Review Article

Herbosome: A Revolutionary Model of Herbal Drug Technology

Ayon Dutta[1*], Dipanjana Ash[2]

1. Department of Pharmaceutical Technology, Bengal School of Technology (A College of Pharmacy), Delhi Road, Sugandha, Hoogly, Pin-712102, West Bengal, India.
2. Department of Pharmaceutical Technology, Brainware University, 398, Ramkrishnapur Road, Barasat, Kolkata 700125, West Bengal, India.

***Corresponding author's E-mail:** dutta8ayon7@gmail.com

Received: 16-04-2020; **Revised:** 22-06-2020; **Accepted:** 30-06-2020.

ABSTRACT

Herbosome, a compatible macromolecular complex, is formed via the interaction of stoichiometric amount of natural or semi-synthetic phospholipids with therapeutically active phytoconstituents in an aprotic solvent, acts as a promising technology for drug delivery system in pharmaceuticals and neutraceuticals. Different methods such as rotary evaporation, anti-solvent precipitation technique is adapted to prepare herbosome. Their ease of manufacture, better stability, prolonged therapeutic effect, bio-membrane penetration potential and enhanced bioavailability offer great advantages. In-vitro characterisations of herbosome include study of microscopical properties, entrapment efficiency, percentage yield, zeta potential, particle size, analysis of surface texture, drug release profile. Some of the instrumental techniques employed are FT-IR spectroscopy, NMR, XRD, DSC, DLS, TEM, PCS etc. Diffusion mediated drug release from vesicle structured herbosome provides efficient barrier and permits design of oral as well as topical drug delivery systems for achieving systemic effect.

Keywords: Aprotic solvent, Bioavailability, Bio-membrane penetration, Herbosome, Phospholipids.

INTRODUCTION

The therapeutic applications of traditional phytomedicines have gained popularity for the management of human disease efficiently since ancient time.[1] The recent advancement of the herbal drug technology comes into force with an objective to improve bioavailability of polar bio-active constituents such as phenolic, glycosides, flavonoids etc. In the field of herbal drug delivery system several approaches, such as ensnare the lipophilic carrier, incorporation of solubility enhancer, physical/chemical or structural modification have been adapted to enhance bioavailability and therapeutic indices of drugs thus achieving better results compared to conventional herbal extracts.

The bioactive ingredients from the whole plant are being extracted, isolated and examined for specific therapeutic applications but there is a chance of partial or total loss of pharmacological activity during isolation and purification process. The traditional herbal formulations usually consist of pharmacologically active constituent along with toxic compound depending on the nature of the plant. Plant extracts often possess low potency *in vivo* or in animal model though exhibiting excellent therapeutic activity *in vitro*. The multi-ring molecular structure and lipid solubility of plant extract retards the absorption process by passive diffusion and limits their ability to cross biological membrane respectively resulting poor bioavailability. Further orally administered bioactive herbal constituents are destroyed by or lost to the gastric juice or they become ineffective due to interaction with other drugs or nutraceuticals.[2, 3]

Herbosome, a revolutionary model, has been successfully developed to achieve remarkable bioavailability of herbal drug and target significant pharmacological response with balanced nutrient safety.[4] The term "Herbo" means plant whereas "some" means cell-like.[5] Herbosome, a compatible macromolecular complex, is prepared by entrapping standardized plant extracts or polar bio-active phytoconstituents into phospholipids.[6] These complex is formed via the interaction of stoichiometric quantity of phospholipids with herbal constituent in an aprotic solvent. [7] Herbosome structures (size range: 50 nm- few hundred µm) are comprised of pharmacologically active phytoconstituents surrounded by natural or synthetic phospholipids like phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine.[8,9] The lipophilic herbosomes are found to be high and moderate solubility in non-polar solvents and fats respectively with definite melting point. Herbosomes are assumed to be micelle being treated with water resembling liposomal structure but possess fundamental difference.[10] Their ease of manufacture, better stability, prolonged therapeutic effect, bio membrane penetration potential and enhanced bioavailability offer great advantages but short half-life, chances of degradation due to phospholipids and high production cost limit the research work on herbosomes.[7, 11, 12]

