Microspheres based on herbal actives: the less-explored ways of disease treatment

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In recent years, focus has been directed towards the development of drug delivery system using biologically active compounds derived from the natural sources. These formulations based on natural products have been reported to have significant activity and are advantageous over the conventional formulations in terms of solubility, enhanced bioavailability, increased pharmacological activity, stability and fewer side effects. Nowadays, people are switching to the natural products over synthetic compounds, which can be easily obtained from the locally available plants and can help in reducing public health costs. The present review aimed at highlighting the development of microspheres based on herbal actives formulations, in which biologically active compounds are delivered to the targeted site. It also summarizes the method of preparation, therapeutic activity and application of herbal formulations in various biomedical fields.

Keywords:
bioactive compound, biomedical applications, delivery system, drug formulation, herbal microspheres

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Introduction

Herbal formulations derived from the natural sources play a pivotal role in healthcare, although natural products have been used throughout human history for various purposes. Nowadays, herbal formulations are also becoming a part of novel drug delivery systems (NDDSs), possessing various advantages, including drug solubility, enhancing dissolution rate, bioavailability, etc. [1]. The term microparticulate may be confusing to readers unfamiliar with this field, but microspheres may be defined as small, solid, spherical, microscopic particles with a diameter of 1–1000 μm either made of polymeric, lipid or other protective materials such as biodegradable synthetic polymers or made of modified natural products such as polysaccharides, gums, proteins, lipids. For example, natural polymers include albumin. Similarly, the synthetic polymers include polyglycolic acid and their derivatives [2,3].

Microparticles can be classified into two types:

(1) Microcapsules that are completely surrounded by a distinct capsule wall.
(2) Microsphere substance that is dispersed throughout the material matrix.

Microspheres are an important part of NDDSs and have the potential to deliver drug in a controlled manner [4]. Advancement in herbal field using novel technology for drug delivery or carriers is significantly enhanced due to its biodegradability and its nontoxic nature with minimum side effects and better therapeutic value. Encapsulated herbal compounds or herbal extracts within microspheres can be used in targeting the site of action with minimum toxicity, thus enhancing bioavailability [5]. NDDS has helped in overcoming the issues of stability and limited absorption attributed to most of the herbal drugs, thereby opening newer avenues towards the development of herbal drug delivery systems [6,7]. Nowadays, with the help of the biomedical system, the use of modern medicine is associated with various side effects, and increased cost of synthetic drugs is the factor that helps in gaining the interest on the use of traditional medicine. The WHO declared that the incorrect use of herbal medicine may cause hazardous or dangerous effects and that further research is needed to ascertain its efficacy and safety. However, for delivery of herbal drugs, modifications to achieve sustained release are required so as to achieve patient compliance [1,8]. From the survey, it can be understood that herbal medicines possess pharmacological activity due to its specific constituents or blend of constituents. Thus, the scientists of this field need to understand the challenges encountered in the use of herbal products (such as, instability in gastric environment, high first pass metabolism, etc.), which prevent the usage over the synthetic drugs, and

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achieve improved development by the use of different carrier systems such as microparticulate system, nanotechnology, liposome, and phytosomes so as to target the specific site with desired concentrations and achieve therapeutic value [9,10].

In this article, an attempt has been made to highlight the development of herbal drugs (e.g. curcumin, quercetin, silybin, gingko, etc.) extracted from the plant material that have been microencapsulated within a polymeric material and used in formulating microspheres, and describe recent works in the field of applied sciences and emerging applications that can help in achieving a better therapeutic response [11,12].

Quercetin is especially found in flavonoid-rich foods, such as apple, tea, berries, cauliflower, onion, nuts, and cabbage. Quercetin occurs in food as an aglycone (attached to the sugar molecule, in which only a small percentage of the ingested quercetin is absorbed in the blood. Quercetin belongs to the flavonoid family consisting of three rings and five hydroxyl groups. Mainly, quercetin is a building block for other flavonoids. Quercetin shows solubility in aqueous ethanol (80% v/v) [13]. It has been shown to have biological properties with its sparing effects on the cardiovascular system and it promotes relaxation of cardiovascular smooth muscle (antihypertensive, antiarrhythmic effects). Other flavonoids have been shown to modify eicosanoid biosynthesis (antiprostanoid and anti-inflammatory responses), having antithrombic effects and promote relaxation of cardiovascular smooth muscles (antihypertensive, antiarrhythmic effects) [14].

