OPEN ACCESS

REVIEW ARTICLE

Novel Drug Delivery Approaches in Formulation Development; Stability Considerations and Quality Features of Herbal Products

Huma Ali[1,*], Anoushia Alvi[1], Amber Nawab[2], Shaukat Salman[3], Farya Zafar[4], Safila Naveed[2]

[1]*Institute of Pharmaceutical Sciences, Jinnah Sindh Medical University, Karachi, Pakistan*
[2]*Jinnah University for Woman, Karachi, Pakistan*
[3]*Hamdard University, Karachi, Pakistan*
[4]*Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan*

Authors' Contributions
1 Conception & Study Design, Data Analysis.
2,4 Data Collection.
3 Data Analysis.
5 Drafting.
6 Critical Review.

Article info.
Received: September 6, 2019
Accepted: October 21, 2019

Funding Source: *Nil*
Conflict of Interest: *Nil*

Cite this article: *Ali H, Alvi A, Nawab A, Salman S, Zafar F, Naveed S. Novel Drug Delivery Approaches in Formulation Development; Stability Considerations and Quality Features of Herbal Products. RADS J. Pharm. Pharm. Sci. 2019; 7(3): 155-164.*

Address of Correspondence Author:
humaali80@live.com

ABSTRACT

Objective: Over the past few years a substantial modification in the drug delivery systems have been noticed which is expected to continue with even a greater velocity in future as well. This is because of the recent developments in the technological aspects and introduction of variety of drug delivery tools and devices in routine healthcare and research sectors. Such advancements have greatly influenced the herbal drug manufacturing technology at consistent pace as well.

Method: In this paper, various literature sources were reviewed for herbal formulations manufacturing methods that can be employed in more sophisticated and palatable forms with improved quality attributes and better effectiveness by using modern tools of dosage form designing. These products offer better physico-chemical features, less prone to degradation and reduced toxicity. Enhanced stability along with improved bioavailability potential are additional attributes. Drug stability may be regarded as the maintenance of product identity, therapeutic efficacy and strength within the adequate limit of specification throughout the shelf life.

Results: It was found that quality attribute is considered crucial for herbal moieties as they are composed of complex nature. The quality of herbal products changes greatly with time under the influence of environmental factors like humidity, temperature, light and oxygen. Range of these alterations may prove significant in altering herbal products' profile in terms of particle size range of drug, microbial contamination and trace metal sources, leachable constituents and loss of therapeutic activity, *etc*.

Conclusion: Henceforth assessment of physical, chemical, therapeutic, microbiological and toxicological parameters can provide an important insight for herbal stability studies.

Keywords: Herbal formulation, novel drug delivery, stability, contamination, dosage form designing.

INTRODUCTION

Herbal drugs are the historical way of treatment known to serve people [1]. Phytomedicines (Herbal drug products) are nearest to the conventional treatment (involves surgery, radiations, chemotherapy, *etc*.) approach than alternative treatment or complementary drug approaches [2]. The

earliest method used for the treatment of ailments is the use of natural plants and their constituents. Herbalism includes the entire plant or any constituent of plant which are really very helpful in treating diseases [3]. In developing countries, people are moving towards the use of traditional/conventional medicines to treat their disease [4]. As per WHO (World Health Organization), to treat their primary illnesses 80% of world's population have trust on herbal medicines. Natural medications have a long history of its utilization and has better patient resilience and compliance. Phytochemicals are affordable and effortlessly accessible in nations like India and Pakistan, where agriculture are at high rate. Only USA has developed an act that reflects phytomedicines as 'Dietary Supplements' [2]. The broad and worldwide acknowledgment and usage of home grown solutions is suggestive of their wellbeing and viability [5]. Herbal drug products are used in many forms, they are available in simple dried packed form, as a pure part of plant or as in decoct form (herbal teas). But for every herbal drug there is a different method for drawing out and Purification [6]. The most prominent around the world is the Western medicines as they have excellent therapeutic or pharmacological effect along with little or no harming effects, that is why, they are still used in Thailand health care sector, as Thai Traditional Medicines [7]. The know-how and facts regarding oriental medications as a rule underpins the utilization of multi-herbal formulas since it exploits combined effect and collaboration between phytochemicals in herbal technique to accomplish remedial adequacy with limiting adverse symptom [8], for example, The JTR formularies ("Jit-Tra-Rom", a traditional Thai hypnotic remedy) include both original (inventive) and modified (altered) composition/formula. The inventive JTR formula holds white pepper seed (*Piper nigrum* Linn.). Some Thai customary specialist trust that the white pepper seed is nephrotoxic herb and it might instigate kidney disease in patients. In this way, the altered JTR formulation utilizes chrysanthemum bloom (*Chrysanthemum morifolium* Ramat.) rather than white pepper seed to sidestep the worsening of side effect of kidney malady patients [9].