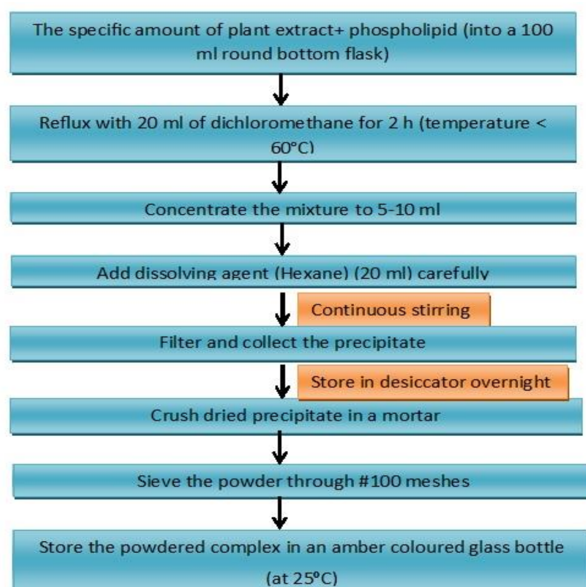
The main approach of formulation methodology, characterisation of herbosomes along with its application in pharmaceutical technology is briefly introduced by this review.

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

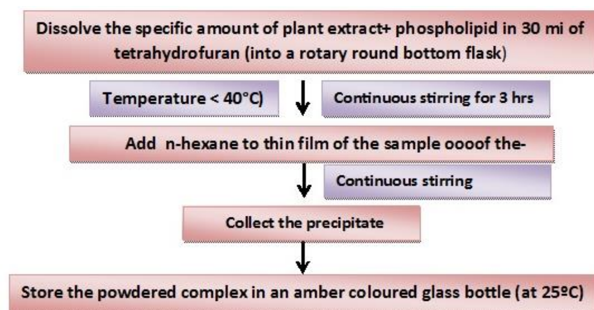
METHODOLOGY

Herbosomes, a molecular complex, are prepared via the interaction of bioactive phytoconstituents with 3-2 moles of phospholipids (preferably with one mole of phospholipids) with or without aprotic solvents like dioxane or acetone and followed the isolation process by either precipitation or lyophilization or spray drying. For the complex formation, the ratio between these two moieties should be maintained in the range of 0.5-2.0 moles. It was reported that the most suitable ratio of phospholipids to flavonoids is 1:1.[10, 13] The different formulation methodologies of herbosomes are described below.

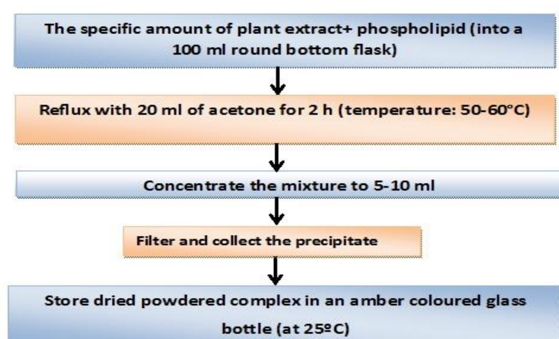
Anti-solvent precipitation technique[7]



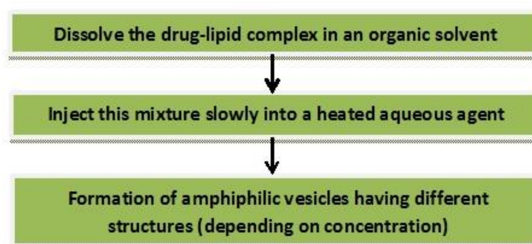
Rotary evaporation technique [7]



Solvent evaporation technique[7]



Ether-injection technique[7]



Working Principle

The amphiphilic nature of phospholipids consists of both polar head and non-polar tail regions. A weak hydrogen bond is formed via the interaction of amine or phosphate group containing polar head of phospholipids with hydrophilic ends of substrates results the formation of a complex imparting lipophilic properties by twisting of non-polar tail of phospholipid itself. Therefore, herbosome becomes suitable for both oral as well as topical delivery of drug. [6, 14]