Curcumin is obtained from *Curcuma longa* (family: Zingiberaceae) (turmeric). Curcumin (diferuloylmethane) is a yellow-coloured polyphenol consisting of two curcuminoids, demethoxycurcumin and bisdemethoxycurcumin. Curcumin has been found to have antioxidant and anti-inflammatory properties [15]. Curcumin is isolated by means of solvent extraction from dried turmeric roots. Curcumin possesses a wide range of biological properties, including anticancer, antibacterial and antifungal properties. It has a short half-life and a short elimination half-life of 28 min and 0.39 h, respectively [16].

Genistein is mainly found in soya beans, peapods and other legumes. Genistein is an aglycone (without sugar component) of the glycoside genistein. It is an isoflavone that belongs to the group of flavonoids. Genistein is similar in structure to that of estrogens and thus it is also a type of phytoestrogen and acts as an antioxidant. It can also be used in topical applications [17].

Resveratrol is a naturally occurring polyphenolic phytoalexin and is present mainly in plants and fruits, including red grapes, eucalyptus, spruce, blueberries, mulberries, peanuts, etc. and the main source is that obtained from the skin of red grapes and the root of *Polygonum cuspidatum* sieb.et Zucc (Japanese knotweed) belonging to the class of polyphenolic compounds called stilbenes. Resveratrol is a fat-soluble compound occurring in a *trans* and a *cis* configuration. Resveratrol has an effective antioxidant, strong anti-inflammatory and antiproliferative properties [18].

Cynara scolymus is also known as artichoke or globe artichoke (family: Asteraceae/Compositae). Steamed globe artichoke is used as an edible material for nutrition. The flowers are mainly used for nutrition purposes and leaves for medical purposes. It is mainly composed of phenolic acid constituents, particularly cynarin and chlorogenic acid. The extracts of the plant also have a protective effect on hepatocytes. It is broadly used in phytotherapy preparations for hepatic infections, obesity and dyspeptic disorders [19].

Silymarin, known as silibinin, is a polyphenolic flavonoid obtained from milk thistle (family: *Silybum marianum*). It consists of three main phytochemicals – namely, silybin, silidianin and silicristin. Silymarin is the main active constituent responsible for the activity of silymarin. The other constituents are silybin, silibinin, silidianin, silychristin and isosilybin. Silymarin is poorly soluble in water and therefore requires an acidic medium for its dissolution. Dose of silymarin is 70–140 mg three times a day and its biological half-life is 6 h. This phytochemical is mainly used for its antitumour effect along with hepatoprotective and antioxidant activity while regulating the intracellular content of glutathione, stabilizing the cell membrane and regulating the permeability of hepatotoxic agents from entering the hepatocytes [20].

Garlic is also known as *Allium sativum* L. (family: Liliaceae). Its leaves, flower and cloves are mainly used in traditional medicine. The main constituents of this plant are organosulphur compounds, including allicin, diallyl disulphide, *S*-allyl cysteine and diallyl trisulfide. *A. sativum* can be used as potential natural sources for development of natural sources. Aqueous, ethanol and chloroform extracts of garlic can act against pathogenic bacteria and can be used as an antibacterial agent. Garlic extract when used for mouth rinsing might be useful in the prevention of dental caries [21].

Camptothecin, obtained from the wood and bark of *Camptotheca acuminata* (family: Nyssaceae), is a pyranoindolizinoquinoline alkaloid. Camptothecin possess a δ-lactone E-ring. It consists of

10-hydroxycamptothecin, 10-methoxycamptothecin and desoxycamptothecin. It is soluble in ethanol, methanol, acetonitrile, dimethyl sulfoxide and methylene chloride. Leaf extracts of *C. acuminata* have been shown to possess antitumor activity. The sodium salt of camptothecin has 1/10 of antitumour activity. Camptothecin microspheres have been shown to be potentially useful in treating the abdominal metastases of colon carcinoma [22].

Advantages of herbal microsphere formulation

Application of novel approaches to the drug delivery system can improve the efficacy of herbal formulations. Following are some advantages of herbal encapsulated microspheres.

