using the novel biocompatible and biodegradable biopolymers. We can use the novel polymeric properties in developing the bio-nano particles for targeting the drug to the brain

via the blood–brain barrier in an easy way. The bio nanoparticles may release the drug to the target insignificant amount. The bio nanoparticles are stable and their excellent release rate controlling properties makes it novel [11, 12].

3.2 Novel sonication method for nanoparticles preparation

The bionanosuspension can be prepared by a novel method called the sonication method [13]. In this method, the biopolymer as bio stabilizer cum bioretardant was mixed with other ingredients like a preservative, surface active agent like PVA, nanosized with the distilled water to make a well-dispersed suspension [14]. Then the mixture was subjected to bath sonication for 10–15 cycles to formulate the nanosized drug-loaded bionanosuspension [15].

3.3 Evaluation parameters for biopolymeric nanoformulation

A number of evaluation parameters can be performed for the prepared nanosuspension as well as bionanosuspension. The different parameters which should be considered are particle size, particle size distribution, zeta potential, particle morphology [16], dissolution study, stability study, dispersibility, % entrapment efficacy, and in vivo study [13].

The analysis of mean particle size and particle size distribution is an important parameter that defines the stability of the bionanosuspension. Nowadays the particle size and stability parameters can be evaluated by the Malvern zeta sizer. The zeta particle size gives an idea about the particle size and a particle size distribution gives an idea about the state of dispersed particle size, any agglomeration, precipitation or any lump is there.

Particle morphology and state of crystallinity is a parameter that gives an idea about for understanding any changes in drug morphology or structure on nanosizing. The amorphous drug-loaded nanoparticles can be characterized in the nanosuspension as well as bionanosuspension. This can be evaluated by x-ray powder extraction, scanning electron microscopy (SEM) characterization, transmission electron microscopy (TEM) characterization. Differential Scanning Calorimetry (DSC) is also another method for characterizing crystallinity [16].

Zeta potential measurement is another parameter for the evaluation of the particle surface charge which defines the stability of the nanosuspension as well as bionanosuspension. Zetasizer can be used for the measurement of the zeta potential. A minimum of ± 30 mV is generally required for the stability of nanosuspension.

The stability of nanosuspension or bionanosuspension evaluation is very important for the preparation of well-dispersed bionanosuspension. As the particle size is reduced to the nano range, the surface energy is increased and the increased surface energy may lead to the instability of nanosuspension as well as bionanosuspension.

So the uniform particle size distribution leads to the stability of nanosuspension as well as bionanosuspension.

3.4 Advantages of biopolymeric bionanoformulations over other formulations

1. Improved stability of bionanosuspension because of inbuilt properties of biopolymers.
2. Maximum drug entrapment efficacy can be obtained by designing bionanosuspension.
3. Biocompatible.

4. Biostabilizing activity.
5. Desired nanoparticles size can be prepared to cross BBB.
6. Suitable for brain targeting through ear route administration.
7. Enhanced bioavailability.
8. Drug may be released in a retardant manner.
9. Dose reduction to many folds because of longer residence.
10. Enhanced solubility of the drug.
11. Reduction of systemic toxicity.
12. Biodegradable.

3.5 Limitations of bionanoformulations

1. Stability is a big challenge for the nanosuspension for long-term storage.
2. Storage at a specified temperature.
3. Rate of sedimentation of particles during long term storage.
4. Precipitation issues during storage.
5. Accurate dose administration in form of nanosuspension.

3.6 Researches on biopolymer

Umashanker et al, NVS et al have isolated biopolymer from testa of *Lallamantia royalena* (Labiateae) and ready mucoadhesive biomaterial. Biopolymer was isolated by non-solvent technique. Mucoadhesivity of the biomaterial was decided by Park and Robinson and the rotating method. Spectrophotometric methods like UV, IR, TLC were conducted. The biomucoadhesivity of the isolated biopolymer was confirmed by the IR method. In vitro and ex vivo evaluation was also conducted. Kala Shivani, NVS et al have formulated and evaluated bio micro dwarfs of nimesulide by isolating biomaterial from the rhizomes of (*Zingiber Officinalis*) common ginger. A simplified method was used for the isolation of biopolymer. IR characterization was administered for confirming the retardant activity of the biopolymer. In vitro studies, entrapment efficiency, and particle size analysis was also conducted. Tangri, Madhav [17] have isolated biomucoreisident from the fruit pulp of *Artocarpus heterophyllus* commonly known as jackfruit (Moraceae), and formulated zidovudine loaded bio micro dwarfs. Particle size analysis, content uniformity, and IN-VITRO studies were conducted. IR spectrophotometry was also performed which confirmed the muco resident activity of the biomaterial. Muco retentive study was performed in the Novel Madhav Shankar study apparatus. Bisht, Upadhyay [18] have prepared polyherbal formulation for the treatment of dyslipidemia. Various sources from which polyherbal formulation was prepared are *Picorrhiza kurroa*, *Emblica Officinalis*, *Syzygium cumini*, *Trachyspermum Ammi*, *Musa paradisiacal*, *Terminalia arjuna*, pistachio, common ginger, onion, burn plant,

