Herbal Nanoparticles: A Recent Trend

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Abstract- *Herbal medicines have been used all over the world from last many years. Especially in India, there is wide market for herbals. Herbal nanotechnology has been a many scientific approach. So many chronic diseases like cancer, wound healing can be cured by nano herbals more effectively as compared to allopathic medicines. Various methods used for the formulation of herbal nanoparticles likes salting out, nanoprecipitation, emulsification etc. Herbal remedies were selected as feasible drug candidate for nanoparticles because of their properties like dose reduction, target specificity, patient compliance. various methods used for characterization of herbal nanoparticles like scanning electron microscopy, in vitro drug release, FTIR,Zeta Potential Etc. Nanoparticulate formulations such as liposomes, polymeric nanoparticles, micro-emulsions, Proliposome, and solid lipid nanoparticles present potential to deliver herbal medicines effectively and also increases bioavailability of drugs.*

Keywords- Herbal Nanoparticles, Method of Preparation, Characterization

I. INTRODUCTION

For a long time, herbal medicines were not considered for development of novel formulations due to lack of scientific justification and processing difficulties but modern phytopharmaceutical research can solve the scientific needs (such as determination of pharmacokinetics, mechanism of action, site of action, accurate dose required etc.) of herbal medicines to be incorporated in novel drug delivery system, such as nanoparticles, microemulsions, matrix systems, solid dispersions. [1] Nowadays, there has been a change in global trend from synthetic to natural medicine, which we can say "back to nature." The efficiency of medicinal plant species, or herbal medicine, depends on the active molecules present since they provide synergistic action and thus enhance the therapeutic [2].

There are three main reasons for the popularity of herbal medicines:

- There is a growing concern over the reliance and safety of drugs and surgery.
- Modern medicine is failing to effectively treat many of the most common health conditions.
- Many natural measures are being shown to produce better results than drugs or surgery without the side effects [3].

The activity of herbal medicines depends on overall function of a variety of active components. Each active constituent plays an important role and they are all related to each other. The invention of nanotechnology is considered as a milestone in medicine world. In case of herbals, nanotechnology becomes a great remedy to overcome the problems arising now days [4].

Nanotechnology in herbal drugs Nanotechnology can be used to enhance delivery of poorly water soluble herbal drugs, targeted delivery in a cell or tissue, also a cross tight epithelial and endothelial barriers, release of large herbal molecules, co-delivery to two or more drugs and observation of sites of drug delivery by incorporating herbal drugs with imaging modalities [6-8]. Applications of nanotechnology formulated herbal drugs are schematically represented in Figure 2. Table 1 summarizes the various nanostructured herbal formulations, their different applications and biological activities [5].

II. NEED FOR HERBAL NANOPARTICLES

Most of the herbal origin drugs possess low lipid solubility character leading to lower bioavailability and increased systemic clearance requiring frequent administration or higher dose, which makes the drug as a poor candidate for therapeutic use. The discovery of nanotechnology is considered as a milestone in medicine world. Before reaching systemic circulation, so many constituents of the herbal drugs will be degrade in the highly acidic pH of the stomach and some other might be metabolized by the liver. Hence, the optimum quantity of the herbal drugs may not reach the systemic circulation. For desire therapeutic effect minimum amount of dose should be there in systemic circulation but due to this degradation one might not get it.Herbal remedies were selected as drug candidates for delivery through a nano delivery system because many effective molecules soluble in chloroform, petroleum ether, acetone, and methanol are not will be suitable for delivery as such. In addition, these are the bulk drugs so dose reduction is intended [2] . Nano carriers applying to herbal remedies will carry optimum amount of the drug to their site of action bypassing all the barriers such as

acidic pH of stomach, liver metabolism and increase the prolonged circulation of the drug into the systemic circulation due to their small size[6] .

Herbal remedies were selected as feasible drug candidate for nanonization because of the following properties:

1. These are the bulk drugs so dose reduction is intended.
2. Patient non-compliance due to large doses and less effectiveness with the available formulations.
3. Currently marketed formulations lack target specificity for various chronic diseases. [4][6]

III. APPLICATION OF NOVEL DRUG DELIVERY SYSTEM FOR HERBAL REMEDIES

NDDS is designed to overcome the drawbacks of the traditional herbal drug system due to its wide applications to mankind.