In-fact, original JTR are available in the powdered from. Powdered product has greater surface area to absorb moisture from the environment and induces microbial growth which in-turn causes degradation of the product [10]. These types of products can be Asd subjected to wet granulation and direct compression method which may enhance the product stability.

From financial and therapeutic point of view, the entire herb's self-assurance and adequacy are at the most extreme imperative [11]. The main concern of every pharmacist is to prepare a therapeutically safe and efficient drug which can be achieved by conducting stability test at every step during drug manufacturing processes. Like semi-synthetic and synthetic drugs, herbal drug products are also subjected to drug stability testing [12].

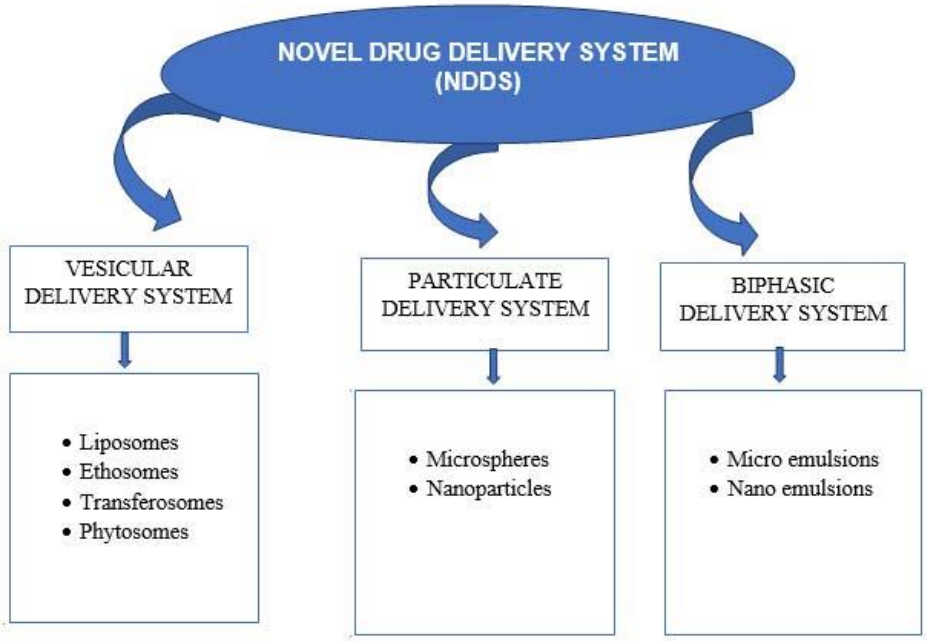
RATIONALE FOR HERBAL DRUG DELIVERY SYSTEM

Certain confinements of herbal products, pharmaceuticals and phytochemicals, such as, precariousness in profoundly acidic pH, pre-foundational digestion in liver, solvency and retention issues, can prompt medication levels underneath therapeutic concentration in the plasma, bringing about less or no helpful impacts. The lipid membrane limits the access of outsized biomolecule *i.e*., polar molecules by means of passive diffusion that leads to the poor absorption, decreases bioavailability and increases the toxicity profile of drug, for example, glycoside, flavonoids and tannins have limitations in drug absorptivity. This problem can be overcome by integration of Novel Drug Delivery System (NDDS) in herbal drugs [13].

NDDS is a modified structure for progress of drug preparation other than customary drug transport system. NDDS implies the philosophies, plans, headways, and structures for moving a pharmaceutical ingredient in the body safely to achieve desirable therapeutic effects. The traditional drugs provide the immediate release patterns and resultant blood levels depend upon type of dosage form. For that reason, it is significant to uphold the drug concentration within therapeutically effective range by incorporating Novel Drug Delivery System [14].

