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RECENT MICROSPHERE FORMULATIONS AND ITS APPLICATIONS IN HERBAL DRUGS – A REVIEW

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ABSTRACT

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Our country has a vast knowledge base of Ayurveda whose potential is only being realized in the recent years. However, the drug delivery system used for administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. This is the basic idea behind incorporating novel method of drug delivery in herbal medicines. Thus it is important to integrate novel drug delivery system and Indian Ayurvedic medicines to combat more serious diseases.

Keywords: Microsphere, Controlled Release, Novel drug delivery, Herbal drugs.

INTRODUCTION

Herbal formulation is one of the novel drug delivery systems which possess various advantages, including increasing drug solubility, enhancing dissolution rate, bioavailability, etc. The purpose of this article is to examine the effect of Microsphere in herbal medicines in the treatment of some diseases.

Herbal formulation is a dosage form where incorporation of various herbs in specified quantities used to diagnose, treat and mitigate various lifestyle diseases. The secret of the natural health is based on the laws of ayurveda and on standardization of phytomedicines that were well documented in the great dissertations. Herbal preparations are prepared by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These phytomedicines were processed under the most hygienic condition and were available in various forms such as tablets, capsules and oral liquids which were dispensed as vacuum-sealed packaging in different quantities. In traditional knowledge systems herbal medicines that developed over generations within various societies before the era of modern medicine. Now a day developing biomedical system encourages the use of modern medicines which are associated with various side effects and the escalating costs of various synthetic drugs are also the cause for renewed interest in traditional systems of medicine. The WHO also notes, though, that inappropriate use of traditional medicines or practices can have negative or dangerous effects and that further research is needed to ascertain the efficacy and safety" of several of the practices and medicinal plants used by traditional medicine systems

Novel technologies have been developed recently for drug delivery systems [1]. Use of herbal medicines has been increased all over the world due to their miraculous therapeutic effects and fewer adverse effects as compared to the modern medicines. However, delivery of herbal drugs also requires modifications with the purpose to achieve sustained release, to increase patient compliance etc. Previously herbal drugs could not attract scientists towards the development of novel drug delivery systems due to processing, standardizing, extracting and identification difficulties. But now days with the advancement in the technology, novel drug delivery systems opens the door towards the development of herbal drug delivery systems. Novel drug delivery technologies have gained the importance to achieve modified delivery of herbal drugs thereby increasing the therapeutic value as well as reducing toxicity. For last one decade the use of liposomes, ethosomes, phytosomes, emulsion, microspheres, solid lipid nanoparticles has enhanced therapeutic effects for herbal drugs e.g. curcumin, quercetin, silybin, ginkgo etc. The objective of this review is to summarize various microsphere drug delivery technologies which have been developed for delivery of herbal drugs, to achieve better therapeutic response.

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MICROSPHERES

Microspheres are spherical particles consisting of size ideally 1-300 μm. Each particle is matrix of the drug dispersed in the polymer and drug is released as a first order process. Firstly the outer dissolution media will diffuse the matrix make the entrapped drug to solubilize in it and then the drug is released from the system this is one type of mechanism in other type the system constituting polymer show surface erosion behavior where the surface erode layer by layer and the release of drug occurs [2,3]. The polymers used for the fabrication of the microspheres are biodegradable or non-biodegradable. Various polymers have been used for fabrication of these microparticulate carriers such as Albumin, Gelatin, Modified Starch, Polypropylene, Dextran, Polylactic acid and Polylactide- co-glycolide etc [4]. The drug release is controlled by the dissolution and degradation of the matrix. The release is effected by the size, type of matrix and polymer concentration etc. These microparticulate systems are also advantageous as they can be ingested or injected and tailored for desired release profiles. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Microspheres are classified as biodegradable or non-biodegradable. Biodegradable microspheres include albumin microspheres, modified starch microspheres, gelatin microspheres, polypropylene dextran microspheres, polylactic acid microspheres, etc. According to the current literature reports on non-biodegradable microspheres, polylactic acid is the only polymer approved to be used by people, and it is used as a controlled-release agent. Solid and hollow microspheres vary widely in density and therefore are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. In addition, reports on immune microsphere and magnetic microsphere are also common in recent years. Immune microsphere possesses the immune competence as a result of the antibody and antigen being coated or adsorbed on the polymer microspheres [5].