CHARACTERISATION

Organoleptic evaluation

The organoleptic properties of herbosomes are found on the basis of colour, odour, and transparency. Solubility and wavelength maxima of the drug are also determined by organoleptic evaluation. Keerthi et al reported that Ashwagandha extract was found to be soluble in phosphate buffered saline (pH 7.4) and dimethylsulphoxide and the standard solution showed linearity at λ_{max} 226nm. Jain et al found that Mangiferin–soya phosphatidylcholine (MF–SPC) complex was soluble in dichloromethane and insoluble in methanol, hexane.[15, 16]

Microscopic study

Several structural characteristics of herbosomes such as morphology, crystallization, stress or magnetic domain and internal structural network are visualized by transmission electron microscopy (TEM) whereas scanning electron microscopy (SEM) provides the information regarding surface texture of herbosome. [7] Rathee et al observed spherical structure of *Citrullus colocynthis* (L.), *Momordica balsamina* and *Momordica dioica* extract containing phytosome (Polyherbal phytosome) without aggregation by TEM and digital microscopy. [17] Nazeer et al also found a spherical shaped phytosome containing methanolic extract of *Allium sativum* with the help of SEM micrographs (at 20KV for the magnification range of 7500).[18]

Particle size and zeta potential

Dynamic light scattering (DLS) in combination with computerized inspection system and photon correlation spectroscopy (PCS) are employed for the determination of particle size and zeta potential. Ittadwar et al reported that the average particle size and zeta potential of umbelliferone phytosome was found to be 1139 nm and -

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

0.05mV respectively. [19] Keerthi et al observed the average particle size of Ashwagandha phytosome was 98.4nm by using by particle size analyzer (Horibo scientific nanopartica SZ100). The value of zeta potential (-28.7mV) indicated good stability of Ashwagandha phytosome. [15]

Percentage yield and Entrapment efficiency

The entrapment efficiency provides information about the percentage of drug entrapped into the herbosome by ultracentrifugation technique. [7] Entrapment efficiency and percentage yield of drug are determined by following equation. [15, 17]

$$\text{Entrapment efficiency } (\%) = [(\text{Weight of total drug} - \text{weight of free drug}) \div \text{Weight of total drug}] \times 100$$

$$\text{Percentage yield} = (\text{weight of herbosomes formed}) \div (\text{weight of drugs and non} - \text{volatile excipients}) \times 100$$

Keerthi et al found the entrapment efficiency of Ashwagandha phytosome (100mg Ashwagandha extract and 300mg Soylecithin) was 90.1%. If the lipid quantity exceeds 300mg, the entrapment efficiency was found to be decreased indicating the more lipid concentration is not suitable for ensnaring drug into the matrix. [15] The entrapment efficiency of *Allium sativum* and Polyherbal phytosome were found to be 97.306 % and 92.1% respectively. [17,18] Studies revealed that greater entrapment efficiency of phytosome (greater than 90%) than conventional dosage forms was due to higher lipid solubility of garlic oil. [20] The percentage yield of Polyherbal extract was found to be 72%. [17]

X-ray diffraction study

The crystalline behaviour and the diffraction pattern are determined by X-ray powder diffraction method. X-ray diffraction pattern of the umbelliferone phytosome showed diffraction peaks of crystallinity at a diffraction angle (2θ) 15.681 to 27.618 by operating Bruker AXS D8 Advance at 35 mA tube current and 40 kV tube voltages.[19]

Drug content

Suitable methods for the determination of drug content such as UV spectroscopy, HPLC, GC-MS are adapted to quantify the amount of drug.[7] The drug content of optimised umbelliferone phytosome (1:2 stoichiometric molar ratios of umbelliferone and phospholipon 90H) was found to be 97.40% by UV spectrometer at 324nm. [19]