TYPES OF NOVEL DRUG DELIVERY SYSTEM (NDDS)

The classification of NDDS which is used with herbal drugs and phytochemicals are described as in Scheme **1**:



Scheme 1. Categories of Novel Drug Delivery System.

1. VESICULAR DELIVERY SYSTEM

A. Liposomal Drug Delivery System [15-20]

LIPOSOMES			
COMPOSITION	METHOD OF PREPARATION	ADVANTAGES	DISADVANTAGES
• A moment circular sac of phospholipid moieties encasing a water globule, particularly as shaped synthetically to convey drug or supplementary materials into tissues. • 0.05-5.0 µm in diameter.	• Passive loading systems: • Mechanical dispersal/ scattering • Solvent dispersal / scattering • Detergent expulsion • Active loading techniques	• They help to diminish the introduction of irritable tissues to harmful medication. • It increases stability *via* encapsulation. • They have adaptability to get tie with explicit ligands to accomplish dynamic focusing on. • Liposomes decreases toxicity profile of drug by increasing its efficacy • *e.g.*, actinomycin-D.	• They have short half-life. • They have low solubility. • Leakage and fusion of encapsulated drugs. • In some cases, phospholipids undergo oxidation and hydrolysis reactions**.** • Cost-effective. • Less stability.

***Examples of Herbal Liposomal Drug Delivery System* [17-20]**

I. Atractylodes and Macrocephala Koidz Herbal Drug: It is recommended in joint pain and joint diseases, which enhances the availability of unchanged drug in the systemic circulation and drug solubility.

II. Quercetin: It is an antioxidant or anti-cancerous (prevents or interrupts in cell damage), which has good bioavailability and less side effects.

III. Tripterygium Wilfordii (Triptolide): It is recommended to treat cluster of cyst present in renal, angiogenesis (stops the formation of new blood vessels), gastrointestinal disorders and has anti-cancerous activity with the objective of increase stability.

B. Ethosomal Drug Delivery System [21-23]

ETHOSOMES			
COMPOSITION	METHOD OF PREPARATION	ADVANTAGES	DISADVANTAGES
a) Ethosomes are composed of: • Water • Phospholipids • Ethanol b) Due to the presence of ethanol in higher content ethosomes enables the drug to arrive at deep layers of skin or the general transmission. c) Ethosomes are non-invasive delivery transporters.	a. Cold method: • Drug ⟹ ethanol ⟹ phospholipid ⟹ heat at 30°C ⟹ rest for 5 minutes. b. Hot method: • Disperse phospholipid in water at 40°C (aqueous phase) • On the other hand, mix ethanol in propylene glycol at 40°C (organic phase). • Mix these 2 phases (mixture). • Add previously dissolved drug *i.e*., dissolved in a suitable solvent, in the mixture.	• It augments the provision of bigger molecules *i.e*., peptides and proteins. • Ethosomes are small sized vesicles that's why it promotes drug permeability through the skin. • Patient acquiescence is high.	• Loss of product during transfer from organic to water media. • Skin irritation can occur due to the excipients present in the ethosomes. • This method is only required for slow released drug.

Examples of Ethosomal Drug Delivery System

I. Sophora Alopencerides (Alkaloid): It enhances the penetrability of the drug *via* Horny Layer (stratum corneum) and it is used for the topical delivery of drug.

II. Ammonium Glycyrrhizinate: The bioavailability has improved as compare to ethanolic ethosomes. It is used to treat inflammatory disease of the skin

C. Transferosomal Drug Delivery System [23-26]

TRANSFEROSOME		
COMPOSITION	ADVANTAGES	DISADVANTAGES
a) ransferosomes are composed of: Phospholipids Surfactants (Edge Activators) Water b) It has modified Transdermal Drug Delivery System. c) They also act as the penetration enhancers. d) Transferosomes up to 500 nm can pass through or penetrate the stratum corneum barrier freely.	• Transferosomes are self-totals, with a unique malleable film which provides the medication reproducibly into or over the skin. These are more versatile than the liposomes that's why they are known as the novel carrier for effective DDS. • They have higher entanglement proficiency more than 90% particularly on account of lipophilic medication. They can be utilized for both topical and fundamental medication conveyance framework. • They act as sustained release drug products *i.e*., as depot system. • Transferosomes go about as medication vectors, staying flawless subsequent to entering the skin.	• They are chemically unstable. • They are not cost effective. • For effectiveness of transferosome drug delivery system, the purity of phospholipids are the topmost criteria.