Eugenia caryophyllus, cereal oat. Various tests that were conducted for the evaluation of the formulation are organoleptic, Physico-chemical investigation, viscosity, surface tension, and crude fat content.

Ojha, Madhav [10] have isolated biomaterial from the fruit pulp of *Phoenix dactylifera* commonly called date palm, and evaluated its mucoadhesivity. IR spectrophotometric was performed for confirmation of the mucoadhesive nature of the biopolymer. Other tests like acute toxicity studies were performed for 14 days on rats. The shear stress method and rotating cylinder method was used for evaluating the mucoadhesive nature of the biopolymer.

Yadav, Madhv, [19] have formulated rosiglitazone bio strips for targeting trans labial drug delivery [4]. Authors have isolated biomaterial from the pulp of jackfruit (Moraceae) by the simplified economical process. Folding endurance, Thickness, content uniformity tests were conducted for evaluated various parameters of the prepared formulation. *In-vitro* drug release and stability study was conducted of the bio lip strips. Bansal Abhishek, NVS, Sharma [20] have isolated biopolymer having bio emulgent activity from the fruit pulp of *Prunus institica* and formulated o/w sort of emulsion. The prepared emulsion was compared with a simple emulsion having acacia as an emulsifier. Various other evaluation tests conducted are FTIR, DSC, HPLC, INVITRO drug release study. Varshney Sugandha [21] isolated biopolymer from the fruit pulp of *Manilkara zapota* and ready bio flexy films having nanosized tiagabine as a model drug. The biopolymer which was isolated from the fruit pulp of *Manilkara zapota* was used on the soft palatal surface due to its biodegradable, biocompatible, and non-irritant in nature. Spectrophotometric tests that were conducted are UV, SEM, IR, colorimetry. For the evaluation of prepared bio flex films following tests were conducted folding endurance, thickness, INVITRO drug release study.

Varshney [21] isolated a unique biopolymer from the pulp of Solano melongena and formulated bio flexy films using nanosized tiagabine as a model drug.. The biopolymer which was isolated from the fruit pulp of eggplant was used on the soft palatal surface due to its biodegradable, bio-compatible and non-irritant. Particle size analysis was through with zeta potential. Other spectrophotometric tests that were processed are UV, IR, SEM, NMR. For the prepared bio flexy films following tests were conducted folding endurance, thickness, INVITRO drug release study, weight uniformity test. Varshney [22] isolated unique biopolymer from the pulp of Ananas Cosmoses and formulated bio flexy films loaded with nanosized tiagabine as a model drug. The prepared bio flexy films were used for targeting taste bud drug delivery and therefore the biopolymer incorporated in formulation had biodegradable, biocompatible nature. Solvent casting technique was used for preparation for bio flexy films. Spectrophotometric tests that were conducted are FTIR, NMR, UV, IR, colorimetry. Other tests were conducted are muco retention time, folding endurance, weight uniformity test, thickness, swelling percentage study.

Varshney [23] isolated a unique biopolymer from the seed of pepper and ready bio flexy films to tend through taste bud drug delivery. In the prepared bio flexy films the isolated biopolymer was used as film former and therefore the bio flexy films were used for the treatment of epilepsy. Spectrophotometric tests conducted were FTIR, UV, NMR, DSC, Colorimetry. For the evaluation of prepared bio flexy films muco retention, mucoadhesion, folding endurance, thickness, content uniformity, IN VITRO drug release study.

Sugandha [24] had isolated a unique biopolymer from the petals of Rosa Polyantha and used the biopolymer to organize bio-flexy films for taste bud drug delivery. Within the bio, flexy films nano- sized Tiagabine was used as the model drug. The isolated biopolymer had inbuilt filmability, biodegradable nature, biocompatible, mucoadhesive nature, so it is often used soft palatal surface.