Thermal analysis

Differential scanning calorimetry (DSC) determines the transition temperature, onset temperature, enthalpy of the vesicle shaped herbosome. It is another approach of drug- excipient compatibility study. Similar endothermic melting transition of anti-diabetic polyherbal extracts and phospholipids indicated the compatibility of phytosome formulation. [17] Ittadwar et al observed the exothermic peak and onset temperature of umbelliferone phytosome at 75.17 °C and 63.55 °C respectively. A little chemical interaction was also detected by DSC thermogram. [19]

Spectroscopic evaluation

The spectroscopic study provides the confirmation of complexity between bio-active herbal constituents and phospholipids moiety therefore helps in the assessment of physical and chemical interaction between them. [17]

Nuclear Magnetic Resonance

In characterization of herbosomes, ^{1}H and ^{13}C-NMR are most commonly used. ^{1}H-NMR spectra of the evodiamine-phospholipid complex indicated some intermolecular interactions whereas intramolecular hydrogen bonding was observed in Mangiferin–soya phosphatidylcholine complex.[21, 16] ^{13}C-NMR study of umbelliferone revealed the signal for carbon at δ 155.57 and138.59 ppm with a hydroxyl and a carbonyl group respectively whereas the umbelliferone phytosome showed chemical shift from δ 155.57 to 160.39 ppm due to shifting of signals on the higher side.[19]

FT-IR spectroscopy

FTIR spectroscopy plays a significant role to determine the stability of herbosomal topical gel as well as herbosomal dispersion system.[7] FT-IR spectrum revealed the interference of resveratrol-phospholipid complexes at polar end group of the Phospholipon 90G. Board band of Phospholipon 90G and trans-resveratrol complex, an indication of intermolecular hydrogen bonding, was employed as a confirmation tool of the complexation. [22]

In vitro drug release and drug release kinetics

In-vitro drug release study is carried out by using dialysis bag or Franz diffusion cell and different kinetic modelling (zero, first, Higuchi, Korsmeyer-Peppas model) are adapted to detect the release kinetics and diffusion mechanism of herbosome. Rathee et al revealed 92% biphasic drug release from the polyherbal phytosome in 12 hrs.[17] Chauhan et al reported that *Aegle marmelos* herbosome (Aegle marmelos: Soylecithin-1:2) showed 91% and 92% drug release in 8 and 12 hrs respectively. [23] The capsules of Ashwagandha phytosomes showed time and concentration dependent 76.8% drug release. [15] Nazeer et al found zero order time dependent 85.35% drug release at the end of 3 hrs from phytosomal complex of *Allium sativum* indicating the reliability for dosage delivery and the drug release followed non-fickian diffusion mechanism. [18] Sikarwar et al revealed first order release profile of Marsupsin–phospholipid complex. [24]

Vesicle stability

The stability study of herbosome follows the measurement of mean size and structural configuration of herbosome over time by DLS and TEM respectively following ICH guidelines. [7] Ashwagandha phytosomes were found to be stabilized at room temperature and refrigerated temperature for 3 months. [15] *Aegle marmelos* herbosome showed higher stability at a frozen temperature (2-4°C). [21]

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

Rathee et al observed no significant changes of polyherbal phytosome on the basis of consistency, phase separation, entrapment efficiency and drug content after 2 months of stability study.[17]

APPLICATION[9, 25-31]

The applications of herbosomes are summarized in Table 1.