1) Nanoparticle can be used to target the herbal medicines to individual organ which improves the selectivity, solubility, drug delivery, safety, effectiveness and reduces the frequent dose.
2) The nanoparticle size drug delivery enhances the entire surface area of the drugs therefore allocating quicker dissolution in the blood.
3) Reduction in toxicity while maintaining therapeutic effects.
4) 4.The enhanced permeation and retention of nanoparticles can cross Blood Brain Barrier (BBB).[7]

IV. TYPES OF NANOPARTICLES [8]

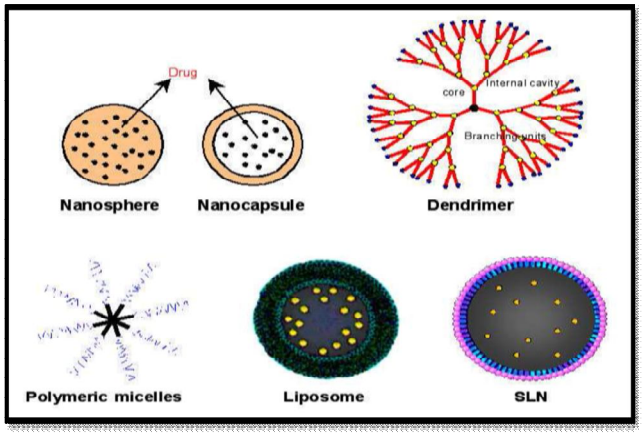

Figure 1.

V. METHOD OF PREPARATION OF HERBAL NANOPARTICLES

a) Solvent Evaporation:

In this method, there is conventional formation of o/w emulsion between a partially water miscible solvent containing the polymer and the drug, and an aqueous phase containing the stabilizer. In this polymer is dissolved in an organic solvent such as dichloromethane, chloroform, but are now replaced with ethyl acetate which has a better toxicological profile. In the conventional methods, two main strategies are being used for the formation of emulsions, the preparation of single-emulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in-water, (w/o)/w. Oil in water (o/w) emulsion is prepared by emulsification of drug and polymer mixture in aqueous solution which contain emulsifying agent, which result in formation of stable emulsion. After that by using pressure reduction method or continuous stirring, organic solvent is evaporated. Afterwards, the solidified nanoparticles can be collected by ultracentrifugation and washed with distilled water to remove additives such as surfactants. Finally, the product is lyophilized [9][10][11].The homogenizer speed, nature and stabilizer concentration along with the property of polymer effect size of nanoparticles. Usually high speed homogenizer or ultrasonication had been used to reduce the size of nanoparticle to an optimum size [10][11][12].

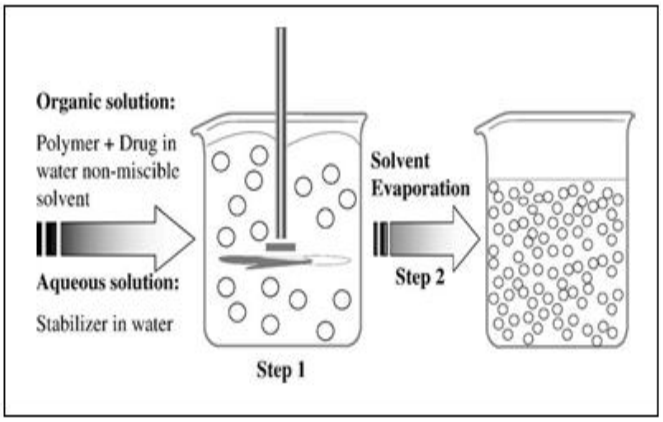

Figure 2. Solvent-Evaporation Technique.

b) Nanoprecipitation Method:

The Nanoprecipitation technique (or solvent displacement method) for nanoparticle manufacture was first developed and patented by Fessi and co-workers. This technique presents numerous advantages such as in that it is a straightforward technique, rapid and easy to perform. The nanoparticle formation is instantaneous and the whole procedure is carried out in only one step [13]. It involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium in the presence or absence of a surfactant [14]. Briefly,