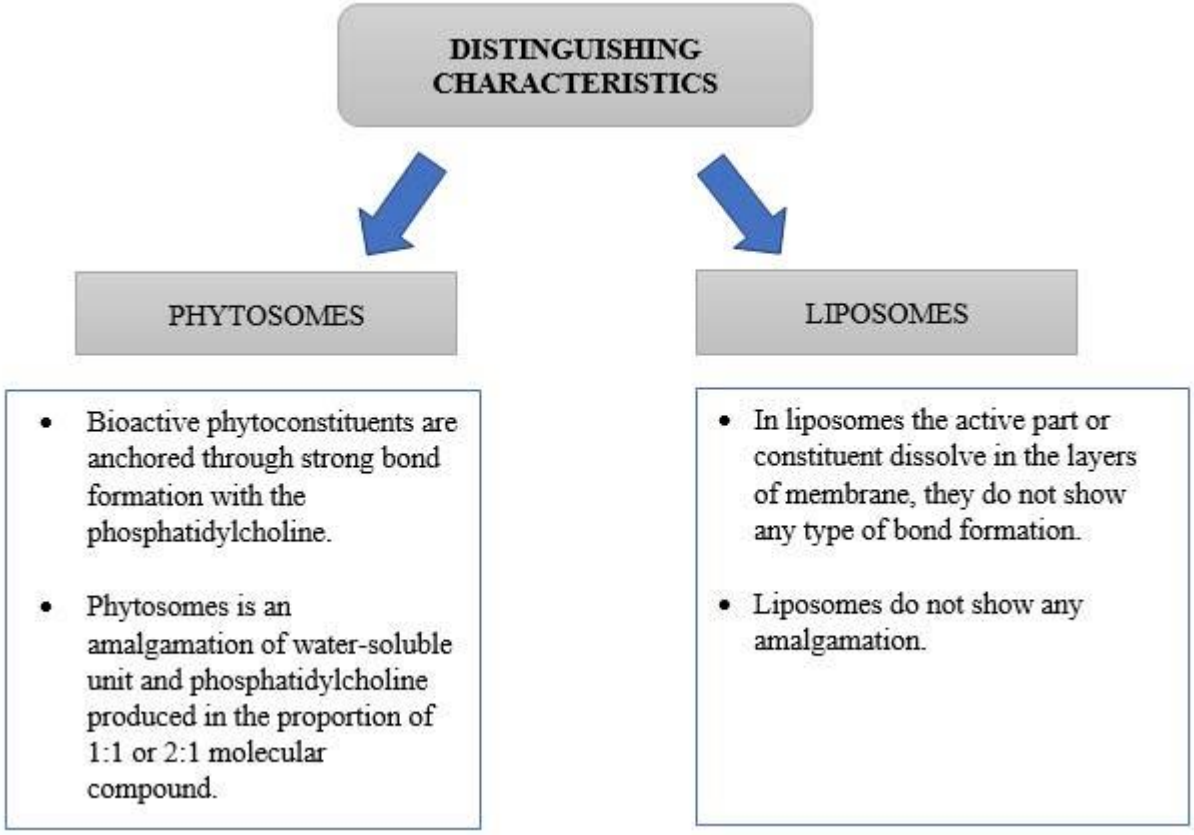
Examples of Transferosomal Drug Delivery System

I. Transferosomal Preparation of Colchicine: Transdermal diffusion is efficient in this system and it is used to treat gout, multiple GI problems associated with colchicines.

D. Phytosomal Vesicular Drug Delivery System [25-28]

PHYTOSOME		
COMPOSITION	ADVANTAGES	APPLICATION
• Phyto = Plant • Some = cell like • Phytosomes are lipid companionable or lipid soluble molecular complex. • Phytosomes are composed of bioactive herb extract (which is water soluble in nature) and phospholipid. .	• Phytosomes overcome the limitation of traditional drug delivery system *i.e*., it can easily pass through the lipid membranes by forming a strong bond between a bioactive herb with phospholipid. • It cannot be degraded by gastrointestinal environment. • The functioning component of phytoconstituent bound with phosphatidylcholine that enhances the penetration power which ultimately leads to good bioavailability. • For example: Milk Thistle Extract has been reported to show 7 times bigger absorption of Silybin as compare to its immersion from regular milk thistle.	• It is used as a CNS stimulant, anti-oxidant and immune-booster, for example: Grape Seed. • It is used to treat hypocholesteremia, thrombus formation. • It is used to treat acute or chronic hepatic illnesses. • It is used to treat skin infections.

