12 Novel Drug Delivery System in Phytochemicals: Modern Era of Ancient Science

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12.1 Introduction

Since primeval times, plants and plant-derived extracts containing bio-active molecules (phytochemicals) have been used as a source of medicines for the treatment of ailments. As per a guesstimate, a total of 25–48% of currently approved medicines by FDA (food and drug administration) is derived from the natural products (Russo 2007; Orlikova and Diederich 2012). Natural products derived from plants (Phytochemicals) are a large diversified group of chemical compounds granting color, flavor,

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aroma, and texture along with various medicinal properties. These phytochemicals are widely distributed among the plant kingdom ranging from vegetables, legumes, grains, fruits, flowers, nuts, seeds, herbs and spices into plant-based beverages such as wine and tea. Potential pharmacologically active phytochemicals are time tested and extracted from edible and medicinal plants, which means they are usually safe and exhibit low or no toxicity at a physiologically relevant concentration on normal human organs and cells. The profusion and readily available plants and plant products (fruits, flowers, bark, leaf, etc.) make the derived chemical constituents diverse and economical to use and study for human benefits.

Naturally occurring compounds derived from plants hold a major proportion of prospective therapeutically active agents (Al-Farsi and Ellis 2014; Overby et al. 2014). It is pertinent to mention that, paclitaxel from *Taxus baccata* (Legha et al. 1986; Riondel et al. 1986; Wiernik et al. 1987), vinblastine from *Vinca rosea* (Costa et al. 1963; Frei et al. 1961) and topotecan a synthetic derivative of natural compound (Cheson and Arbuck 1993; Wall et al. 1992), have been successfully developed into clinically used drugs for the treatment of cancer. However, several encumbrances are to be overcome for their extensive use as drugs. These encumbrances range from low solubility, poor penetration into the targeted cells, and high hepatic clearance due to first pass effect, to narrow therapeutic index (Lipinski 2000; Mastropaolo et al. 1995). Additionally, undesired pharmacokinetic profile and emerging drug resistance are also major obstacles for the development of phytochemicals in the clinically used drugs (Lin et al. 2003).

Novel drug delivery system (NDDS) is a novel approach to drug delivery that overcomes the restrictions of the traditional drug delivery systems of phytochemicals. Modern medicine exerts its actions by targeting precisely the affected areas of a patient and delivering the drug to the particular organ or area. The drug targeting with NDDS to individual organs improves selectivity, drug delivery and effectiveness with dose reduction, and safety, and increases compliance. The NDDS as an ideal drug carrier should be capable of extended circulation in the bloodstream, tiny enough to penetrate target cells and tissues, and finally delivering the active constituents in a predetermined manner.

12.2 Novel Drug Delivery Systems

The NDDS are classified by multiple schemes depending on the types and techniques—based on therapeutic group of drug loaded, the physical form of the NDDS, administration route, mode of delivery or action, etc. Therefore, a few most popular and promising NDDS have been discussed in the following sections which are Polymeric Nanoparticles, Liposomes, Ethosomes, Phytosomes, Nanoemulsion/Microemulsion, Microsphere, Micelles, Transferosome, Implants, Cyclodextrins, Niosomes, Transdermal Patches, etc.

12.2.1 Nanoparticles

There has been substantial research interest in the particulate drug delivery systems (submicron particle size ranging 10–1000 nm) as a transporter for small and large molecules of therapeutic interest. Nanoparticles have many advantages, such as solubility enhancement, thereby leading to bioavailability enhancement, reduction in dose, improvement in therapeutic effectiveness, better stability, and improved absorption of herbal medicines or phytochemicals in comparison with the respective crude formulation or preparations. The nanoparticles can be designed with different particle size and surface characteristics for controlled and targeted drug delivery of both hydrophobic and hydrophilic phytochemicals. The phytochemical release from nanoparticles is either through bulk erosion in the matrix or by surface erosion in the polymer depending on the drug characteristics and method adopted for preparation (Chan et al. 2010a, b; Kumari et al. 2010; Rao and Geckeler 2011; Leo et al. 2006). There are various methods employed for the preparation of nanoparticles, viz. salting out method, solvent evaporation

method, nanoprecipitation, and dialysis method. Polymeric nanoparticles are extensively used in nanotechnology due to their tiny size and exceptional biocompatibility. Interesting synthetic polymers for research include chitosan (Anitha et al. 2011; Das et al. 2010), poly (D,L-lactide-co-glycolide) (PLGA) and PEG (Anand et al. 2010; Shaikh et al. 2009; Yallapu et al. 2010). Among these, PLGA is considered an efficient material for the formulation of a variety of nano delivery systems.