Tests like DSC, UV, ZETA SIZING, Colorimetry was performed. The shear stress method was used for evaluating the muco adhesivity of the biopolymer. Prepared bio flexy films were evaluated for tests like thickness, folding endurance, content uniformity, mucoadhesion, EX VIVO retention study, cell line toxicity studies. Raina and Madhav [25]. Isolated biopolymer from the berries of pepper and ready bionanosuspension using escitalopram as a drug for brain targeting through the ear. Biopolymer isolated from pepper was used as a bio retardant within the bionano-suspension. Formulations were subjected to varied tests like pH, content uniformity, release study, and EXVIVO study. Raina Deepika et al. [26, 27] had isolated biopolymer from the kernels of almond and used the isolated biopolymer for preparing bionanogel loaded with chlorpromazine for brain targeting via the nose. Prepared nanoparticles were evaluated for drug content uniformity, entrapment efficiency, IN -VITRO, muco -adhesivity, SEM, and IR. Mala et al [28] isolated biopolymer from *Cucumis sativus* (cucumber) and used the isolated bioexcipient with cefuroxime to organize bionanogel for the treatment of encephalitis [29]. The isolated biopolymer was characterized by drug-polymer interaction study, Physico-chemical characterization, and acute toxicity study. The prepared bio nanoparticles were subjected to various evaluation tests like pH study, Viscosity, entrapment efficiency, IN VITRO release, in vivo release, and stability study. Kirti Singh et al [30] performed the isolation of biopolymer from the roots of *Rosa centifolia* and *vinifera* and prepared terbinafine loaded bioadhesive layers for the treatment of nail disease onychomycosis. Within the formulation, Beta Vulgaricus was used as a bio penetrant. The formulated films were evaluated for various parameters like nail adhesivity, folding endurance, thickness, content uniformity, and IN VITRO drug permeation and stability studies. Kirti Singh et al [31] prepared bio flexy films containing atorvastatin as model drug and biopolymer isolated from Tapioca Sago. For the evaluation of biopolymer following tests were conducted UV, IR. The prepared bio flexy films were evaluated for parameters like weight, thickness, content uniformity, folding endurance, IN VITRO drug permeation, and surface Ph. Yogita Tyagi, et al [15] performed a search work on the preparation of aripiprazole loaded bionanogel containing bio retardant isolated from the bark of *Cinnamomum verum*. Prepared bio-nano gels were targeted for the brain targeting through layers of skin meninges, transcranial nerves. For the evaluation of prepared bionanogel following tests were administered ph measurement, IN VITRO drug release, and texture, spreadability, and a couple of entrapment efficacy and stability studies. NVS, Yogita Tyagi et al [32] developed bionanogel containing nanosized aripiprazole for brain targeting. The biopolymer used as a bioretardant and bio stabilizer within the nanogel was isolated from Pudina (*Mentha arvensis*). Isolated biopolymer was evaluated spectrophotometrically by IR and UV. Following tests were performed ph measurement, surface pH study, texture, spreadability, % entrapment efficacy, and IN VITRO drug release. Singh Bhavana et al [33] conducted a search study for the preparation of bio flex films containing Venlafaxine drug for the treatment of depression. For the preparation of bio Flexi films, biopolymer was isolated from the fruits of *Luffa acutangula* (angled loofah). Various physicochemical tests were conducted for the evaluation of biopolymers like color, solubility, and chemical tests. Different batches of bio flexy films were evaluated for IN VITRO and in vivo drug release, folding endurance, thickness. Bioflexy films were successful in sustaining the drug release so it is often concluded that biopolymer isolated from angled loofah has promising inbuilt mucoadhesive nature. Tyagi and Madhav [34] developed bionanosuspension having biopolymer which is isolated from seeds of *Buchanania lanzan* (Chironzi). In the bionanosuspension, the isolated biopolymer was used as a bioemulgent. Prepared bionanosuspension was used for the treatment of depression and its safety and compatibility were proved through various evaluation

tests. For the characterization of biopolymer various spectrophotometric tests like DSC, UV, IR, SEM, and NMR were used. Bionanosuspensions was evaluated with the assistance of Particle size distribution studies, IN VITRO release, pH stability studies. Tyagi and Madhav [13] developed bio nanosuspension of fluvoxamine for the management of depression. The bio nanosuspension was incorporated with the novel biopolymer *Santalum album* (sandalwood tree) and it had been designed for ophthalmic delivery of the drug. Isolated biopolymer from solvent evaporation method was subjected to varied spectrophotometric tests like IR, DSC, SEM; AND NMR. Prepared bionanosuspension was evaluated for various evaluation tests like particle size, zeta potential, entrapment efficacy, IN VITRO drug release, stability studies. Ophthalmic delivery of fluvoxamine was proved to be the novelistic approach for the treatment of depression.