(1) Administration of herbal medication by means of the microparticulate system is advantageous in many ways as microspheres can be ingested or injected. They can be modified for desired release profiles and used for site-specific delivery of drugs, and in some cases can even provide organ-targeted release [23].
(2) Formulation of mucoadhesive drug delivery systems using herbal active constituents can be used to enhance the efficacy of therapy, as drug delivery in the form of microparticulate system makes the dosage form localize itself resulting in the enhancement of bioavailability [7].
(3) Site-specific targeting of drug protects the specific function of drugs, which releases the drugs into an outer phase for a long period [24].
(4) Microparticulate systems based on herbal medicines are likely to be less harmful, and the human body can easily digest them with minimum side effects.
(5) Herbal drugs when encapsulated into microspheres result in considerable enhancement of their solubility, resulting in better bioavailability profiles [9].
(6) Incorporation of plant actives in formulating NDDSs is helpful in curing a variety of diseases with less toxicity and better therapeutic effects [12,25].

Disadvantages of herbal microsphere formulations

There are certain limitations associated with microsphere formulations encapsulating herbal active principles. First, as these phytochemicals are unstable in highly acidic pH conditions, presystemic metabolism in the liver and solubility and absorption problems can result in further lowering of drug levels, sometimes even below the therapeutic levels in plasma, and leading to no or low therapeutic effects [26].

Second, as most of the plant constituents such as glycosides, tannins, flavonoids, etc. are polar molecules and are poorly absorbed due to their large molecular size, which restricts the absorption through passive diffusion, and causes poor lipid solubility, thereby restricting their ability to cross the lipid-rich biological membranes. Such limitations lead to the lowering of therapeutic index and thus bioavailability is reduced for the plant actives [27].

General fabrication methods and techniques for preparation of microspheres

There are various methods and techniques using which microparticulate carriers for drug delivery can be prepared. Selection of technique varies depending upon several factors such as the drug, nature of polymer used, its intended use and the duration of therapy [28].

(1) Single emulsion technique:
    (a) Thermal cross-linking.
    (b) Chemical cross-linking agent.
(2) Double emulsion technique.
(3) Polymerization technique.
    (a) Normal phase polymerization:
        (i) Bulk.
        (ii) Suspension.
        (iii) Emulsion.
    (b) Interfacial polymerization.
(4) Spray-drying technique.
(5) Solvent evaporation.
(6) Wet inversion technique.
(7) Complex coacervation.
(8) Hot melt microencapsulation.
(9) Extrusion–spheronization.
(10) Quasi-emulsion solvent diffusion method.

Single emulsion technique

The following two steps are required to be carried out in this method:

(1) Dispersion or solution of natural polymers in aqueous solution followed by dispersion in nonaqueous solution such as oil.
(2) Cross-linking of the dispersed globules using either thermal cross-linking method or a chemical cross-linking agent (such as glutaraldehyde, formaldehyde, butanol, etc.) [29].

The method is classified on the basis of the type of cross-linking:

(1) *Thermal cross-linking method*: In this method, a cross-linking agent is added to the solution or

dispersion that has been previously maintained at a specific temperature. Thereafter, the dispersed phase is added to the previously heated oil with continuous stirring, resulting in the formation of microspheres of desired size range [30].

(2) *Chemical cross-linking agent*: In this method, the drug is added to the prepared solution or dispersion, and the dispersed phase is added to the continuous phase followed by continuous stirring to form a water in oil emulsion. Thereafter, the cross-linkers are added slowly in the following interval to obtain microspheres, which are dried and stored [31] (Fig. 1).

Double emulsion technique

This method is also called the hydrous technique and suited best for water-soluble drugs. This method involves the formation of multiple emulsions or double emulsion of the type water in oil in water. In the formulation of microspheres both natural and synthetic polymers are used. It is carried out in various steps:

(1) Aqueous solution of drug and polymer is dispersed in an organic lipophilic continuous phase with vigorous stirring to form a homogenous primary emulsion [32].
(2) This primary emulsion is sonicated before addition of aqueous solution of polyvinyl alcohol, leading to the formation of double emulsion. Once the double emulsion is obtained, volatile organic phase is evaporated by means of solvent evaporation or solvent extraction.
(3) Large amount of water is added to preformed double emulsion, resulting in the formation of solid microspheres, which are separated by means of filtration and washing [33] (Fig. 2).

Polymerization technique

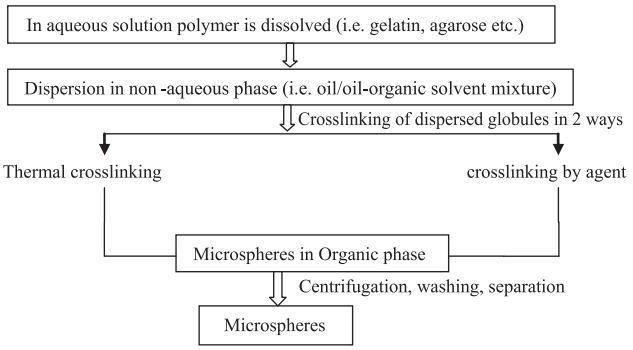
Microspheres are prepared using the polymerization technique, which is further classified into two types: normal polymerization and interfacial polymerization.

