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Nanotechnology: A New Approach In Herbal Medicine

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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. The new approach in herbals as nanotechnology have a sound future which has a scientific approach to deliver the component in sustained manner which increase the patient compliance and avoid repeated administration. By developing new formulation as nano herbal medicines like nanofiber, nanoparticles, dendrimers, herbal market get good feedback. So many chronic diseases like cancer, wound healing can be cured by nano herbals more effectively as compared to allopathic medicines. The next most important step for herbal formulations is their standardization which establish consistent biological activity, consistent chemical profile or simply a quality assurance program. The article focused on the various techniques employed in preparation, identification and characterization of herbal drugs.

Keywords: nanofiber, nanoparticles, dendrimers

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INTRODUCTION

Since ancient time, herbal remedies and natural products are being used to cure the diseases. Unlike widely used allopathic system, the herbal remedies have thousands of constituents that all work simultaneously against the diseases**.** The activity of herbal medicines depends on overall function of a variety of active components, as all the constituents provide synergistic action and thus enhance the therapeutic value. Each active constituent plays an important role and they are all related to each other.[1] However, most of the herbal origin drugs possess insoluble character leading to lower bioavailability and increased systemic clearance requiring repeated administration or higher dose, which makes the drug as a poor candidate for therapeutic use. The invention of nanotechnology is consider as a milestone in medicine world.[2,3] In case of herbals, nanotechnology becomes a great remedy to overcome the problems arising now a days. In phyto-formulation research, developing nano dosage forms has large number of advantages for herbal drugs, including enhancement of solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improving tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation, etc. various techniques are involved in preparing nanoherbal extract such as nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsion, microspheres, tranferosomes and ethosomes. These techniques gives the robust strength to herbal products against physical, chemical & environmental degredation, which in turn increase the safety & pharmacological activity of drugs.

The world market for products using nanotechnology is estimated to reach US$ 1trillion by 2015. In 2006 India & Australian government contributes to start Australia-India Science Research Funding Program. The market value of the worldwide Nano medicine industry was $63.8 billion & $72.8 billion in 2010-2011 respectively. The market is estimated to grow up to $130.9 billion by fiscal year 2016.[4]

Standardization of herbal drug are very important tool to prove its quality & safety, based on the concentration of their active principle. Quality checking is fundamental requirement for industry & other organization dealing with Ayurvedic and herbal product. It is for sure that herbal industry needs to follow strict guideline & such regulations are necessary. As per the rules of WHO guideline, herbal product needs to be standardized with respect to safety before marketing.[5, 6]

There are many techniques for determination of herbal drugs like physical, chemical, microscopic etc but now a day's one technique is widely use for determination of nano drugs and that is AFM i.e. Atomic Force Microscopy which determine the nano structure. Recently AFM is used for the Chinese herbal medicine *Yunnan baiyao* which is used to treat wounds. The AFM is a very high-resolution type of scanning probe microscopy and it is one of the foremost tools for imaging, measuring, and manipulating matter at the nano scale.[7]

Nanotechnology For Herbal Remedies

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. 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.[8]

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 formulation's lack target specificity for various chronic diseases.

Types of nano pharmaceuticals[9]

- Polymeric nanoparticles
- Solid lipid nanoparticles
- Magnetic nanoparticles
- Metal and inorganic nanoparticles
- Polymeric micelles
- Phospholipids micelles
- Colloidal nano-liposomes
- Dendrimers
- Nano crystals

There are various techniques which are used for the preparation of above nanopharmaceuticals

1. Complex coacervation method[10, 11]

This is a spontaneous phase separation process of two liquid phases in colloidal systems, which results by the interaction of two oppositely charged polyelectrolytes upon mixing in an aqueous solution.

It mainly includes three steps

1. Formation of three immiscible chemical phases.
2. Depositing the liquid polymer coating upon the core material.
3. Rigidizing the coating.

2. Co-precipitation method[10]

This method is a modification of the complex coacervation method for the preparation of nano scale core-shell particles. This method has been reported to provide good dispersion stability to poorly water-soluble drugs.