MICROSPHERE HERBAL FORMULATION AND THEIR APPLICATIONS

Various methods such as evaporation technique, ionic crosslinking technique have been reported for preparation of [6,7] mucoadhesive, buoyant microspheres . These microparticulate systems are advantageous as they can be ingested or injected, produce sustained release action and site specific delivery. A number of plant ingredients have been microencapsulated for various applications (Table 1). Gastroretentive floating microspheres of silymarin have been reported for sustained delivery of the drug. Prolonged release of drug (12 hours) was achieved in simulated gastric fluid and resulted in increased drug bioavailability as well as patient [8] compliance. Microencapsulation of *Zedoary* turmeric oil into microspheres via emulsion-solvent diffusion has used been used for bioavailability enhancement and sustained [9] release application. Microspheres of turmeric oleoresin were prepared after emulsification by using spray drying technique. The stable emulsion product protected the resin from degradation from light, oxygen, heat and alkaline [10] conditions and showed increased therapeutic effect. Encapsulation of the herbal extracts of *Piper sarmentosumn* was done by absorption with calcium alginate beads and it was found that there is no effect of method of encapsulation on the encapsulation efficiency so the process can be used at industrial scale for the encapsulation of the herbal extracts. Site specific delivery of rutin from its microspheres (rutinalginate- chitosan) was observed via targeting to [11] cardiovascular and cerebrovascular regions. Oxidised cellulose microspheres containing Camptothecin were prepared by using spray drying process, Oxidised cellulose microspheres have been successfully used to enhance [12] solubility and cytotoxicity of Camptothecin .

Many other novel drug delivery systems can be utilized to enhance the efficacy of herbal medicines[13]. Sublingual dissolving tablets can be used for the administration of phytoconstituents for quick onset of action, since sublingual mucosa is rich in blood supply, drug directly bypass the first past metabolism which is the main problem associated with the herbal drugs. Mucoadhesive drug delivery system can also be utilized to enhance the efficacy of the therapy, reason is that whether the drug delivery is in the form of unit dosage form or multiparticulate system it makes the dosage form to locate itself around the absorption window of the drug molecule which may lead to the enhancement of bioavailability [14]. Floating drug delivery yet another approach which can be used in the case of the drugs having absorption in the upper GI tract. Its utilization is limited since most of the herbal drugs are unstable at gastric pH [15,16].

MICROSPHERES CONTAINING ZEDOARY TURMERIC OIL – HEPATOPROTECTIVE ACTIVITY

The purpose of this study was to design a sustained-release formulation of an oily drug. The sustained-release microspheres with self-emulsifying capability containing zedoary turmeric oil (ZTO) were prepared by the quasi-emulsion-solvent-diffusion method. The micrometric properties, the efficiency of emulsification and the drug-release behavior of the resultant microspheres were investigated. The bioavailability of the microspheres was compared with conventional ZTO self-emulsifying formulations for oral administration using 12 healthy rabbits. An HPLC method was employed to determine the concentration of germacrone in plasma, which was used as an index of ZTO. Spherical and compacted microspheres with average diameters of 100-600 microm have been prepared, and their release behavior in distilled water containing 1.2% (w/v) of polysorbate-80 can be controlled by the ratio of polymer/Areosil200 in the microspheres. The resultant emulsions with mean droplet sizes of 200-500 nm are produced when the microspheres are immersed in phosphate buffer (pH 6.8) under gentle agitation. The

stability and the droplet size of the resultant emulsions are also affected by the polymer/Areosil200 ratio in the formulation, while the amount of talc has a marked effect on the self-emulsifying rate. The plasma concentration-time profiles with improved sustained-release characteristics were achieved after oral administration of the microspheres with a bioavailability of 135.6% with respect to the conventional self-emulsifying formulation (a good strategy for improving the bioavailability of an oily drug). In conclusion, the sustained-release microspheres with self-emulsifying capability containing ZTO have an improved oral bioavailability. Our study offers an alternative method for designing sustained-release preparations of oily drugs [17].