Normal polymerization

This method is utilized in different techniques such as bulk polymerization, suspension polymerization and emulsion polymerization process.

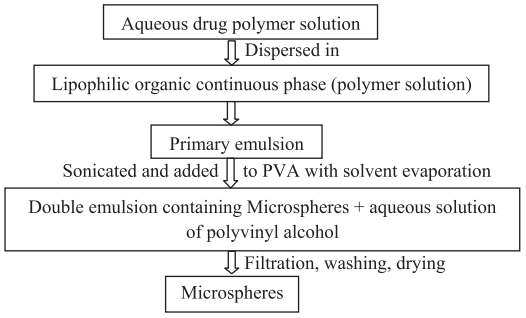
(1) *Bulk polymerization*: In this method, a monomer or a mixture of monomers is heated with the initiator and drug to accelerate the polymerization process. The polymer thus obtained is moulded or fragmented as microspheres, leading to the formation of a pure polymer, but difficulty arises in heat dissipation from reaction, which may degrade the final product [34] (Fig. 3).
(2) *Suspension polymerization*: This polymerization is also known as bead or pearl polymerization.

Figure 1



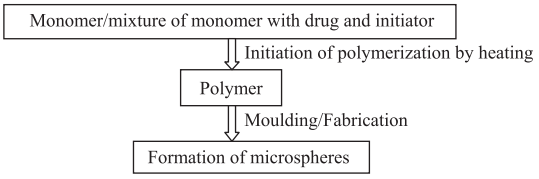
Schematic representation of the single emulsion method.

Figure 2



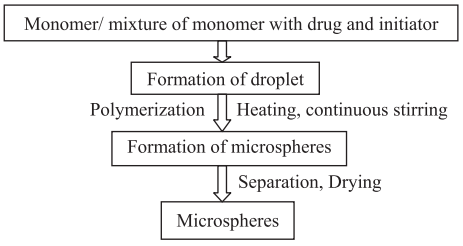
Schematic representation of the formation of microspheres using the double emulsion method.

Figure 3



Formation of microspheres using bulk polymerization.

Figure 4



Method of formulation of microspheres using suspension polymerization.

The drug is heated along with the monomer or a mixture of monomers as droplet dispersion in which the initiator is in a continuous phase. Suspension polymerization is carried out at low temperature. As the continuous external phase is water, heat is easily dissipated out. High molecular weight microspheres are formed faster through this method [35] (Fig. 4).

(3) *Emulsion polymerization*: Emulsion polymerization is similar to suspension polymerization. However, the difference occurs at one stage. The initiator present in the aqueous phase later diffuses to the surface of the micelles or emulsion globules [36] (Fig. 5).

Figure 5

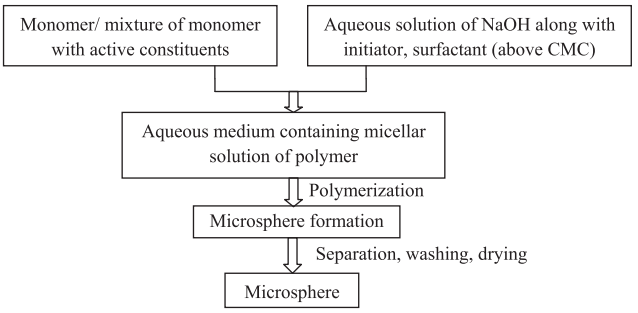
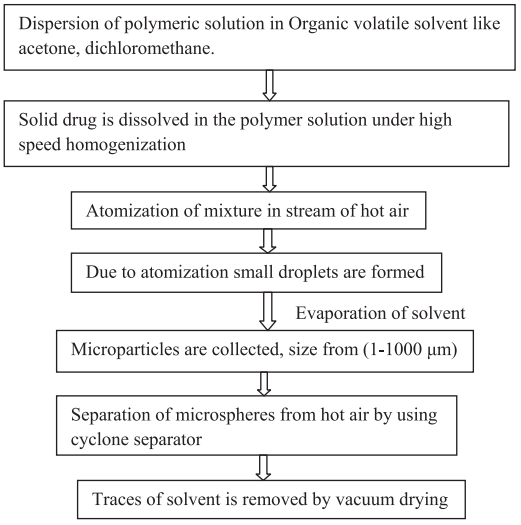


Illustration of method of formulation of microspheres using emulsion polymerization.