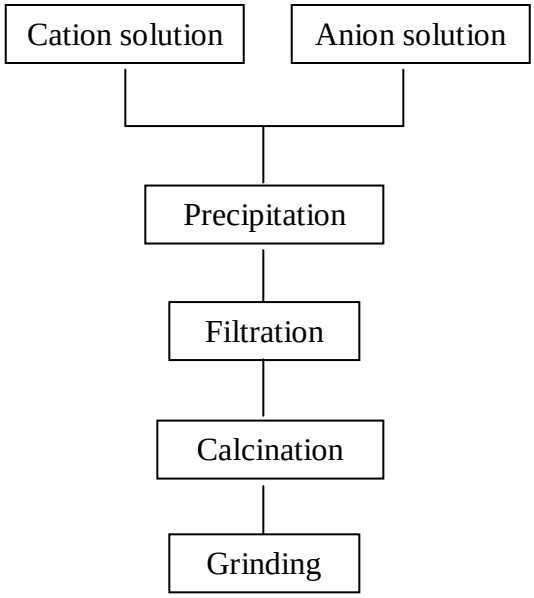

Figure 1: Co-precipitation method

3. Salting-out method[10, 12]

This method is based on the phenomenon that the solubility of a non-electrolyte in water is decreased upon addition of an electrolyte.

Acetone is generally chosen as the water miscible solvent because of its solublizing properties and its well known separation from aqueous solution by salting out method with electrolytes.

The diffusion of acetone from the droplets is the most imp step. This diffusion which takes place on dilution with excess water, can generate interfacial turbulence leading to polymer aggregation in the form of nanoparticles.

4. Nanoprecipitation method or solvent displacement method[10, 13]

As biodegradable nanoparticles meet with increasing interest for drug delivery applications, a series of investigations were carried out to understand the mechanism of the formation of drug-loaded nanoparticles using the solvent displacement method.

This method is based on interfacial deposition of a polymer after displacement of a semipolar solvent miscible with water from a lipophilic solution, thereby resulting in a decrease in the interfacial tension between the two phases, which increases the surface area with a subsequent formation of small droplets of organic solvent even without any mechanical stirring.

5. Solvent emulsification–diffusion method[10, 14]

The method involves preparation of an o/w emulsion using oil phase containing polymer like PLGA and oil in an organic solvent which is emulsified with the aqueous phase containing stabilizer in high shear mixer followed by addition of water to induce the diffusion of organic solvent, thus resulting in formation of nanoparticles.