Disparity Between Phytosomes and Liposomes



Examples of Phytosomal Drug Delivery System

I. Ginkgo Biloba: It contains Ginkgo Flavonoids which defends from damage of brain and vascular linings.

II. Olea Europaea Oil: It contains Polyphenols used as anti-inflammatory and anti-aging.

2. PARTICULATE DELIVERY SYSTEM

MICROSPHERES (Controlled Release Drug Delivery System)		
COMPOSITION	ADVANTAGES	DISADVANTGES
a) They are made up of polymers *i.e.*, • Gelatin • Albumin • Modified starches b) They are spherical in shape. c) They are consisting of 1-1000 micrometer in size. d) They follow 1st order kinetics which causes the drug to get disseminated evenly.	• Their compatibility with biomolecule is very high which enhances drug bioavailability. • They have can be used as controlled drug release drug delivery system. • They can be given as PO or by parenteral route.	• Difficulty of huge scale producing. • Deterioration of medication under processing. • Less control of medication discharge rates like, Nutropin Depot.

Examples of Microsphere Drug Delivery System

I. Rutin: Specific delivery to cardiovascular and cerebrovascular region and used as cardiovascular and cerebrovascular agent.

II. Turmeric Oil: Sustained release with better bioavailability and prevent from liver damage, anticancer, antibacterial.

STABILITY

Stability testing is a critical segment of natural medications and herbal drug products (HDPs) improvement process. Medications administrative offices over the globe have suggested rules for the direct of dependability considers on HDPs, which require that solidity information ought to be incorporated into the item enrollment dossier. From the logical perspective, various material constituents in an herbal medication are at risk to fluctuated synthetic responses impaired of various conditions amid its timeframe of realistic usability. Numerous information's on strength testing of HDPs have showed up in writing since the most recent 10 years. An audit of these reports uncovers that there is wide fluctuation in temperature (-80 to 100°C), dampness (0–100%) and length (a couple of hours – three years) for steadiness evaluation of HDPs. The key difficulties are delegated substance multifaceted nature and biochemical structure changeability in crude material, determination of marker(s) and impacts of compounds [30].

Herbal drug product consists of variable phytoconstituents and they may cause deterioration of the drug product when expose to different environmental changes like change in temperature, humidity and UV light. These factors affect the efficiency of drug product because of the presence of different classes of chemical entity that may have different nature, like, due to presence of hydrogen bonds and hydrophobic interactions in polyphenols, they form a reversible molecular complex with polysaccharides and protein which in-turn deplete the levels of polyphenols in the body [31]. Solidness testing is necessary to guarantee that the item is of agreeable quality throughout its whole stockpiling period. Strength studies ought to be performed on at minimum three generation bunches of the home-grown items for the proposed shelf-life, which is typically signified as long-term solidness and is performed under regular air conditions. Dependability information can also be created under accelerated barometrical states of temperature, mugginess and light, which is alluded as short-term security and the information so got is utilized for foreseeing timeframe of realistic usability of the item [32].

STABILITY CHALLENGES OF HERBAL DRUG PRODUCT

The nature and quality of the trial medicine must be assured for batch to batch consistency of the dynamic constituents. It is extremely hard to have dynamic and control batches with indistinguishable shading, smell and taste of the home-grown medication, which can't be imitated while producing a fake treatment. These difficulties can be lessened or overwhelmed by applying latest strategies and rules for clinical trials (a carefully intended and planned research, in which humans take a drug (or some other intervention), usually for the rationale of concluding safety or efficacy, and the analysis may be distributed into segments) [33]. It is recommended that the incorporation criteria can be construct either with respect to present day medication or herbal drugs determination. The comprehension of the ailment, and henceforth the infection criteria can be diverse in home grown and existing medication consideration. Research on home grown medication represents a few difficulties that should be tended to. These incorporate issues, for example, those identified with the money related, moral, item institutionalization (quality control), the plan of the examination and the administrative necessities previously documenting an investigational new medication for directing huge stage 3 trials [34].