Table 1: Application of herbosomes

Phytosome	Phytoconstituent	Dose (mg)	Application(s)
Leucoselect®	Procyanidolic oligomers from Grape seeds extract	50-100	Systemic antioxidant
Greenselect®	Epigallocatechin 3-O-gallate from *Camelia sinensis*	50-100	Systemic antioxidant, Anti-cancer, Hypolipidemic
Siliphos™ milk thistle	Silybin from Silymarin		Skin protective and Hepatoprotective
Ginkgoselect®	24% ginkgo flavono- glycosides From *Ginkgo biloba*	120	Cerebro-protective
Bilberry (Mertoselet)	Anthocyanosides from *Vaccinium myritillus*	-	Antioxidant, Capillary tone enhancer
Palmetto (sabalselect)	Fatty acids, alcohols & sterols from Serenoarepens	-	Anti-oxidant, Benign Prostatic hyperplasia
Hawthorn	Flavonoids	100	Potential against cardiac disorders
Glycyrrhiza	18-β glycyrrhetinic acid		Anti-inflammatory
Mirtoselect®	Anthocyanosides from an extract of Bilberry	-	Potent antioxidant, Capillary tone enhancer, Maintain blood vessel permeability, Effective against venous insufficiency
Lymphaselec™	A standardized extract of *Melilotus officinalis*	-	Effective against chronic venous insufficiency of the lower limbs.
Oleaselect™ -	Polyphenols from olive oil		Anti-inflammatory, Antioxidants, Capacity to reduce the oxidation of low density lipoprotein. cholesterol, and also have
Polinacea™	Echinacosides from *Echinacea angustifolia*	-	Improve immunity

CONCLUSION

Herbosomes, a promising herbal drug technology, can overcome the barrier to formulate the dosage forms with hydrophilic therapeutically active phytoconstituents and show better bioavailability than conventional herbal extracts. Their simple formulation methodology and characterisation techniques pay attention to the reasearchers. Moreover, many patents are endorsed for these novel formulations. Herbosome offers a great future by providing permission in the design of oral and topical drug delivery systems.

Author's Contributions: Authors contributed equally to the design and implementation of the review and the writing of the manuscript.

REFERENCES

1. Gold J, Laxer D, Rochon P, Herbal remedies; a critical perspective, Annals of the royal college of physicians and surgeons of Canada, 33, 2000, 497-8.

2. Khan A, Alexander J, Ajazuddin A, Recent advances and future prospects of phytophospholipid complexation technique for improving the pharmacokinetic profile of plant actives, International Journal of Health Research, 168(1), 2013, 50-60.

3. Bhattacharya S, Phytosomes: the new technology for enhancement of bioavailability of botanicals and nutraceuticals, International Journal of Health Research, 2(3), 2009, 225-32.

4. Kumari P, Singh N, Cheriyan P, Neelam, Phytosome: a novel approach for phytomedicines, International Journal of Institutional Pharmacy and Life Sciences, 1, 2011, 89-100.

5. Nimbekar T, Wanjari B, Bais Y, Herbosomes- herbal medicinal system for the management of periodontal disease, International Journal of Biomedical and Advance Research, 3(6), 2012, 468-72.

6. Ravi GS, Chandur V, Shabaraya AR, Sanjay K, Phytosome: an advanced herbal drug delivery system, International Journal of Pharmaceutical Research and Biosciences, 4(3), 2015, 415-32.

7. Chaudhury I, Deb P, Das S, A review on formulation and characterization of herbosome complex, International Journal of Current Pharmaceutical Research, 11(4), 2019, 42-6.

8. Monica G, Naik VV, Herbosomes: a potential caarriers for the bioavailability enhancement of herbal extracts, World Journal of Pharmacy and Pharmaceutical Science, 4(1), 2014, 1052-79.

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

9. Dewan N, Dasgupta D, Pandit S, Ahmed P, Review on-herbosomes, a new arena for drug delivery, Journal of Pharmacognosy and Phytochemistry, 5(4), 2016, 104-8.

10. Rudra PS, Ramakant N, Preparation and evaluation of phytosome of lawsone, International Journal of Pharmaceutical Science and Research, 6(12), 2015, 5217-26.

11. Bombardelli E, Mustich G, Bilobalide phospholipid complex, their uses and formulation containing them, U. S. Patent, 1991.

12. Kidd PM, Phosphatidylcholine: a superior protectant against liver disease, Alternative Medicine Review: A Journal of Clinical Therapeutic, 1(4), 1996, 258-74.

13. Prachi U, Omprakash B, Phyto-phospholipid complex vesicles for phytoconstituents and herbal extracts: a promising drug delivery system, International Journal of Herbal Medicine, 4(5), 2016, 14-20.