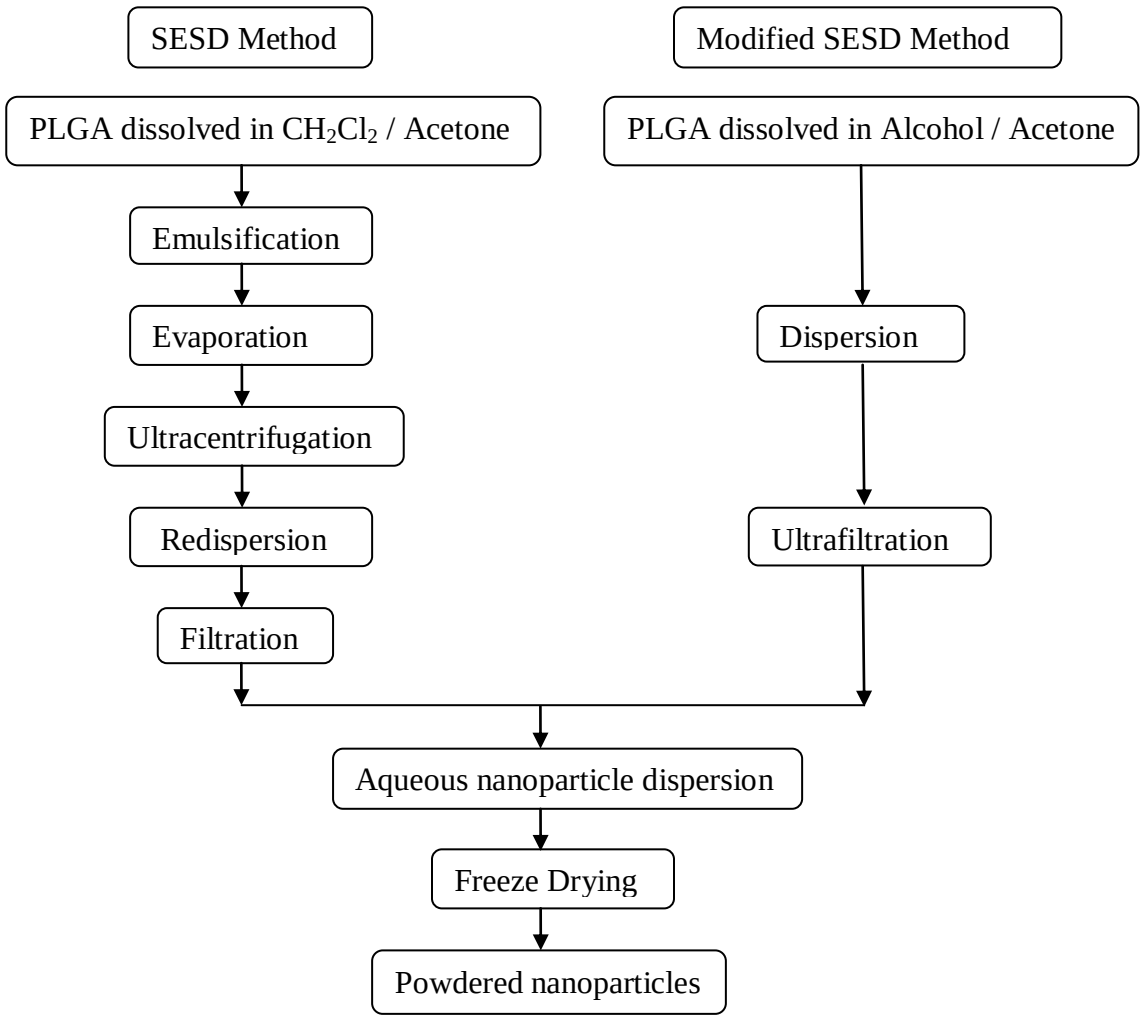

Figure 2: solvent emulsification solvent diffusion method

6. Supercritical fluid methods[10, 15]

A supercritical fluid (SCFs) can either be a liquid or gas and used above its thermodynamic critical point of temperature and pressure. The most commonly used SCFs are carbon dioxide. Particles that have the smooth surfaces, small particle size and distribution and free flowing can be obtained with particular SCF techniques. Rapid Expansion of Supercritical Solutions (RESS), Supercritical Anti Solvent (SAS) and Particles from Gas Saturated Solutions (PGSS) are three groups of processes which lead to the production of fine and monodisperse powder.

7. High-pressure homogenization method[10]

In this method, the lipid is pushed with high pressure (100 to 2000 bar) through a very high shear stress, which results in disruption of particles down to the submicrometer or nanometer range. High-pressure homogenization method is a very reliable and powerful technique for the large-scale production of nano structured lipid carriers, lipid drug conjugate, SLNs, and parenteral emulsions.

STANDARDIZATION OF NANO HERBAL MEDICINES

Herbal product cannot be considered scientifically valid if the drug tested has not been authenticated and characterized in order to ensure reproducibility in the manufacturing of the product.[5] Hence, standardization is necessary for herbal medicines. Standardization ensures a predefined amount of quantity, quality & therapeutic effect of ingredients in each dose.[16]

Therapeutic activity of an herbal formulation depends on its phytochemical constituents. The development of authentic analytical methods which can reliably profile the phytochemical composition, including quantitative analysis of marker/ bioactive compounds and other major constituents, is a major challenge to scientists. In view of the above, standardization is an important step for the establishment of a consistent biological activity, a consistent chemical profile, or simply a quality assurance program for production and manufacturing of an herbal drug.[17] The authentication of herbal drugs and identification of adulterants from genuine medicinal herbs are essential for both pharmaceutical companies as well as public health and to ensure reproducible quality of herbal medicine.[18]