The medications in natural pharmaceuticals are unpredictable comprising the blend of dynamic parts and include different administration protocols. Therefore, the accomplishment of home grown treatment result relies upon patient's will and inspiration to finish the treatment.

Though, these considerations can be abated by incorporation of following procedures:

- Blinding
- Randomization

PARTIAL RANDOMIZATION

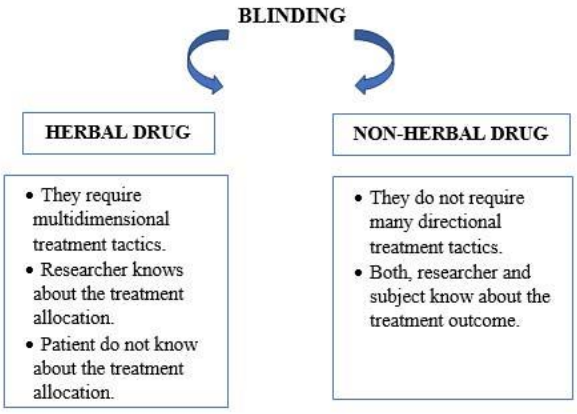
It is trusted that randomization may dispose of the act of inclinations given to the subjects to choose a treatment of decision. Patients are gotten some

information about their decision and are given treatment inclination of their decision while the individuals who don't express an inclination are randomized [35].

RANDOMIZATION (Blinding or Double-Blinding)

Randomization or randomized clinical trials (RCT) are generally rely on Double-Blinding in which agent and dependent do not know the therapy apportioning [36].

There are 2 types of randomization process depending upon the type of drug product used:



REGULATORY CONSIDERATIONS OF HERBAL DRUG PRODUCTS

According to WHO, if the expiry date is given for a phytomedicines material or home-grown readiness, some dependability information which bolsters the proposed time span of usability under the predefined stockpiling conditions ought to be accessible. Steadiness information is constantly required to help the timeframe of realistic usability for the completed natural items [37, 38].

The national medication administrative specialist must guarantee issue of permit for shippers, wholesalers, makers and constructing agents of home grown medicines. As of now, the merchants of imported home grown therapeutic items need to apply for at least one of the licenses relying upon the sort of business like, permit of merchants, wholesalers, makers, and constructing agents. Quality control guarantees nature of the items by following all around organized and standard specifications to check the nature of home-grown items, different systematic procedures might be utilized. While, picking expository strategies factors, for example, legitimacy, exactness, precision, and strength of the technique must be considered. Such data about standard details can be found in official pharmacopeias, monographs and handbooks [39].

PAKISTAN STANDING IN HERBAL INDUSTRY

Herbs have constantly been significant sort of arrangement in Pakistan and before long these are getting the chance to be evidently renowned across the globe. They have been assuming a critical part in mitigating human sufferings by contributing natural prescriptions in essential social insurance arrangement of rustic and remote uneven regions where over 70% of masses depends on standard plan of prescriptions. The clarification behind their pervasiveness is a result of staggering expense of allopathic meds and responses of these medications. Before long, the total estimation of pharmaceuticals ate up in country both imported and created by national and global medicine associations is in excess of 100 billion rupees consistently with 95% foreign resources. It is a general understanding that fulfillment of financial advancement of a person of a nation prompt improvement of general nation. Identify that what are the most valuable open doors for advancement in those territories. Distinctive research papers show that all zones of Pakistan in Himalayan range are improving with regularly creating herbs, which are of high motivation in pharmaceutical endeavors and their legitimate use could prompt financial advancement of the people and the nation.

A central point denying the improvement of the botanicals as a business venture in Pakistan has been absence of data on the social and monetary benefits that could be gotten from the modern usage of restorative plants. Individuals simply use the herbs utilizing their indigenous learning for their wellbeing needs. Because of absence of data about appropriate promoting of home grown prescriptions and exchanging conceivable outcomes the genuine capability of these herbs for financial improvement could not abused [40, 41].