Madhav [35] stated that a novel biopolymeric the material can be used to prepare drug-loaded biomicrodwarfs from *Arachis hypogea* seeds. The goal was to produce a product with a significant processing advantage that satisfies pharmaceutical formulators in scale-up processes. The biopolymer was isolated and characterized for its capability and efficacy to control the release of the drug. Gupta et al. [36] have reported a method for isolation of a novel biodispersant from the seeds of *Cicer arietinum* and formulation of Escitalopram granules containing bio-dispersant. Bio-dispersant was isolated by the treatment of the extract from seeds of *Cicer arietinum* with double distilled water and with ethanol and the bio-dispersant was collected and further analyzed for physicochemical properties like color, odor, particle size, shape, solubility, and IR spectral studies. The preparation of Escitalopram, granules were done using drug, lactose, bio-dispersant, bio-binder, and other processing agents. We have prepared six different formulations with varying bio-dispersant concentration and bio-binder concentrations. Tangri et al., [37] detailed a method for the formulation and evaluation of sustained-release tablets of atorvastatin by utilizing the biomaterial as a novel binder for the formulation of tablets. For the isolation of biomaterial unripe fruit pulp of *Artocarpus heterophyllus* was taken and the process of isolation used was simplified economic process. The extracted biomaterial was subjected for various physical and chemical parameters like color, color changing point, chemical tests, and I.R. spectral study. Various formulation additives were used to prepare Ibuprofen sustained-release tablets. The three atorvastatin-loaded formulations (FA1-FA3) were prepared by using different drug-polymer ratios of 1:1, 1:3, 1:5, and other excipients like starch, talc, and lactose as diluents. Erasmus et al. [38] reported that cereal grains can also be used as an agricultural raw material rich in several biopolymers. Cereal grains contain major biopolymers like starch, protein, non-starch polysaccharides, and lipids. Dry milling, wet milling, or a combination of both can be used for the primary extraction of the biopolymers. The grain is separated into its anatomical components by conventional dry milling. Anatomical components can be enriched in certain biopolymers like endosperm flour consist of approximately 80% starch. Madhav et al. [39] described the novel biomaterial from the unripe fruit pulp of *Artocarpus heterophyllus* and the evaluation of its bio-emulsifying ability by the formulation of escitalopram loaded emulsions. The isolation of biomaterial was done from the unripe fruit pulp of *Artocarpus heterophyllus* by the simple and economic process. It was subjected to various Physicochemical parameters like color, color changing point, different chemical tests, and I.R. spectral study. Four drug-loaded emulsions were formulated (AH1-AH4) by using varying ratios of the biomaterial. Escitalopram was used as a model drug for the formulation of emulsions. Evaluation parameters like globule size, pH, the effect of centrifugation, viscosity, surface tension, creaming, freezing and thawing cycles, and *in-vitro* release were conducted on the formulated emulsions. The

presence of saturated hydrocarbons, aromatic ring secondary, and tertiary alcohol groups was reported in the IR spectra of the isolated biomaterial. Singh [40] described the various components involved in pharmaceutical formulation development apart from active pharmaceutical ingredients. In recent years, the core area of research in pharmaceutical drug delivery is the excipient development because of its effect on the formulation designing development and targeted drug delivery process in various ways. Because of their low toxicity, biodegradability, stability and renewable nature biopolymers have become the choice of research as excipients. In this review, some of the most commonly used biopolymers as excipients in pharmaceutical drug delivery systems designing have been discussed. Velde et al. [41] described that to know the most suitable matrix polymer, before starting the designing it is very important to know the properties of the available polymers. It was reviewed to give information on the most suitable property of a range of biodegradable polymers. Since the data are widely scattered over many sources and are very scarce compared to the conventional polymer. Data were presented mostly as ranges as well as in graphs for quick comparison reasons. One specific application, thermoplastic pultrusion with flax as reinforcement has been also studied. Singh et al. [42] isolated the biopolymer from Tapioca sago. After isolation, it was characterized for different parameters like viscosity, pH, conductivity, and other physical characteristics. The biopolymer was also tested for the presence of carbohydrates and proteins. The isolated biopolymer was also analyzed for different spectral analysis like FTIR. The isolated biopolymer was used for the preparation of bio gel loaded with curcumin for the dermal delivery. It was concluded that the curcumin-loaded bio gel can be effectively used for the treatment of the wound by using a novel isolated biopolymer from sago as a novel retardant cum stabilizer.