Incorporation of nanotechnology in herbal increases solubility, stability, bioavailability, pharmacological activity of many popular herbal extracts including *Ginkgo biloba*, grape seed, green tea, ginseng using nano dosage forms such as polymeric nanoparticles, nanospheres, nanocapsules, liposomes, proliposomes, solid lipid nanoparticles, and nanoemulsion has been reported.[19] On the other hand herbal nanomedicine include protection from toxicity, improving tissue macrophages distribution, sustained delivery, protection from physical and chemical

degradation.[20] Silver nanoparticles of *Ocimum sanctum* extract exihibited maximum antibacterial activity at a dose of 150µg in wistar rats.[21]

Standardization methods

There are various techniques which are used for the standardization of herbal drugs, like physical, chemical, biological and botanical (microscopic & macroscopic).[22]

Further, advances in microscope technology have increased the accuracy and capabilities of microscopy as a mean of herbal crude material identification due to the implication of light and scanning electron microscopes (SEM) in herbal drug standardization.[23]

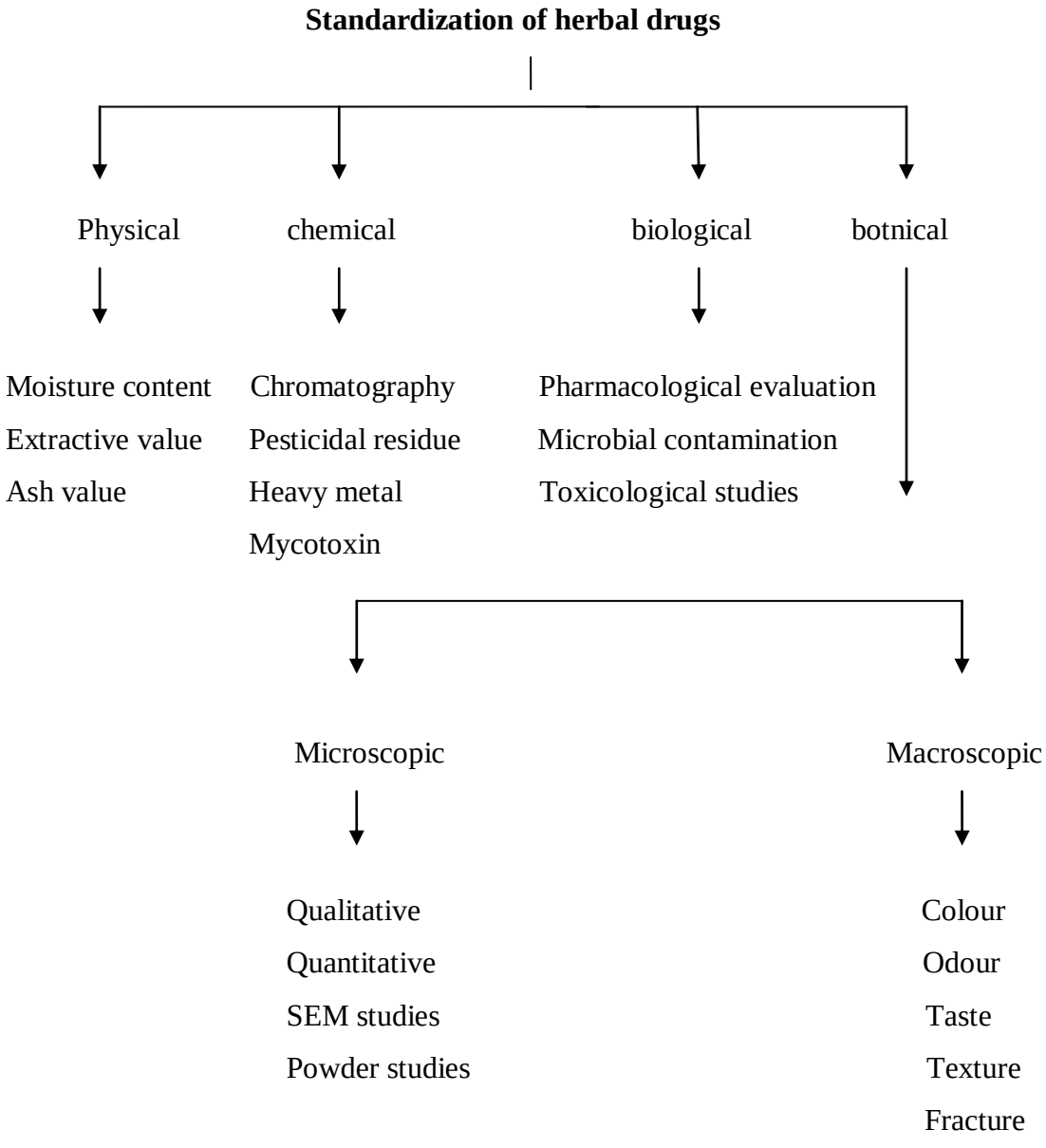

Figure 3: A schematic representation of herbal drug standardization methods.

Furthermore, various advanced methods such as chromatographic, spectrophotometric, combination of chromatographic spectrophotometric methods, electrophoresis, polarography, and the use of molecular biomarkers in fingerprints are currently employed in standardization of herbal drugs.[24-28]

Advanced techniques for identification and characterization of nano herbal medicine

HPLC

Preparative and analytical HPLC are widely used in pharmaceutical industry for isolating and purification of herbal compounds.[29, 30] Vasicine, the major bioactive alkaloid of *Adhatoda vasica*, was estimated by HPLC in two polyherbal drug formulations - Shereeshadi Kashaya and Yastyadivati, and its content was found to be 18.1 mg/100 g in Shereeshadi Kashaya and 0.7 mg/100g in Yastyadivati.[31] Standardization of the Triphala (an antioxidant-rich herbal formulation) mixture of *Emblica officinalis*, *Terminalia chebula* and *Terminalia belerica* in equal proportions has been reported by HPLC method by using the RP18 column with an acidic mobile phase.[32] The combination of HPLC and LC/MS is currently the most powerful technique for the quality control of Chinese herbal medicine Gan-Cao (licorice).[33]