PULMONARY TARGETING MICROPARTICULATE CAMPTOTHECIN DELIVERY SYSTEM – ANTICANCER ACTIVITY

Large (>6 microm) rigid microparticles (MPs) become passively entrapped within the lungs after intravenous (i.v.) injection making them an attractive and highly efficient alternative to inhalation for pulmonary delivery. In this study, PEGylated 6 microm polystyrene MPs with multiple copies of the norvaline (Nva) alpha-amino acid prodrug of camptothecin (CPT) were prepared. Surface morphology was characterized using a scanning electron microscope. CPT was released from the CPT-Nva-MPs over 24 h in rat plasma at 37 degrees C. In-vivo CPT plasma concentrations were low (approximately 1 ng/ml or less) and constant over a period of 4 days after a single i.v. injection of CPT-Nva-MPs as compared with high but short-lived systemic exposures after an i.v. injection of free CPT. This suggests that sustained local CPT concentrations were achieved in the lung after administration of the MP delivery system. Anticancer efficacy was evaluated in an orthotopic lung cancer animal model and compared with a bolus injection of CPT. Animals receiving free CPT (2 mg/kg) and CPT-Nva-MPs (0.22 mg/kg CPT and 100 mg/kg MPs) were found to have statistically significant smaller areas of lung cancer ($P<0.05$ and 0.01, respectively) than untreated animals. In addition, 40% of the animals receiving CPT-Nva-MPs were found to be free of cancer. The CPT dose using targeted MPs was 10 times lower than after i.v. injection of free CPT, but was more effective in reducing the amount of cancerous areas. In conclusion, CPT-Nva-MPs were able to achieve effective local lung and low systemic CPT concentrations at a dose that was 10 times lower than systemically administered CPT resulting in a significant improvement in anticancer efficacy in an orthotopic rat model of lung cancer [18].

GASTRORETENTIVE FLOATING MICROSPHERES OF SILYMARIN – ANTIOXIDANT, SCAVENGER ACTIVITY

Silymarin is a standardized seed extract which is rich in a type of flavonoid compounds known as flavonolignans [19-20]. The main flavonolignans in silymarin are the isomers, silybin (also known as silibinin), silydianin, and silychristin. Silymarin acts as an antioxidant, scavenger and regulator of the intracellular content of glutathione, cell membrane stabiliser and permeability regulator to prevent hepatotoxic agents from entering hepatocytes. It also acts as a promoter of ribosomal RNA synthesis [21] of the transformation of stellate hepatocytes into myofibroblasts - the process responsible for the deposition of collagen fibres, leading to cirrhosis. Silymarin is poorly soluble in water and, therefore, an acidic medium is essential for its dissolution. Its dose is 70 - 140 mg three times a day and has low bioavailability. The low bioavailability of the drug is due to rapid biotransformation in the liver, and has a biological half-life of 6 h. Its reatively short half-life, poor bioavailability and lipophillic nature make it a suitable candidate for gastroretentive drug delivery system. stimulator of liver regeneration and inhibitorCellulose microspheres – formulated with hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC) – and Eudragit microspheres – formulated with Eudragit® S 100 (ES) and Eudragit® RL (ERL) - were prepared by an emulsion-solvent evaporation method. The floating microspheres were evaluated for flow properties based on parameters such as angle of repose and compressibility index, as well as for various other physicochemical properties including particle size, incorporation efficiency, in vitro floatability, and in vitro drug release. The shape and surface morphology of the microspheres were characterized by optical and scanning electron microscopy.

Mean particle size increased while drug release rate decreased with increasing EC and ES contents of cellulose and Eudragit microspheres, respectively. Scanning electron microscopy showed pores on the surface and interior of the microspheres. The microspheres exhibited prolonged drug release for 12 h while still remained buoyant. Drug release kinetics, evaluated using the linear regression method, followed Higuchi kinetics and drug release mechanism was of the non-Fickian type [19].

IMMUNOMODULATORY EFFECTS OF POLY(ETHYLENE GLYCOL) MICROSPHERES ADSORBED WITH NANOFRACTIONS OF *MOMORDICA CHARANTIA* L.- DIABETIC HUMAN BLOOD PHAGOCYTES