3.7 Bionanoformulation in drug targeting

Madhav et al. [6] developed and evaluated duloxetine loaded bionanosuspension. The bionanosuspension was prepared by using the biopolymer isolated from *Prunus amygdalus* seeds. The biopolymer was characterized for different Physico-chemical characterization and different spectral characterization. The biopolymer was isolated by the simple economical extraction process and treatment with propanone and then solicited. The residue was recovered and dried to get the free-flowing powder. The duloxetine loaded bionanosuspension was prepared by the bath sonication method. The prepared bionanosuspension was then evaluated for different parameters like particle size, entrapment efficacy, dispersibility, zeta potential, in-vitro release, and in-vitro kinetic study, and also in-vivo study for the determination of the amount of duloxetine reached to brain via external acoustic meatus.

Madhav et al. [6] explored the feasibility of external acoustic meatus for targeting escitalopram bionanosuspension to the brain. The research reveals that escitalopram loaded bionanoparticles were found to be targeted to the brain via external acoustic meatus administration. The bionanosuspension was prepared by using the biopolymer from *Piper nigrum* in a different ratio. The biopolymer consists of the novel retardant properties to release the drug in a sustained manner. The research reveals that *Piper nigrum* can be safely used for the development of bionanosuspension for targeting the brain via external acoustic meatus. Raina et al. [6, 14, 25, 39, 43] described the preparation of duloxetine loaded bionanogel for brain targeting via external acoustic meatus. In the research work, the biopolymer was isolated from Tagetes papule and its ability in developing the duloxetine loaded bionanogel for brain targeting. In the findings of the research, the biopolymer was found to have a novelistic characteristic as polymeric nature in developing the

bionanosuspension. The bionanosuspension was found to be suitable for delivering the drug to the brain. So the conclusion was that the external acoustic route can be used as the promising route for drug targeting to the brain in the treatment of depression. Madhav et al. [14] describe the formulation of chlorpromazine bionanogel by using the isolated biopolymer as a bioretardant from *Prunus amygdalus* [44]. The prepared bionanogel was evaluated for the delivery of chlorpromazine targeting to the brain. The nanoparticles were prepared by the solvent evaporation method. The formulated bionanogel were evaluated for the t50%, *in-vitro* release, *in-vivo* release study, and pharmacokinetic study. FA8 (1:15) was selected as the best formulation. Madhav et al. [6] researched the development of nanosized duloxetine via external acoustic meatus. The bionanosuspension was developed by using the biopolymer from the berries of *Piper nigrum*. The prepared bionanosuspension was evaluated for the different parameters like pH, % transmittance, content uniformity, and *in vitro* drug release and *ex Vivo* study. The obtained results were found to be significant for the treatment of CNS disorder. The drug was found to be targeted to the brain insignificant amount and this route was found to be suitable for the delivery of duloxetine and in the treatment of depression.

Tyagi et al. [28, 45–47] researched on a new novel innovative approach for the development of the fluvoxamine-loaded bionanosuspension. The bionanosuspension was prepared by using the isolated biopolymer from the *Santalum album*. The biopolymer was characterized for *in-vitro release*, t50%, r² values, and kinetic study to know the drug release mechanism. The results were evaluated for identifying the best fit model in drug release. Thus it was concluded that the isolated biopolymer can be suitably used for the development of stable drug-loaded bionanosuspension [16, 48–50].

3.8 Isolation and characterization of biopolymers

1. Isolation of biopolymer from natural sources.
2. Preformulation study of biopolymers system.
 - a. Physical appearance, taste, shape, and texture.
 - b. Solubility study.
 - c. Particle size analysis by optical microscopy.
 - d. Bulk density determination.
 - e. Tapped density.
 - f. The angle of repose.
 - g. Percentage consolidation Index.
 - h. Melting point testing.
 - i. Chemical test.
 - j. SEM analysis.
 - k. FTIR spectroscopy.

l. NMR spectroscopy.

m. Mass spectroscopy.

n. DSC testing.

o. Cell line toxicity study.