Figure 6



Flowchart of the spray-drying method.

Interfacial polymerization

As the term denotes, an interface is formed between two immiscible liquid phase when reacting various monomers to form a polymer film, which envelops the dispersed phase. In this, one monomer is soluble in the continuous aqueous phase and the other monomer is dispersed in the continuous phase and is emulsified. Monomers in either phase diffuse and polymerize rapidly at interface [37].

Spray-drying technique

This technique is also known as an anhydrous technique in which the core material is dispersed and the coating substance is dissolved in coating solution, and polymer is insoluble. This dispersion is atomized in a stream of hot air [38].

This technique is carried out in three steps:

(1) *Homogenization*: the drug in solid form is disf organic solvent such as dichloromethane, acetone, etc. and then homogenized with high speed.
(2) *Atomization and evaporation*: The dispersion is atomized to form small droplets or fine mist from which solvent is evaporated instantaneously, resulting in the formation of microspheres ranging in the size 1–1000 μm. The process is carried out in a cyclone separator.
(3) *Drying*: Vacuum drying is used to remove traces of solvent from the microparticles, and finally the dried microspheres are obtained [39].

Example: Microparticles of chitosan and zolmitriptan used for nasal delivery are formulated using the spray-drying technique [40] (Fig. 6).

Solvent evaporation technique

This technique is most popular and commonly used. It utilizes both microencapsulation and the o/w emulsion system [41] for preparation of microspheres. When drug loading is low, this method is used for formulation of microparticles.

Example: Triclosan-loaded microspheres using chitosan was prepared using solvent evaporation technique [42] (Fig. 7).

Wet inversion technique

In this technique, a polymeric solution in acetic acid is added drop wise through a small-sized nozzle to an aqueous solution of a counter ion such as sodium tripolyphosphate, leading to the formation of microspheres, which are kept undisturbed for some time. A cross-linking agent such as ethylene glycol diglycidyl ether is used as a cross-linker. Hardened microspheres are then washed and freeze-dried [43].

Example: Chitosan microspheres were prepared using the wet inversion technique [39].

Complex coacervation

Because of the simplicity of this method it is broadly applicable for water immiscible solvents containing dissolved polymer in which aqueous solution of drug is encapsulated. The aqueous droplet is surrounded by the surface of polymer layer on subsequent evaporation of the volatile solvent [44]. These microparticles are formed by interionic interactions of oppositely charged polymer solutions. The obtained microspheres are hardened in the counter ion solution and then washed and dried [45].

Example: Microcapsules of hyaluronic acid and gelatine are prepared using the complex-coacervation method [40] (Fig. 8).

Hot melt microencapsulation

This method is basically used for water labile polymers (e.g. polyanhydrides). First, the polymer is melted and then mixed with a drug of size less than 50 μm. The mixture is then suspended in a nonmiscible solvent (such as silicone oil) and stirred continuously and heated. After the stabilization of emulsion it is cooled, resulting in the solidification of polymer particles. The microspheres obtained are washed by means of decantation with petroleum ether. The microparticles easily sustain the drug in a controlled manner [46] (Fig. 9).

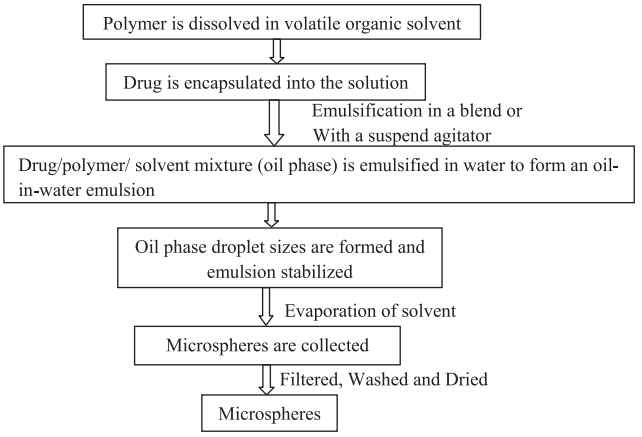
Extrusion–spheronization

Using the extrusion/spheronization technology chitosan pellets were prepared. Increasing the acetic acid concentrations to more than 0.2 N leads to the formation of a sticky extrudate or pellets with rod-like appearance. As the chitosan quantity is increased, particle size decreases, and the powder is extruded with the same acid concentrations and with constant power (180 W). Chitosan is obtained with flake-like characters. Therefore, as the chitosan particles are partly dissolved in the solution they stick to the pellets. When the quantity of the granulating liquid and the acid concentrations is adjusted to the higher amount of chitosan, a low abrasion is achieved [47].