HPTLC

HPTLC technique is widely employed in pharmaceutical industry in process development, identification and detection of adulterants in herbal product and helps in identification of pesticide content, mycotoxins and in quality control of herbs and health foods.[34] HPTLC technique was reported for simultaneous determination of Withaferin A and β sitosterol *d*-glucoside in four *Ashwagandha* formulations.[35] *Syzygium Jambolanum* was quantitatively evaluated in terms of stability, repeatability, accuracy and phytoconstituents such as glycoside (jamboline), tannin, ellagic acid and gallic acid by HPTLC.[36]

UPLC

Ultra performance liquid chromatography (UPLC) was used to evaluate decocting-induced chemical transformations and chemical consistency between traditional and dispensing granule decoctions.[37, 38]

LC-MS

LC-MS has become method of choice in many stages of drug development.[39] LC-MS analysis of Amino glycosides showed that these drugs are highly soluble in water, exhibited low plasma protein binding, and were more than 90% excreted through the kidney. Further this technique helps in analysis of amino glycosides in plasma samples with ion pairing chromatography.[40]

GC-MS

It is the system used for identification of large number of components present in natural and biological systems.[41] The identification and quantification of chemical constituents present in polyherbal oil formulation (Megni) consisting of nine ingredients, mainly *Myristica fragrans*, *Eucalyptus globulus*, *Gaultheria procumbens* and *Mentha piperita* was analyzed by GC-MS method.[42] Thirty-five volatile compounds were separated and identified.[43]

Capillary Electrophoresis

The methodology of CE was established to evaluate one herbal drug in terms of specificity, sensitivity and precision.[44] Several CE studies dealing with herbal medicines have been reported and two kinds of medicinal compounds i.e. alkaloids[45] and flavonoids[46] have been studied extensively. Furthermore, the analysis time of the CE method was two times shorter than that in HPLC and solvent consumption was more than 100 fold less.[47] The hyphenated CE instruments, such as CE-diode array detection, CE-MS and CE-NMR, have been utilized.[48]

AFM (Atomic Force Microscopy)

It is a very high resolution type of scanning probe microscopy, with demonstrated resolution on the order of fractions of a nanometer, more than 1000 times better than the optical diffraction limit.[49]