3. Formulation of drug-loaded bionanoparticles as dispersed bionanosuspension using biopolymer.

3.9 Isolation of biomaterial from *the natural source*

200 gm of *natural sources like* seeds, bark, fruits, legumes, kernels, flowers are soaked overnight in purified water. The upper covering of the almond was then removed. About 100 ml of water was added to this and this mixture was mixed in a mixer. This slurry was filtered with the help of muslin cloth and thus the biomaterial was separated by filtration. The resultant was obtained as filtrate. After that, the mixture was subjected to centrifugation at about 4000 rpm for 15 minutes and then the resultant supernatant layer was properly separated and taken. Then acetone was added in the ratio of 1:1 and mixed properly. This mixture was kept in the refrigerator overnight at 4°C and the solution was centrifuged at 4000 rpm for 30 minutes. The residue was collected having biomaterial and dried in desiccators for 24 hours. This residue of biomaterial was washed with acetone and the biomaterial was dried naturally for 10 hrs for getting free-flowing powder. The collected biomaterial for stored in airtight containers after passing through sieve no. 120 for further use. The schematic flow chart of the isolation procedure has been summarized in Flow chart 4.1. This procedure was repeated six times and optimized and then the percentage yield was calculated and reported [6, 25].

4. Physicochemical characterization and evaluation of isolated biomaterial

4.1 Physicochemical characterization

The color, odor, taste of isolated biomaterial were physically evaluated. The shape of the biopolymer was also observed under the optical microscope. The color-changing point was determined by using the melting point test apparatus. The isolated biomaterial powder was filled in the capillary tube completely and it was kept in a melting point test apparatus (Cystronics). The apparatus was switch on and observed for the temperature at which color changing was observed and melting of biomaterial starts. The temperature was observed with the help of a thermometer. The organoleptic properties like color, odor, taste were observed. The pH was determined for 1% w/v aqueous solution with the help of a digital pH meter (Cystronics). The tests were performed in triplicate (n = 3) and reported [4, 51–57].

4.2 Solubility

The solubility study of the isolated biopolymers was performed in different solvents like water, acetone, methanol, ethyl acetate, 10%w/v hydrochloric acid

solution, and diethyl ether and reported. The excess of the isolated biomaterial was added in 10 ml of the specific solvent system in the beaker gradually. The solution was dispersed well and kept for 24 hours on an orbital shaker for achieving an equilibrium state.

Then the solution was centrifuged at 400 rpm in the centrifuge for 10 minutes and then filtered to get the clear solution. Then the filtrate was allowed for measurement in a UV spectrophotometer machine (Mapada). The procedure was performed in triplicate for each isolated biopolymer [4, 25, 56–59].

4.3 Particle size analysis

This was performed by using the optical microscopy method. The isolated biomaterial was taken on the glass slide and added 1 drop of glycerin. The coverslip was placed on the drop and examined with the help of calibrated eyepiece micrometer under the optical microscope. During the examination, about 100 particles were counted and the particle size distribution was determined [56]. This was performed in triplicate, calculated, and reported with the help of the following equation.

$$Xg = 10 \times \left[\left(\sum n_i \times \log X_i \right) / N \right]. \quad (1)$$

Xg is geometrical mean diameter, n_i is the number of particles in range, X_i indicates to the midpoint of the range of particle size and N refers to a total number of particles.

5. Flow property

5.1 Bulk density

The bulk density of the isolated biomaterial powder was calculated by taking accurately pre-weighed biopolymer in the measuring cylinder and then the bulk volume of the filled powder was measured. This was performed in triplicate. The bulk density was calculated and reported [56].

5.2 Tapped density

Tapped density of the isolated biomaterial was determined by taking a pre-weighed biopolymer in a measuring cylinder and then tapped for 100 tappings. Then the tapped volume was determined. This was performed in triplicate. The tapped density was calculated and reported [56].

5.3 Angle of repose

The angle of repose of isolated biopolymer was determined by the funnel method. Accurately weight the biopolymer was taken in the funnel. The funnel was adjusted at a height so that it just touches the apex of a heap of biopolymer powder. The powder was subjected to flow through the funnel freely on the surface. This was performed in triplicate. Thus the angle of repose was calculated and reported. The obtained results were correlated with <25° with excellent flow, 25–30° with good flow, and 30–40° –passable [60–62].

5.4 Carr's Index of compressibility

It was used for the determination of flow properties. It is a very simple, fast, and widely used method for determining powder flow characteristics. % consolidation index calculated and reported this was performed in triplicate [56].

5.5 Tapped density

According to Carr index powder with 10% flowability is considered as excellent flow characteristics. Powder with less than 15% flowability is considered as a powder with good flow characteristics [56].

6. Chemical tests of isolated biomaterial

6.1 Tests for carbohydrate

1 ml of freshly prepared biomaterial solution (5% w/v prepared biomaterial solution in double-distilled water) was taken in the test tube. Add two drops of Molisch reagent. Add 1–2 ml of conc. Sulfuric acid in the test tube and observed for the appearance of purple color at the interface of two layers formed. The test was performed and reported [4, 5, 40, 56, 63–65].