Quasi-emulsion solvent diffusion method

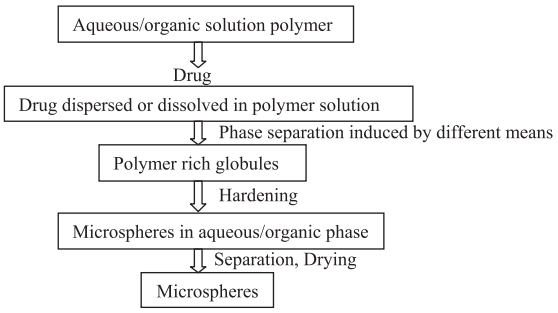
This is a novel technique used for the preparation of the microparticulate system. In this method, an ethanol solution of drug and acrylic resin was poured into an aqueous medium with continuous stirring. The finely dispersed ethanolic droplet-like coacervates formed in the aqueous medium were solidified and transformed into microspheres during agitation. The microspheres obtained have a sponge-like or matrix-like texture having a characteristic advantage compared with the conventional reservoir-type device drug, such as microcapsule [48].

Figure 7



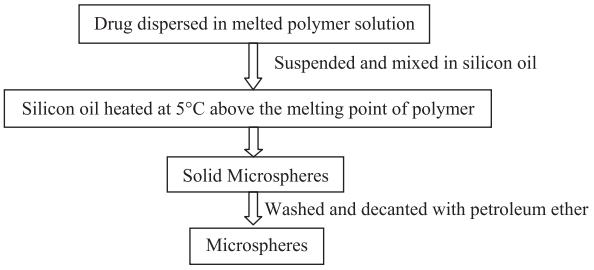
Schematic diagram of preparation of microspheres using the solvent evaporation method.

Figure 8



Formulation of microsphere by means of complex coacervation.

Figure 9



Formation of microspheres using Hot melt microencapsulation.

Example: Felodipine microspheres were prepared using polyvinyl pyrrolidone, polyvinyl alcohol and polyethylene glycol (PEG) agglomerates using the quasi-emulsion solvent diffusion method [49] (Fig. 10).

Herbal microsphere formulations with their biomedical applications

There are various types of microspheres such as mucoadhesive and buoyant microspheres.

Figure 10

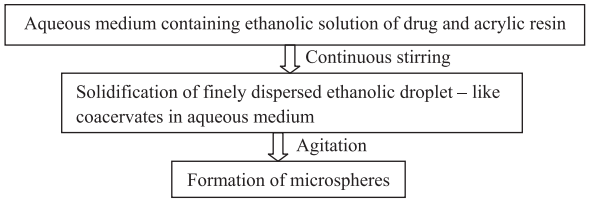


Illustration of microspheres using the quasi-emulsion solvent diffusion method.

These microparticulate systems offer various advantages by maintaining therapeutic plasma drug concentrations [50] when ingested or injected to produce prolonged or sustained release action of drug. There are a number of plant actives that have been encapsulated for various applications (Table 1).

Hepatoprotective activity of zedoary turmeric oil microsphere

A formulation of a sustained release microsphere containing zedoary turmeric oil with self-emulsifying capability was prepared using the quasi-emulsion solvent diffusion method. The focus of the study was to sustain the release of an oily drug. The resultant microspheres were investigated with efficiency of emulsification and the drug-release behavior, and the bioavailability of the microspheres was compared with ZTO self-emulsifying formulations for oral administration using 12 healthy rabbits. The HPLC method was used to determine the concentration of germacrone in plasma, which was used as an index of ZTO. After oral administration of the microspheres, plasma concentration time profiles with improved sustained release characteristics were achieved with 135.6% bioavailability in comparison with the conventional self-emulsifying formulation resulting bioavailability of an oily drug was sustained containing zedoary turmeric oil [63].