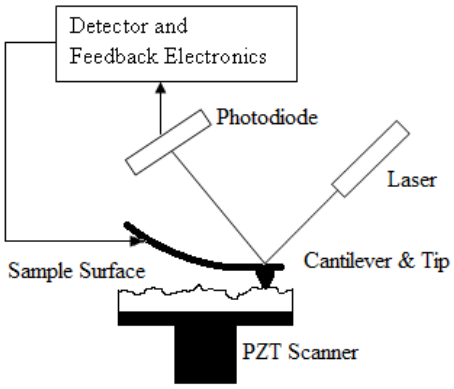

Figure 4*:* Block diagram of atomic force microscope using beam deflection detection

AFM provides a three dimensional surface profile.[50] AFM images revealed uniform nano fibers present in relatively high abundance in a solution of the medicine, *Yunnan Baiyao.* It is a traditional Chinese herbal medicine that has been used to treat wounds for over 100 years. Now a day's this technique is most widely used in China.[7]

Future Prospective

All over the world, the research has been going on herbal remedies and natural products. The only requirement is to develop the better systems for the proper delivery of such drugs at the sites and in the whole body in the doses which will not compromise with the existing treatment.

Something that would not only give relieve from side effects like toxicity and hypersensitive reactions but also will increase the patient's strength from inside is very much desirable. Hence, using "herbal remedy" in the nano carriers will increase its potential for the treatment of various chronic diseases and health benefits. The collaborative research among the traditional "Herbal remedies" and newer approaches of modern drug delivery system, i.e., "Nanotechnology" has established the attractive therapies to the pharmaceutical in near future that will enhance health of people.[51]

CONCLUSION

Standardization of herbal drugs comprises total information and controls to essentially guarantee consistent composition of all herbals including analytical operations for identification, markers and assay of active principles. Moreover, all herbal products manufacturers must follow WHO guidelines for quality control. Further, the combination of qualitative fingerprinting and quantitative multi component analysis is a novel and rational method to address the key issues of quality control of herbal medicines. The applications of high-technology oriented advanced hyphenated techniques will serve as a rapid and unambiguous tool in the herbal research, thereby, benefiting the entire pharmaceutical industry.

REFERENCE

1.Yadav D, Suri S, Choudhary AA, Sikender M, Hemant, Beg NM, et al. Novel approach: Herbal remedies and natural products in pharmaceutical science as nano drug delivery systems. Int J Pharm Tech. 2011; 3:3092–116.

2.Singh RP, Singh SG, Naik H, Jain D, Bisla S. Herbal excipients in novel drug delivery system. Int J Comprehensive Pharm. 2011; 2:1–7.

3.Sungthongjeen S, Pitaksuteepong T, Somsiri A, Sriamornsak P. Studies on Pectins as Potential Hydrogel Matrices for Controlled-Release Drug Delivery. Drug Develop Ind Pharm. 1999; 25:1271–6.

4.Shahu AN. Nanotechnology in herbal medicines and cosmetics. Int. J Res. Ayurveda Pharm. June 2013; 4(3).

5.Vaidya ADB, Devasagayam TPA. Current status of herbal drugs in India: An overview. J Clin Biochem 2007; 41(1):1–11.

6.Sachan V, Kohli Y, Gautam R. Regulatory issues for herbal products – a review. Pharmainfo.net,12/16/2009;http://www.pharmainfo.net/justvishal/publications/regulatory issues-herbal-products review.

7.Lenaghan SC, Xia L, Zhang M. Identification of nanofibers in the Chinese herbal medicine: Yunnan Baiyo. J Biomed Nanotechnol. 2009; Oct.5(5):472-6.

8.Bairwa NK, Sethiya NK, Mishra SH. Protective effect of stem bark of Ceiba pentandra Linn. against Paracetamol-induced hepatotoxicity in Rats. Pharmacognosy Res. 2010; 2:26–30.

9.Mohammadreza A. Nanodrugs an Natural Pharmaceutical Products. Journal of Natural Pharmaceutical Products. 2012; 7(2):39-40.