CONCLUSION

In this situation, to secure and protect the legacy of herbal industry, it is currently laid in the shoulders of the administrative bodies to screen controlled and quality stream of herbal items and to encourage their improvement to clinical trial stages. The objective would not be far away if the administrative experts work intimately with the scholastic organizations, investigate foundations, inquire about facilities and focuses, healing centers, industry, and drug store resources. Application of novel medication conveyance frameworks to phytoconstituents can prompt improved bioavailability, expanded dissolvability and porousness, in this way decreasing the measurements and subsequently, symptoms. Reliability testing of herbal items with referred to substance constituents is same as artificially characterized APIs however is the significant concern. With the expanded utilization of standardized herbal items, the future overall marking practice ought to sufficiently address quality angles.

REFERENCES

1. De Smet PA. The role of plant-derived drugs and herbal medicines in healthcare. Drugs. 1997; 54(6):801-40.
2. Mills S. Herbal medicine. In: Lewith GT, Jonas WB, Walach H, Editors. Clinical Research in Complementary Therapies: Principles, Problems and Solutions. New York: Elsevier Science, Churchill Livingston; 2003. pp. 211-27.
3. Gossell-Williams M, Simon OR, West ME. The past and present use of plants for medicines. West Indian Med J. 2006; 55(4):217-8.
4. Chow EK, Zhang XQ, Chen M, Lam R, Robinson E, Huang H, *et al*. Nanodiamond therapeutic delivery agents mediate enhanced chemoresistant tumor treatment. Sci Transl Med. 2011; 3(73):73ra21.
5. Bansal D, Hota D, Chakrabarti A. Research methodological issues in evaluating herbal interventions. Open Access J Clin Trials. 2010; 2:15-21.
6. Indian Pharmacopoeia. Volume I (A-O) and Volume II (P-Z). Government of India-Ministry of Health and Family Welfare. A-53, 54, 89.
7. Ansari SH, Islam Farha, Sameem M. Influence of nanotechnology on herbal drugs: A Review. J Adv Pharm Technol Res. 2012; 3(3):142-6.
8. Lee HJ, Lee EO, Rhee YH, Ahn KS, Li GX, Jiang C, *et al*. An oriental herbal cocktail, ka-mi-kae-kyuk-tang, exerts anti-cancer activities by targeting angiogenesis, apoptosis and metastasis. Carcinogenesis. 2006; 27(12):2455-63.
9. Suntorn S. Tam Ra Ya Hom (Textbook of aromatic powder). Bangkok: Amytrading; 2001.
10. Summers M. Powders and granules. In: Aulton ME, Editor. Pharmaceutics the Science of Dosage Form Design. Spain: Churchill Livingstone; 2002. pp. 361-3.
11. Mosihuzzaman M, Choudhary MI. Protocols on safety, efficacy, standardization, and documentation of herbal medicine (IUPAC Technical Report). Pure Appl Chem. 2008; 80(10):2195-230.
12. Bansal G, Suthar N, Kaur J, Jain A. Stability Testing of Herbal Drugs: Challenges, Regulatory Compliance and Perspectives. Phytother Res. 2016; 30(7):1046-58.
13. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004; 79(5):727-47.
14. Uhumwangho MU, Okor RS. Current trends in the production and biomedical applications of liposomes: a review. J Med Biomed Sci. 2005; 4(1):9-21.
15. Wen Z, Liu B, Zheng Z, You X, Pu Y, Li Q. Preparation of liposomes entrapping essential oil from Atractylodes macrocephala Koidz by modified RESS technique. Chem Eng Res Design. 2010; 88(8):1102-7.
16. Li HR, Li SF, Duan HQ. Preparation of liposomes containing extracts of Tripterygium wilfordii and evaluation of its stability. Zhongguo Zhong Yao Za Zhi. 2007; 32(20): 2128-31.
17. Priprem A, Watanatorn J, Sutthiparinyanont S, Phachonpai W, Muchimapura S. Anxiety and cognitive effects of quercetin liposomes in rats. Nanomedicine. 2008; 4(1):70-8.
18. El-Samaligy MS, Afifi NN, Mahmoud EA. Evaluation of hybrid liposomes-encapsulated silymarin regarding physical stability and in vivo performance. Int J Pharm. 2006; 319(1-2):121-9.
19. Sinico C, De Logu A, Lai F, Valenti D, Manconi M, Loy G, *et al*. Liposomal incorporation of Artemisia arborescens L. essential oil and in vitro antiviral activity. Eur J Pharm Biopharm. 2005; 59(1):161-8.
20. Mahajan A, Mangat P, Bhatia A, Katare OP. A novel herbal capsaicin loaded liposomal formulation: design, development and evaluation. Pharm Sci., section 11. 2010.
21. Chen JG, Liu YF, Gao TW. Preparation and anti-inflammatory activity of triptolide ethosomes in an erythema model. J Liposomal Res. 2010; 20(4):297-303.
22. Satyam G, Shivani S, Garima G. Ethosomes: A novel tool for drug delivery through the skin. J Pharm Res. 2010; 3(4):688-91.