Scavenging and antioxidant activity of gastroretentive floating silymarin microspheres

Floating microspheres of silymarin were formulated to prolong the gastric residence time and increased drug bioavailability. Because of the poor solubility of silymarin in water, its dissolution is essentially carried out in an acidic medium. The short half-life and low bioavailability and lipophilic nature of silymarin make it reliable for gastroretentive formulations in which cellulose microspheres are formulated with hydroxyl propyl methyl cellulose and ethyl cellulose, and Eudragit microspheres are formulated with Eudragit S100 and Eudragit RL using the emulsion solvent evaporation technique. The microspheres formulated using this technique exhibited prolonged release for up to 12 h while still remaining buoyant. The drug-release kinetics was evaluated using linear regression following Higuchi kinetics and was confirmed with non-Fickian type [51]. Gastroretentive floating microspheres of silymarin showed antioxidant and scavenging activity while regulating the intracellular content of glutathione and stabilizing the cell membrane. It also acts as a promoter of ribosomal RNA synthesis of the transformation of stellate hepatocytes into myofibroblasts – the process in which collagen fibres are deposited, leading to liver cirrhosis [64].

Anticancer activity of colon-targeted camptothecin microspheres

In this study, camptothecin microspheres were prepared by loading PCL–PEG–PCL (PCEC) so that camptothecin can be protected from hydrolysis and its release time can be extended and its treatment efficacy on colorectal peritoneal carcinomatosis and tumour growth in mice can be enhanced. These microspheres were prepared using the oil-in-water emulsion solvent evaporation technique. A CPT-loaded PCEC microsphere was confirmed with particle size, morphological characteristics, encapsulation efficiency, in-vitro drug release studies and in-vitro cytotoxicity. The in-vivo studies were carried out by applying CPT-loaded PCEC microspheres to the abdominal cavity of mice once a week in which free CPT was used as a positive control. On the 14th day of treatment, the antitumour activity of CPT-loaded PCEC microspheres was evaluated, which showed a significant decrease in the number of tumour nodes. CD34-stained tumour tissues revealed that these CPT-loaded PCEC microspheres significantly reduced MVD-positive cells and were confirmed for the potential treatment of abdominal metastases of colon carcinoma [65].

Anti-inflammatory and antiarthritic activity of quercetin microsphere

Quercetin had been shown to inhibit allergic and inflammatory responses of the immune system by inhibiting nuclear factor κB, a central transcription factor in inflammatory and proliferative diseases. Hence, quercetin could be an effective antiarthritic agent [66]. As quercetin has limited therapeutic window, it is challenging to produce therapeutic concentrations in the joints. In this work, the aim was to develop intra-articulate drug delivery system

Table 1 Microsphere-based herbal products with biomedical applications [26,51–62]

Formulations	Active drug	Method of preparation	Application of formulation	Therapeutic activity
Quercetin microspheres	Quercetin	Solvent evaporation	Dose size is significantly decreased	Anticancer, anti-inflammatory
Curcumin floating microspheres	Curcumin	Emulsion solvent diffusion method	Curcumin-loaded floating microspheres prolonged gastric residence time to improve the absorption kinetics of curcumin resulting in enhanced bioavailability	Antioxidant, anticancer
Cynara scolymus microspheres	*C. scolymus extract*	Spray-drying technique	Sustained release of neutraceuticals	Nutritional supplement
Zeodary oil microspheres	Zeodary oil	Quasi-emulsion solvent diffusion method	Increased bioavailabilty and controlled release	Hepatoprotective
Rutin–alginate–chitosan	Rutin	Complex-coacervation method	Targeting into the cardiovascular and the cebrovascular region	Cardiovascular and cerebrovascular
CPT-loaded microspheres	Camptothecin	Oil-in-water solvent evaporation method	Controlled release of camptothecin	Anticancer
Piper betle microspheres	Piper betle leaves	–	Targeting to cancerous tumours cells for chemoprevention	Anticancer and antioxidant
Garlic-encapsulated powder	Garlic	Modified fluidization bed-technique	Protect allinase activity throughout stomach and controlled release in stomach	Treatment of stomach-related infections
Polylactide (PLA) microspheres encapsulating ginsenoside	Ginsenoside	Emulsion solvent evaporation	Enhancement of solubility and stability	Anticancer
Piperine gastroretentive microspheres	Piperine	Inclusion spheronization	Decrease in the serum levels of the enzymes	Hepatoprotective and antiulcer properties
Thymol microparticles	Thymol	Spray-drying technique	Remarkably enhanced bioavailability	Local treatment of intestinal infections
Caulis sinomenii microspheres	*Caulis sinomenii*	Emulsion solvent evaporation	Pain with low toxicity and side effect	Treatment of rheumatoid arthritis therapy
Carum carvi	Extracts of *C. carvi*	Complex coacervation	Enhanced bioavailability	Treatment of lung infections
Ocimum sanctum	Extracts of *O. sanctum*	Modified emulsion technique	Enhanced bioavailability	Treatment of lung infections
Encapsulated *Bidenis pilosa* microparticles	*B. pilosa* extract	Spray-drying technique	Permeability and solubility is enhanced with the maintenance of stability and storage conditions	Hepatoprotective and antioxidant activities