it requires two solvents that are miscible with water. Ideally, both the polymer and the drug must dissolve in the first one (the solvent), but not in the second system (the non- solvent). Nanoprecipitation occurs by a rapid desolvation of the polymer when the polymer solution is added to the non-solvent (aqueous solution). Indeed, as soon as the polymer-containing organic solvent has diffused into the aqueous medium, the polymer precipitates, involving immediate drug entrapment [13]. Polymer deposition on the interface between the water and the organic solvent, caused by fast diffusion of the solvent, leads to the instantaneous formation of a colloidal suspension [15]. This method does not require extended shearing/stirring rates, sonication or very high temperatures. This technique is mostly suitable for compounds having a hydrophobic nature which is soluble in ethanol or acetone, but displays very limited solubility in water. Consequently, reduced or even zero drug leakage toward the outer medium led to nanoparticles with entrapment efficiency values reaching 100% .However, recent research dealing with water-soluble drug incorporation has also provided encouraging results[12][13]. This method has been applied to various polymeric materials such as PLGA36, PLA43, PCL44, and poly (methyl vinyl ether-comaleic anhydride) [9][16].

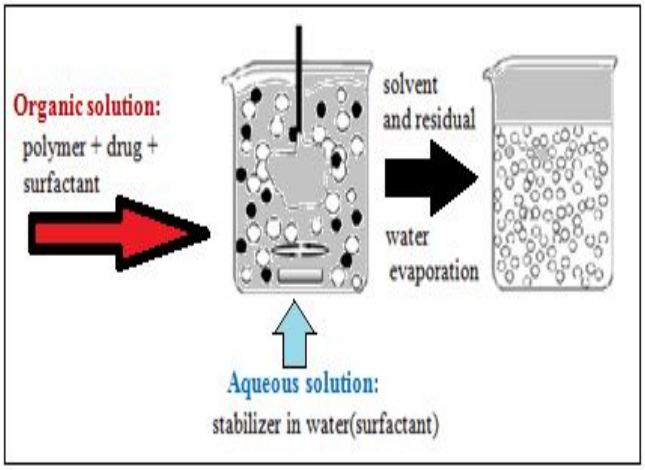

Figure 3. Nanoprecipitation Technique.

c) Emulsification/solvent Diffusion (ESD):

It is also known as modified version of solvent evaporation method. In this method, two phase solvent is used, one is water miscible and other is water immiscible i.e. organic in nature which act as oil phase. In this method interfacial turbulence is created, by immediate diffusion between two solvents (which are differing in phase) which lead to the formation of small particles [11]. Finally, the solvent is eliminated by evaporation or filtration, according to its boiling point. This technique presents several advantages, such as high encapsulation efficiencies (generally >70%), no need for homogenization, high batch-to-batch reproducibility, ease of scale-up, simplicity, and narrow size distribution. Disadvantages are the high volumes of water to be eliminated from the suspension and the leakage of water-soluble drug into the saturated-aqueous external phase during emulsification, reducing encapsulation efficiency [9]. As with some of the other techniques, this one is efficient in encapsulating lipophilic drugs [15]. Several drug-loaded nanoparticles were produced by the ESD technique, including mesotetra (hydroxyphenyl) porphyrin-loaded PLGA (p-THPP) nanoparticles, doxorubicin-loaded PLGA nanoparticles, plasmid DNA-loaded PLA nanoparticles, coumarin-loaded PLA nanoparticles, indocyanine, cyclosporine (Cy-A)-loaded gelatin and cyclosporin (Cy-A)-loaded sodium glycolate Nanoparticles [10]. A reduction in particle size can be gained by increasing the concentration of water miscible solvent. This method can be used for preparation of hydrophilic and hydrophobic drugs [11].

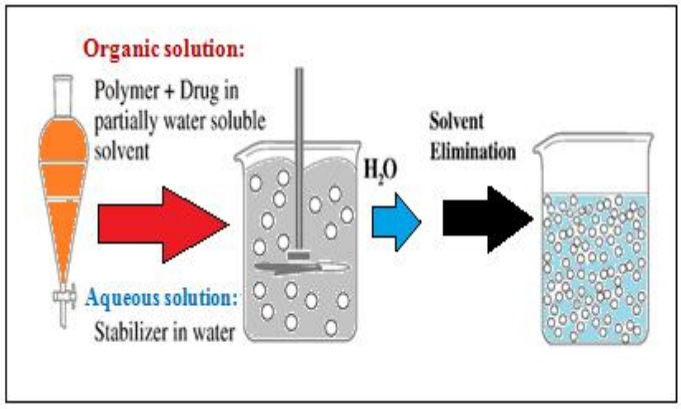

Figure 4. Emulsification/Solvent Diffusion Technique.