14. U Citernesi, M Sciacchitano, Phospholipids active ingredient complexes, Cosmetics and Toiletries, 110, 1995, 57-68.

15. Keerthi B, Pingali PS, Srinivas P, Formulation and evaluation of capsules of Ashwagandha phytosomes, International Journal of Pharmaceutical Sciences Review and Research, 29(2), 2014, 138-42.

16. Jain PK, Kharya M, Gajbhiye A, Pharmacological evaluation of mangiferin herbosomes for antioxidant and hepatoprotection potential against ethanol induced hepatic damage, Drug Delivery and Industrial Pharmacy, 39(11), 2013, 1840-50.

17. Rathee S, Kamboj A, Optimization and development of antidiabetic phytosomes by box-benhken design, Journal of Liposome Research, 28(2), 2017, 1-26.

18. Nazeer AA, Veeraiyan S, Vijaykumar SD, Anti-cancer potency and sustained release of phytosomal diallyl disulfide containing methanolic allium sativum extract against breast cancer, International Research Journal of Pharmacy, 8(8), 2017, 35-40.

19. Ittadwar PA, Puranik PK, Novel umbelliferone phytosomes: development and optimization using experimental design approach and evaluation of photo-protective and antioxidant activity, International Journal of Pharmacy and Pharmaceutical Sciences, 9(1), 2016, 218-28.

20. Wencui Z, Ying QiW, Di W, Preparation of solid lipid nanoparticles loaded with garlic oil and evaluation of their in vitro and in vivo characteristics, European Review for Medical and Pharmacological Sciences, 19(19), 2015, 3742-50.

21. Tan Q, Liu S, Chen X, Wu M, Wang H, Yin H, He D, Xiong H, Zhang J, Design and evaluation of a novel evodiamine-phospholipid complex for improved oral bioavailability, AAPS PharmSciTech, 13(2), 2012, 534-47.

22. Agarwal A, Kharb V, Saharan VA, Process optimisation, characterisation and evaluation of resveratrol-phospholipid complexes using Box-Behnken statistical design, International Current Pharmaceutical Journal, 3(7), 2014, 301-8.

23. Chauhan J, Gupta H, Pandey K, Shah V, Kamble B, Herbosome an approach to deliver Aegle marmelos extract: formulation, characterization and stability study, Journal of Drug Delivery and Therapeutics, 9(3-s), 2019, 356-65.

24. Sikarwar MS, Sharma S, Jain AK, Parial SD, Preparation, characterization and evaluation of Marsupsin-phospholipid complex, AAPS PharmSciTech, 9(1), 2008, 129-37.

25. Murray MT, Phytosomes: herbal support- increase the absorption of herbal extracts, [Internet], 2004, Available at: www.doctomurray.com/articles/silybin.htm. [Accessed on: 8 May 2020]

26. Kidd PM, Phytosomes: highly bioavailable plant extracts, [Internet], Available at: http://www.indena.com. [Accessed on: 8 May 2020]

27. Vitamedics, Phytosome products, [Internet], Available at: http://www.vitamedics.com. [Accessed on: 8 May 2020]

28. Joshi A, Chaturvedi S, Kumar V, Phytosomes-a revolution in herbal drugs, Kongposh Publications,2007.

29. Naik SR, Pilgaonkar VW, Panda VS, Evaluation of antioxidant activity of *Ginkgo biloba* phytosomes in rat brain, Phytotherapy Research, 20(11), 2006, 1013-6.

30. Murray MT, Siliphos: nature's potent liver remedy, [internet]. Available at: http://www.doctormurray.com/articles/silybin.htm. [Accessed on: 8 May 2020]

31. Bombardelli E, Curri SB, Della LR, Anti-inflammatory activity of 18-beta glycyrrhetinic acid in phytosome form, Fitoterapia, 60, 1989, 29-37.

Source of Support: None declared.

Conflict of Interest: None declared.

For any question relates to this article, please reach us at: editor@globalresearchonline.net
New manuscripts for publication can be submitted at: submit@globalresearchonline.net and submit_ijpsrr@rediffmail.com

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.