by controlling the release of quercetin-loaded microspheres for the treatment of rheumatoid arthritis using the solvent evaporation technique. It showed biocompatibility with in-vitro and in-vivo studies using rabbit synovial cells and Wistar rats. Release of quercetin from the microspheres of selected formulations showed its biphasic nature due to initial burst followed by a controlled release, and the result confirmed that quercetin-loaded microparticulate could be a viable strategy through intra-articular injection for tailoring the release of quercetin in the joint cavity for more than 30 days. This study appears to be a promising choice for the management of rheumatoid arthritis by means of intra-articular administration [67].

Immunomodulatory activity of poly (ethylene glycol) microspheres adsorbed with nanofractions of *Momordica charantia L.*

M. charantia L. was used in experimental studies of individuals with diabetes, which has also been shown to improve the immune system. Microspheres of PEG can absorb organic compounds and can be used for the delivery of active agent. The purpose of this study was to investigate the in-vitro immunomodulatory effect of PEG microspheres adsorbed with nanofractions of *M. charantia* L. on blood phagocytes in diabetic patients. Blood samples were collected on the basis of glycaemic status: normal glycaemia (n = 120) and clinical diabetes (n = 120). PEG microspheres were fabricated using plant extract thermal adsorption. The effect of adsorbed PEG microspheres with plant extract feasibility on blood phagocytes, superoxide release, phagocytosis and microbicidal activity was determined. Collected blood samples of diabetic patients showed that the superoxide release was increased in the phagocytes in the presence of the PEG microsphere and phagocytosis was increased significantly in the control group. Bactericidal activity of phagocytes was low against EPEC in the diabetic patients. This investigation suggests that the microspheres encapsulated with PEG adsorbed with nanofractions of *M. charantia* L. possess a potential nanomaterial that can be used in clinical applications of diabetes [68].

Antiulcer activity of microcapsules of plantago major and *Calendula officinalis*

Herbal water-soluble extracts of plantain plantago major and *C. officinalis L.* (PCE) microcapsules were prepared using calcium carbonate microparticles on which layer-by-layer adsorption of carrageenan and oligochitosan was induced by subsequent dissolving after treatment with EDTA. Coprecipitation and adsorption technique were used for the entrapment of PCE. Entrapment of PCE into carbonate matrix using the coprecipitation method was better compared with the adsorption technique. HCl of pH 1.2 was used for in-vitro release study using a model of acetate ulcer in rats. From the research investigation it has been found that PCE released from the microcapsules were considered an effective agent in clinical application for the repair of gastric tissue [69].

Conclusion

The present review aimed at presenting the comprehensive details of the herbal-based microsphere formulations. As these herbal actives possess a lot of therapeutic potential, they can be utilized in the formulation of newer approaches of treating various ailments. Worldwide, attention has been directed towards formulations based on natural products, which are being globally accepted as an alternative system of therapy in the field of pharmacy due to their low toxicity and side-effect profiles, complete biodegradability and easy availability from the renewable resources. Therefore, herbal-based formulations have great potential when developed using recent advancements in microparticulate drug delivery systems, particularly microspheres, thereby providing efficient and economical drug delivery.

Current and future developments

The future beholds an extensive research in the area of using plant extracts and active principles for the treatment of various diseases being formulated using various drug delivery systems aiming at site-specific delivery for preserving the activity of these constituents at the desired site of action. However, research in this area is still in the exploratory stage. In addition, more attention has to be directed towards the fabrication of carrier materials and tailoring of their properties to reduce toxicity of drugs and enhance and improve the overall quality of the active agents. Herbal microspheres have enormous therapeutic potential. The use of plant extracts such as alkaloids, flavonoids, terpenoids, tannins, etc. is of vital importance as these when administered with the help of the recently developed drug delivery systems show better absorption, enabling them to cross the biological membranes, resulting in enhanced bioavailability. Therefore, great potential can be foreseen in the development of microparticulate drug delivery systems encapsulating herbal active constituents and extracts.

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Conflicts of interest

There are no conflicts of interest.

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