10. Sahni JK, Baboota S, Ali J. Promising Role of Nanopharmaceuticals in Drug Delivery. Pharma Times. 2011; 43:16–8.

11. Lachman L, Lieberman HA, Kanig JL. The Theory and Practical of Industrial Pharmacy. 3rd edition, 420.

12. Sheehan D, Blackwell W. Physical biochemistry. 2009; 285.

13. Fessi H, Puisieux F, Devissaguet JP, Ammoury N, Benita S. Nanocapsule formation by interfacial polymer deposition following solvent displacement. Int J Pharm. 1989; 55:R1-4.

14. Back BM, Rytting E, Lebhardt T, Wang X, Kissel T. Department of pharmaceutics & biopharmacy, Eur. J Pharm Science. 2010; Oct.9.

15. Jung J, Perrut M. Particle design using supercritical fluids: Literature and patent survey. J Supercrit Fluids. 2001; 20:179–219.

16. Zafar R, Panwar R, Sagar Bhanu PS. Herbal drug standardization: The Indian Pharmacist 2005; 4(36):21-25.

17. Patra KC, Pareta SK, Harwansh RK, Jayaram Kumar K. Traditional approaches towards standardization of herbal medicines -A review. J Pharm Sci Technol 2010; 2 (11):372-379.

18. Straus SE. Herbal remedies. New Engl J Med 2002; 347:2046–2056.

19. Huang S, Chang WH. Advantages of nanotechnologybased Chinese herb drugs on biological activities. Curr Drug Metabol 2009; 10(8):905-13.

20. Musthaba, SM, Sayeed A, Alka A, Javed A. Nano approaches to enhance pharmacokinetic and pharmacodynamic activity of plant origin drugs. Curr Nanosci 2009; 5(3):344-352.

21. Prabhu N, Divya Raj T, Gowri Yamuna K, Siddiqua Ayisha S, Joseph N. Synthesis of silver phyto nanoparticles and their antibacterial efficacy. J Nanomater Biostruct 2010; 5(1):185–189.

22. Patel PM, Patel NM, Goyal RK. Quality control of herbal products. The Indian Pharmacist 2006; 5(45):26-30.
23. Bhutani KK. Herbal medicines enigma and a challenge for science and guidelines for new initiatives. J Nat Prod 2003; 19(1):3-8.
24. Quality Control Methods for Medicinal Plant Materials, WHO, Geneva, 1996.
25. Mosihuzzaman M, Choudhary MI. Protocols on safety, efficacy, standardization, and documentation of herbal medicine. Pure Appl Chem 2008; 80(10):2195–2230.
26. Seitz U, Bonn G, Oefner P, Popp M. Isotachophoretic analysis of flavonoids and phenolcarboxylic acids of relevance to phytopharmaceutical industry. J Chromatogr 1991; 559, 499-504.
27. O'Shea TJ .Capillary electrophoresis/electrochemistry. Curr Sep 1995; 14(1):18-23.
28. Svicekova M, Havranek E, Novak V. Determination of heavy metals in samples of herbal drugs using differential pulse polarography. J Pharm Biol 1993; 42(2):68-70.
29. Chimezie A, Ibukun A, Teddy E, Francis O. HPLC analysis of nicotinamide, pyridoxine, riboflavin and thiamin in some selected food products in Nigeria. Afr J Pharm Pharmacol 2008; 2(2):29-36.
30. Saravanan J, Shajan A, Joshi NH, Varatharajan R,Valliappan K. A simple and validated RP-HPLC method for the estimation of methylcobalamin in bulk and capsule dosage form. Int J Chem Pharm Sci 2010; 1(2):323-324.
31. Anupam S, Krishan L, Handa SS. Standardization: HPLC determination of vasicine in polyherbal formulations. Pharm Biol 1992; 30(3):205-208.
32. Singh DP, Govindarajan R, Rawat AKS. High-performance liquid chromatography as a tool for the chemical standardisation of Triphala an ayurvedic formulation. Phytochem Anal 2007; 19(2):164-168.
33. Zhang Q, Ye M. Chemical analysis of the Chinese herbal medicine Gan-Cao (licorice). J Chromatogr A 2009; 1216(11):1954-1969.
34. Soni K, Naved T. HPTLC- Its applications in herbal drug industry. The Pharma Review 2010; 112-117.
35. Jirge SS, Tatke PA, Gabhe S. Development and validation of a novel HPTLC method for simultaneous estimation of beta-sitosterol- d-glucoside and Withaferin A. Int J Pharm Pharmaceut Sci 2011; 3(Suppl 2):227-230.
36. Shanbhag DA, Khandagale NA. Application of HPTLC in the standardization of a homoeopathic mother tincture of *Syzygium jambolanum*. J Chem Pharm Res 2011;