d) Salting Out:

It is one of commonly used method for preparation of nanoparticles. This method involves the mixing of saturated aqueous solution of polyvinyl alcohol (PVA) into an acetone solution of the polymer under magnetic stirring resulting in the formation of o/w emulsion. The precipitation of the polymer occurs when sufficient amount of water is added to external phase to allow complete diffusion of the acetone from internal phase into aqueous phase [9][11].Salting out is based on the separation of a water miscible solvent from aqueous solution via a salting out effect. The salting out procedure can be considered as a modification of the emulsification/solvent diffusion. Polymer and drug are initially dissolved in a organic solvent such as acetone, which is subsequently emulsified into an aqueous gel containing the salting-out agent such as magnesium chloride, calcium chloride, and magnesium acetate, or non- electrolytes such as sucrose and a colloidal stabilizer such as polyvinylpyrrolidone or

hydroxyethylcellulose. This oil/water emulsion is diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of acetone into the aqueous phase, thus inducing the formation of nanospheres. The selection of the salting out agent is important, because it can play an important role in the encapsulation efficiency of the drug. Both the solvent and the salting out agent are then eliminated by cross-flow filtration. This technique used in the preparation of PLA, poly (methacrylic) acid, nanospheres leads to high efficiency and is easily scaled up. The main advantage of salting out is that it minimizes stress to protein encapsulants. Salting out method is useful for thermo sensitive material because it does not require does increase of temperature [10][12].

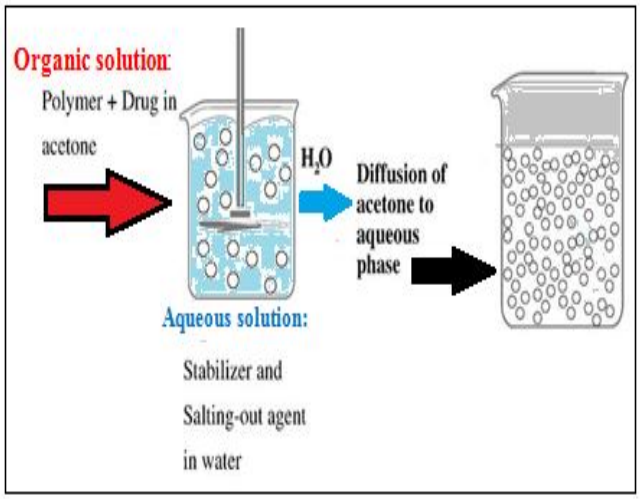

Figure 5. Salting Out Technique.

VI. CHARACTERIZATION OF HERBAL NANOPARTICLES

a) Physical Appearance:

The Organoleptic properties of the Nanoparticles, like colour, odour and physical appearance were checked by visual observation.

b) Determination of Practical Yield:

Polymer and drug accurately weighed and then after preparation and drying of the Nanoparticles, weight of Nanoparticles was taken. Production yield was calculated using following formula.

$$PY\ (\%) = \frac{\text{Amount of Product Obtained}}{\text{Amount of Total Solid used in the preparation (Polymer+Drug)}} \times 100$$

c) Percentage drug loading and Entrapment Efficiency:

The weighed samples of drug loaded Nanoparticles (10mg) were dissolved in 10 ml of dichloromethane under sonication for 1.0 hr. The samples were filtered using membrane filter and absorbance of samples was read at 248 nm using spectrophotometer. The percentage drug loading and entrapment efficiency were calculated by formulas given below. All analyses were carried out in triplicate [17].

$$\%\ \text{Drug Loading} = \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of nanoparticles Recovered}} \times 100$$

$$\%\ \text{Entrapment Efficiency} = \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of drug used in preparation}} \times 100$$

d) Particle Size Analysis of Nanoparticles:

Determination of mean average particle size of Budesonide nanoparticles was carried out by using Malvern instrument ver.6.12.The analysis was performed by introducing 0.3 ml sample into the viewing unit the Dynamic Light Scattering is used to measure particle size and molecule size. The particle size analysis was performed at a scattering angle of 90°C at room temperature. The diameter was averaged from three parallel measurements and expressed as mean ± standard deviation. This technique measures the diffusion of particles moving under Brownian motion, and converts this to size and a size distribution [18].