6.2 Test for protein

For testing the presence of protein in the isolated biomaterial was treated with 0.1% solution of ninhydrin reagent and 10% tannic acid solution. The presence of blue color and yellow color precipitate indicates the presence of protein. The test was performed and reported. Madhav and Yadav et al. [4] reported about the proteinous nature of biomaterials.

Biuret test was performed for the confirmation of proteins. 2 ml of *Prunus amygdalus* biomaterial was taken in the test tube (5% biopolymer solution in distilled water), add 1 ml of sodium hydroxide solution with the addition of copper sulfate solution drops. The mixture was kept aside for five minutes and observe any color changes. The appearance of violet color confirms the presence of proteins [37]. The test was performed and reported [4, 5].

6.3 Spectral analysis of the biomaterial

Spectral analysis of the isolated biomaterial was conducted like I.R, NMR, Mass spectroscopy, SEM studies. The biomaterials were subjected to IR, NMR, Mass spectroscopy studies, and the obtained spectra were interpreted and reported. SEM studies of different biomaterials were also performed and the obtained results were interpreted and reported. I.R, N.M.R, Mass spectroscopy was studied at Central Drug Research Institute, Lucknow, and SEM studies were studied at Birbal Sahani Institute of Paleobotany, Lucknow [62].

6.4 SEM (Scanning electron microscopy)

The isolated biomaterial's surface morphologies were characterized by Scanning Electron Microscope. In SEM analysis the external surface and internal structure were characterized. **Figure 1.** reveals about the flaky and rough surface of biopolymer [4].

Figure 1.
SEM of isolated biomaterial *Litchi chinesis* 1500x.

6.5 FTIR spectroscopy

The FTIR spectroscopy was done by preparing the KBr discs. 1 mg of isolated biomaterial was taken and mixed with 100 mg of dried and desiccated solid powder of potassium bromide. The mixture was uniformly mixed in mortar and pestle and placed in an IR lamp to remove any moisture. The mixture was converted into a disc under the pressure of 10 tons. The prepared disc was placed in the disc holder in the path of infrared radiation. In the range of 4000–200 cm^{-1} , the spectrum was recorded [4, 62] **Figure 2.** Defines the FTIR spectroscopy

Figure 2.
IR spectrum of the isolated biomaterial *Litchi chinesis*.

of the isolated biopolymer from Litchi chinesis. The biopolymer showed the presence of The IR spectra revealed the presence of secondary alcohol (1099.83 cm^{-1}), aromatic nitro and phenol groups (1316.59 cm^{-1}), aromatic rings (1544.70 cm^{-1}), and the presence of alkenes (1652.02 cm^{-1}), with $-\text{CH}_2$ and $-\text{COOH}$ stretching (2928.35 cm^{-1}) along with β -diketones and $\text{O}-\text{NO}_2$ (1652.02 cm^{-1}). The presence of these functional groups were found to be similar with the functional groups observed in standard polymers. This functional groups revealed its polymeric nature [4].

6.6 Mass spectroscopy

It is a useful powerful technique used to quantify known materials and for identification of unknown materials and the elucidation of the structure and chemical properties of the molecule. It is an accurate method for determining the molecular mass of the compound. This is the laboratory technique in which the sample of biopolymers was introduced through the inlet system. The gas-phase ions of the compound were produced. Then molecular ion fragmentation, the ions separated in mass spectrometer according to their mass to charge ratio.

6.7 NMR spectral analysis

The NMR spectroscopy is done for spectral analysis of isolated biopolymer. The NMR spectra of different isolated biomaterials confirmed the biopolymeric nature of standard polymers [4].

6.8 Differential scanning calorimetry

In DSC testing is the thermal analysis technique in which the heat flow in or out of the sample for testing is determined as the function of temperature. Here the biopolymer sample was taken and exposed to a controlled temperature program. The glass transition temperature was determined. The heat flow range was $50\text{--}300^\circ\text{C}$. The DSC thermogram was recorded, interpreted, and reported [4, 62].

6.9 Cytotoxicity evaluation of biomaterial

Cytotoxicity evaluation of isolated biopolymer was done on the Neuroblastoma cell line. The materials used are Cell line–SHSY-5Y, (human breast cancer cell line), Ham F-12 media, Fetal Bovine Serum (FBS), the antibiotic-antimicotic solution from Thermo scientific and MTT reagent from Sigma Aldrich, USA. Tissue culture flask, 96,6 well micro-culture plates from Eppendorf, Germany. In the method, the maintenance of cell lines, the subculturing procedure of cell lines, trypsinization, cryopreservation of cell lines was done. In MTT assay the formazan product is analyzed spectrophotometrically (540 nm) after dissolution in DMSO, the spectra of treated and untreated cells giving an estimate of the extent of cytotoxicity [13, 66].