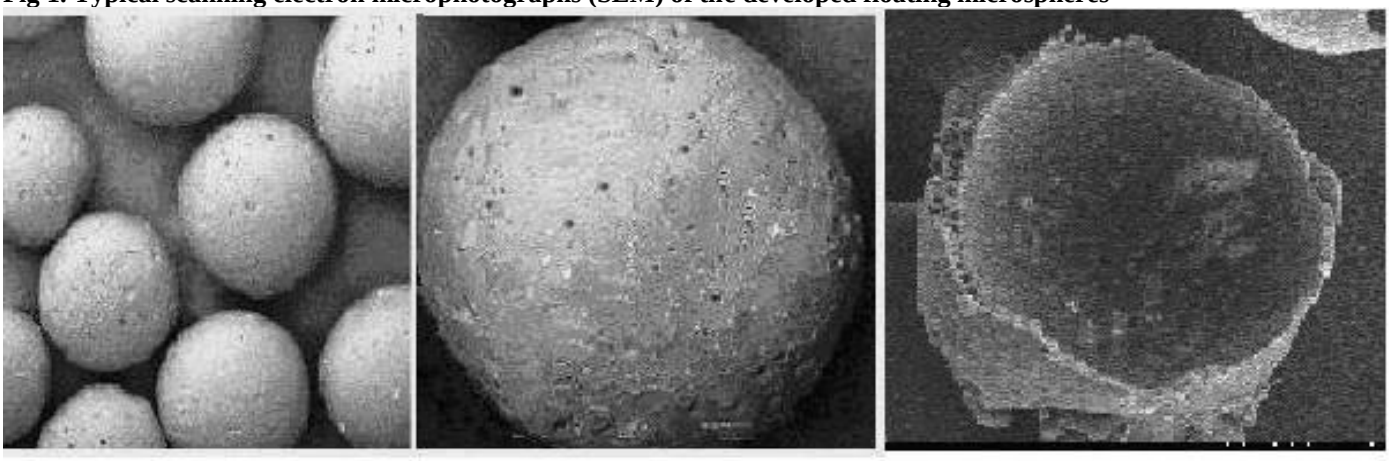
Polyethylene glycol (PEG) based microspheres have the capacity to absorb organic compounds and are a promising strategy for the delivery of therapeutics. In Brazilian ethnopharmacology and experimental studies on individuals with diabetes, the use of *Momordica charantia* L. has been shown to improve the immune system. The aim of this study was to evaluate the adsorption of *Momordica charantia* L. onto PEG microspheres and to verify the in vitro immunomodulatory effect of this nanomaterial on blood phagocytes from diabetic patients. Blood samples were collected according to glycemic status: normal glycemia (N = 120) and clinical diabetes (N = 120). We

explored the use of PEG microspheres fabricated via thermal adsorption of plant extract. We determined the effects of PEG microspheres adsorbed with plant extract on the viability, superoxide release, phagocytosis and microbicidal activity of blood phagocytes. In the presence of the PEG microspheres, superoxide release increased in the phagocytes collected from the clinical diabetes patients, and phagocytosis increased significantly in the control group. Phagocytes had low bactericidal activity against EPEC in the diabetic group. These data suggest that PEG microspheres adsorbed with nanofractions of *Momordica charantia* L. represent a potential nanomaterial for future clinical applications of diabetes [22].

Table 1. Microspheres Herbal Formulation and their Applications

Name of Bioactive component/ Plant	Application
Zedoary turmeric oil (hepatoprotective)	Increase in bioavailability as well sustained release occurs
Rutin (cardiovascular & Cerebrovascular diseases)	Specific delivery to cardiovascular and cerebrovascular region
Campothecin	Significant decrease in dose
Ginsenoside (Anticancer Activity)	Enhance solubility & Stability
Quercetin (Antioxidant & Anti-inflammatory activity)	Enhance bioavailability & Sustain release
Silymarin	Sustained release
Extract of *Piper sarmentosumn*	Used for industrial scale

Fig 1. Typical scanning electron microphotographs (SEM) of the developed floating microspheres



CONCLUSION

It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because it is having the advantage of target specificity and better patient compliance. Its applications are enormous as they are not only used for delivering drugs but also for imaging tumors, detecting bimolecular interaction etc. In future by combining various other strategies, microspheres will find the central place in novel drug delivery. Herbal medicines have been widely used all over the world since ancient times and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines. The drugs of ayurvedic origin can be utilized in a better form with enhanced efficacy by incorporating in modern dosage forms. However, phytotherapeutics need a scientific approach to deliver the components in a novel manner to increase patient compliance and avoid repeated administration. This can be achieved by designing Microsphere drug delivery systems for herbal constituents. Microsphere drug delivery systems not only reduce the repeated administration to overcome non-compliance, but also help to increase the therapeutic value by reducing toxicity and increasing the bioavailability and so on. Recently, pharmaceutical scientists have shifted their focus to designing a drug delivery system for herbal medicines using a scientific approach. The novel research can also aid in capturing as well as to remain in the market. But there are many challenges with herbal drugs which need to be overcome like difficulty of conducting clinical research in herbal drugs, development of simple bioassays for biological standardization, pharmacological and toxicological evaluation methods' development, investigation of their sites of absorption, toxic herbal drugs in use, discovering various animal models for toxicity and safety evaluation, legal and regulatory aspects of herbal drugs and so on. Hence there is great potential in development of Microsphere drug delivery system for valuable herbal drugs as it provides efficient and economical drug delivery and the trends of incorporating Microsphere Drug Delivery system for herbal drugs have also been adopted at industrial scale.

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