23. Zhou Y, Wei Y, Liu H, Zhang G, Wu XA. Preparation and in vitro evaluation of ethosomal total alkaloids of Sophora alopecuroides loaded by a transmembrane pH-gradient method. AAPS PharmSciTech. 2010; 11(3):1350-8.
24. Chuanping N, Hongzhao C, Weiying G. Preparation and Study on Properties of Ibuprofen Transfersomes. J Math Med. 2010; (2):203-5.
25. Nanda A, Nanda S, Dhall M, Rao R. Transferosomes - A novel ultra-deformable vesicular carrier for transdermal. Drug Deliv. 2005; 5:395.
26. Xiao-Ying L, Luo JB, Yan ZH, Rong HS, Huang WM. Preparation and in vitro and in vivo evaluations of topically applied capsaicin transfersomes. Yao Xue Xue Bao. 2006; 41(5):461-6.
27. Dhandapani NV, Sumanraj KS, Charitha CH, Tulasi K. Phytosomes-a review. Int J Pharm Sci. 2014; 4(4):622-5.
28. *Barzaghi* N, Crema F, Gatti G, Pifferi G, Perucca. Pharmacokinetic studies on IdB 1016, a silybin-phosphatidylcholine complex, in healthy human subjects. Eur J Drug Metab Pharmacokinet. *1990*; 15(4):333-8.
29. Kim KK, Pack DW. (2006) Microspheres for Drug Delivery. In: Ferrari M, Lee AP, Lee LJ, Editors. BioMEMS and Biomedical Nanotechnology. Springer, Boston, MA; 2006. pp. 19-50.
30. CPMP. Guideline on specifications: Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products. EMA/CPMP/QWP/2820/00 Rev. 2, Committee for Medicinal Products for Human Use. European Medicines Agency, London, UK 2011.
31. McManus JP, Davis KG, Beart JE, Gaffney SH, Lilley TH, Haslam E. Polyphenol interactions. Part 1. Introduction; some observations on the reversible complexation of polyphenols with proteins and polysaccharides. J Chem Soc Perkin Trans. 1985(9):1429-38.
32. Koll K, Reich E, Blatter A, Veit M. Validation of standardized high-performance thin-layer chromatographic methods for quality control and stability testing of herbals. J AOAC Int. 2003; 86(5):909-15.
33. Kumar K. Fundamentals of Clinical Trials. USA: Howard University, USA in Collaboration with NIPRD, Abuja, Nigeria, and Xechem International Inc. 2005; 178.
34. Leung PC. Complementary Medicine. In: Machin D, Day S, Green S, editors. Textbook of Clinical Trials. First edition. Chichester: John Wiley & Sons; 2004; pp. 63-84.
35. Richardson J. The use of randomized control trials in complementary therapies: exploring the issues. J Adv Nurs. 2000; 32(2):398-406.
36. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. BMJ. 1989; 299(6694):313-5.
37. Supplementary Guidelines on Good Manufacturing Practices for the Manufacture of Herbal Medicines. WHO Technical Report Series, No. 937, 2006, Annex 3; 85-106.
38. Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements. Proposed Rule, United States Food and Drug Administration, Rockville, MD 2003.
39. World Health Organization. Legal Status of Traditional Medicine and Complementary/Alternative Medicine: A Worldwide Review. Geneva: World Health Organization, 2001. (WHO/EDM/TRM/2001).
40. Aslam M. Cultivation, collection, conservation and propagation of medicinal herbs: Prospects and Precautions. 2006.
41. Alam S, Ali R, Akhter S, Haque A, Ansari SH. Role of herbals in drug delivery system. The Pharma Review. 2007; 6:106-7.