6.10 Reagents

- 1.5 mg/ml MTT solution prepared in DPBS
2. Cell culture grade DMSO

6.11 Preparation of drug dilutions: (serial dilution method)

Firstly 50 mg/ml stock solution was prepared using 100% DMSO solution. From this prepared stock solution various desired final concentrations like 62.5, 125, 250, and 500 µg/ml of test compound solution was prepared as follows:

The dilution factor was 2 for the MTT assay.

For 500 µg/ml: 10 µL sol. Was taken from stock and to this 990 µl media was added.

For preparation 250 µg/ml: From 500 µg/ml solution the 500 µl was taken and was diluted with the 500 µl with media.

For preparation 125 µg/ml: From 250 µg/ml solution the 500 µl was taken and was diluted with the 500 µl with media.

For the preparation of 62.5 µg/ml: From 125 µg/ml solution the 500 µl was taken and then diluted with the 500 µl with media.

Exponentially the well-growing cell lines were collected from a 25 cm² Tissue culture flask and a stock cell suspension of 5X10⁴ cell/ml was prepared. A 96-well flat-bottom tissue culture plate was seeded with 5 x10³ cells in 0.1 ml of F12 medium supplemented with 10% FBS and then allowed to attach for 24 hours. Test compounds were prepared just before the experiment conduction and serial dilution was done with medium to get the working stock of different 200, 100, 50, and 25 µg/ml solutions. After incubation for 24 hours, the cells were treated with 100 µl of test solutions from respective above stocks, and after treating the cells were incubated for 48 hrs. The cells present in the control group received only the medium containing the 0.5–0.25% DMSO. Each treatment procedure was performed in triplicates. After the treatment duration, 30 µL 5 mg/ml MTT solution was then added to each well, and the whole was incubated for 3 hours at 37°C in maintained sterile conditions. After the completion of incubation time, the MTT containing media was removed carefully from all wells then formazan crystals were dissolved by adding 100 µL of DMSO. The plate was shaken for 5 minutes on a gyratory shaker machine and the optical density was noted at 540 nm in an ELISA plate reader. The percentage of cell viability was calculated. O.D of each well was read and expressed as % cell death: (Absorbance of control wells- absorbance of test wells/absorbance of control wells) x 100. Results were expressed as the mean ± S.E.M. The O.D values (proportional to cell death) were plotted against the tested drug concentrations and then interpreted [3, 4, 13, 34, 45].

7. Formulation of drug loaded bio-nanoparticulate system

The different formulations of bio-nanosuspension were prepared by using different drug-biopolymer ratio and drug-standard polymer ratio. 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 nanosizing agent [9, 13, 67, 68]. The lamotrigine, biopolymer, and other excipients were accurately weighed and triturated with the 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 of the formulations was made up to 10 ml with double distilled water having sodium benzoate 0.1–0.5%). Add dextrose if necessary as a nanosizing agent and allowed for sonication for 15 cycles at 4000 rpm. After sonication, the bionanosuspension was refrigerated for two days [11, 41, 69, 70]. If no settlement is there then it means the formulation is optimized. If the settlement is there, then 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 were prepared. In the same way, the nanosuspension was also prepared by using lamotrigine with a standard polymer like hydroxypropyl methylcellulose [3, 4, 13].

8. Future aspects

1. The isolated biopolymers still have not explored for their novel inbuilt characteristics in drug delivery, which can be used as an alternative to standard polymers as these are biodegradable, biocompatible, and bio-retardant cum bio stabilizer in nature [71–75].
2. The biopolymers may be isolated in economical ways from the different edible natural sources [76–78].
3. Thus economically isolated biopolymer can be safely used for developing the most suitable and stable drug-loaded bio-nanosuspension in drug targeting in a very significant way route with maximum patient compliances [36, 38, 57, 79–81].
4. Thus the isolated biopolymers have a number of novel properties which can be used as a novel bioexcipient in design of novel drug delivery design. Apart of these inbuilt novel properties these isolated biopolymer are economical in production. The current researches and finding provide an alternative to standard polymers and retardant excipients in very economical rate of production with a number of smart inbuilt bioretardant cum biostabilizing properties.

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