3(1):395-401.

37. Li SL, Lai SF, Song JZ, Qiao CF, Liu X, Zhou Y, et al. Decocting-induced chemical transformations and global quality of Du–Shen–Tang, the decoction of ginseng evaluated by UPLC–Q-TOF-MS/MS based chemical profiling approach. J Pharm Biomed Anal 2010; 53:946–957.
38. Li SL, Song JZ, Qiao CF, Zhou Y, Qian KD, Xu HX. UPLC– PDA–TOFMS based chemical profiling approach to rapidly evaluate chemical consistency between traditional and dispensing granule decoctions of traditional medicine formulae. J Pharm Biomed Anal 2010; 52:468–478.
39. Mike Lee S, Edward Kerns H. LC/MS applications in drug development. Milestone Development Services, Pennington, New Jersey, 24 July 1999.
40. Shen AQ, Morgan L, Barroso ML, Zhang X .Tandem Method development of LC-MS analysis of aminoglycoside drugs: Challenges and solutions. Answering Pharmaceutical Questions with Discipline and Ingenuity. 2010; 5(2):567-569.
41. Binit DK, Sunil K, Nayak C, Mehta BK. Gas chromatography mass spectrometry (GC-MS) analysis of the hexane andbenzene extracts of the Piper beetle from India. J Med Plant Res 2010; 4(21):2252-2255.
42. Kasthuri KT, Radha R, Jayshree N, Anoop A, Shanthi P. Development of GC-MS for a polyherbal formulation-MEGNI. Int J Pharm Sci 2010; 2(2):81-83.
43. Shaa YF, Shenb S, Duan GL. Analysis of *Rhioxma Curcumae Aeruginosae* volatiles by solid-phase microextraction with gas chromatography-massspectrometry. Z. Naturforsch 2004; 59C:533-537.
44. Ganzera M. Quality control of herbal medicines by capillary electrophoresis: Potential, requirements and applications. Electrophoresis 2008; 29:3489–3503.
45. Wen HG, Lin SY, Jia L, Guo XK, Chen XG, Hu ZD. Analysis of protoberberine alkaloids in several herbal drugs and related medicinal preparations by non-aqueous capillary electrophoresis. J Sep Sci 2005; 28(1):92-97.
46. Pietta P, Mauri P, Rava A, Sabbatini G. Application of micellar electrokinetic capillary chromatography to the determination of flavonoid drugs. J Chromatogr 1991; 549:367-373.
47. Sombra LL, Gómez MR, Olsina R, Martínez LD, Silva MF. Comparative study between capillary electrophoresis and high performance liquid chromatography in ‘guarana’ based phytopharmaceuticals. J Pharm Biomed Anal 2005; 36:989–994.

48. Tistaert C, Dejaegher B, Heyden YV. Chromatographic separation techniques and data handling methods for herbal fingerprints: A review. Anal Chim Acta 2011; 690:148–161.
49. Lang KM, Hite DA, Simmonds RW, McDermott R, Pappas DP, Martinis JM. Conducting atomic force microscopy for nanoscale tunnel barrier characterization. Review of Scientific Instruments 2004; 75:2726–2731.
50. Geisse, Nicholas A. AFM and Combined Optical Techniques. Materials Today July–August 2009; 12(7-8):40–45.
51. Sethiya NK, Trivedi A, Patel MB, Mishra SH. Comparative pharmacognostical investigation on four ethanobotanicals traditionally used as Shankhpushpi in India. J Adv Pharm Tech Res. 2010; 1:388–95.