e) Zeta Potential Measurement:

The analysis was performed by using the Malvern zetasizer ver. 6.12 (Malvern instrument UK) the electrophoretic mobility was converted to the zeta potential. To determine the zeta potential, nanoparticles samples were diluted with KCl (0.1 mM) and placed in electrophoretic cell where an electrical field of 15.2 V/cm was applied. All measurement was performed triplicate. Malvern Instruments' Zetasizer Nano provides a simple, fast and accurate way to measure zeta potential. The unique disposable capillary cell ensures there is no cross contamination between samples, which improves the simplicity, speed and accuracy of the measurement [19].

f) Determination of solubility in distilled water:

Solubility of pure drug and all batches of nanoparticles in distilled water obtained by adding an excess of the pure drug and dried nanoparticles in 10 ml of distilled water in conical flask. This conical flask kept on orbitary shaker for 24 hrs. to ensure saturation. After the equilibrium solubility was attained, clear supernant was filtered and after

the appropriate dilutions resultant sample was analysed by UV spectrophotometer at 248 nm. [20].

g) Scanning Electron Microscopy (SEM):

Nanoparticles were coated with a thin gold-palladium layer by sputter coater unit (VG- Microtech, United Kingdom), and the surface topography was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (SEM; Cambridge, United Kingdom) operated at an acceleration voltage of 10 kV.

h) Fourier Transform Infrared Spectroscopy:

The FTIR spectra are used to identify the drug and help to detect the interaction of drug with polymers. FTIR spectrum of pure drug and optimized nanoparticles prepared batch were obtained on FTIR (Bruker Alpha-T, India) instrument. The procedure was performed by dispersing a sample in excess of potassium bromide nearly at the ratio 1:100, mixed well and then mixture kept into sample holder for analysis. The spectrum of pure drug and potassium bromide (1:100) was taken. The spectrum optimized batch of nanoparticles with potassium bromide (1:100) was taken. The spectrum was scanned over the wave number range of 4000-400 cm-1.

i) Powder X-ray Diffraction Analysis:

X-ray powder diffraction of pure drug and optimized batch of nanoparticles were analyzed by Philips PW 1729 x-ray diffractometer. Samples were irradiated with monochromatized Cu Kα –radiations (1.542 A°) and analyzed between 2- 60° (2θ). The voltage and current used were 30kV and 30 mA respectively. The range was 5 x 103 cycles/s and the chart speed was kept at 100 mm/2θ.

j) Differential Scanning Calorimeter Analysis:

Thermal properties of pure drug and optimized batch of nanoparticles were analyzed by DSC (TA Instruments, USA, and Model: SDT 2960). Indium standard was used to calibrate the DSC temperature and enthalpy scale. Nitrogen was used as the purge gas through DSC cell at flow rate of 50 ml per min and 100 ml per min through the cooling unit. The sample (5-10 mg) was heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 0 to 300°C at a heating rate of 10°C/ min.

k) In-Vitro Drug Release Studies of Nanoparticles:

The in vitro release experiment was developed to measure the drug release kinetics from the polymeric nanoparticles in a sink condition. Nanoparticles samples were placed in dialysis bags, which were sealed and placed in a dissolution medium; the normal sink condition was maintained. Drug release study was carried out using the USP dissolution apparatus under the change over conditions at 37 ± 0.5 ºC and stirred at 75 rpm. The nanoparticle formulations are tested for drug releases for 2 hr in acidic buffer of pH 1.2. Then the dissolution medium was replaced with phosphate buffer of pH 7.4 tested for drug release for next 3 hrs. upto 8 h. At each time interval 5 ml of sample was collected and replaced with fresh respective buffers, the collected sample was filtered by using whatman filter paper no.41.after the appropriate dilution the sample analyzed spectrophotometrically [17].

VII. FUTURE PROSPECTS OF NANO HERBAL MEDICINES

Nanoparticles drug delivery systems for herbal drugs which potentially enhance the biological activity of herbal drugs and minimize the problems associated with herbal drugs. To improve the proper delivery systems like sustained drug delivery of drug at the sites or locations in the whole body in a particular dose. In the future, the concept of herbal nanoparticles for the treatment of chronic diseases such as cancer, diabetes mellitus, and anemia is the advance one. Herbal nanoparticles drug delivery may also increases interest in some potential research groups.

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