Curcumin, a natural diarylheptanoid polyphenol is an indispensable curcuminoid present in the turmeric rhizome—*Curcuma longa* (L.) (Family: Zingiberaceae) and is accredited as "Wonder drug of life". Despite its enormous therapeutic potential against a wide variety of physiological disorders, the poor aqueous solubility, resulting poor systemic bioavailability and quick degradation are a few of the major constraints which put a ceiling on the clinical development of curcumin (Gera et al. 2017). To advance clinically applicable parameters of curcumin, the nanoparticle has been prepared using different polymers by many researchers with enhanced aqueous solubility and site-specific delivery of curcumin that prompts to augment the bioavailability, transportation, and quick treatment leading to better clinical applications. Mathew et al. coupled Tet-1 peptide with PLGA coated-curcumin nanoparticles, and reported that this complex of curcumin encapsulated-PLGA nanoparticles is non-cytotoxic and exerted the antioxidant property alongside destroying amyloid aggregates. The PLGA encapsulated curcumin does not hamper its intrinsic therapeutic potential and so, the PLGA encapsulated curcumin nanoparticles provides a hope for its use as a drug with multiple therapeutic potentials in the treatment of Alzheimer's disease (Mathew et al. 2012). Yallapu et al. reported enhanced intracellular uptake of curcumin-PLGA nanoparticles and antibody conjugation attributed in cancer cells (Yallapu et al. 2010). Furthermore, Curcumin loaded PLGA nanoparticles with thiolated chitosan such as bis sulfosuccinimidyl suberate facilitated conjugation of annexin A2 and displayed efficient delivery of curcumin to annexin A2-positive MDA-MB-231 cancer cells (Thamake et al. 2011). Curcumin encapsulated in polycaprolactone nanoparticles (650 nm) showed elevated intracellular levels of curcumin in liver cells upon intravenous administration to male wistar rats. This study demonstrated the therapeutic efficiency of this formulation in liver diseases (Anuradha and Aukunuru 2010).

In another study, a remarkable improvement in A549 cells (human lung adenocarcinoma epithelial cell line) cytotoxicity was reported by the combinations of PLGA encapsulated quercetin (a naturally occurring flavonoid) nanoparticles and etoposide-loaded PLGA nanoparticles, as compared to free quercetin and etoposide (Pimple et al. 2012). Quercetin has been studied extensively as a potential drug candidate for the treatment of cancer but its implementation as a clinically used therapeutic drug are limited because of the poor aqueous solubility and low oral bioavailability. Nanoformulations developed for quercetin have shown promising epithelial system uptake as well as enhanced targeted delivery to the site.

Triptolide, a diterpenoid epoxide, is known for its anti-inflammatory, anti-fertility, antineoplastic and immunosuppressive properties. It shows some of the undesirable toxic effects because of the poor aqueous solubility. The anti-inflammatory activity of nanoparticles and microemulsions containing triptolide were evaluated in the rat paw oedema model and the solid lipid nanoparticle (SLN) formulation displayed better activity than the microemulsion (Mei et al. 2003). PLA nanoparticles encapsulating Taxol, produced by emulsion solvent evaporation method, displayed improved bioavailability with sustained release pattern compared to the free drug (Fu et al. 2006). SLN of silibinin showed the hepatoprotective effects and an improved bioavailability due to improved circulation time and enhanced (Zhang et al. 2007).

12.2.2 Liposomes

Liposomes are microscopic, vesicular phospholipids/cholesterol carrier system formulated by

one or more concentric lipid bilayers encapsulating small proportion of the solvent in which they unreservedly diffuse into the interior of the liposomes. It is built of polar lipids containing both hydrophilic and lipophilic groups on the same molecule (Lasic 1993). The interaction of polar lipids with water results in self-assembly of the polar lipids to form self-organized colloidal particles. Hydrophilic molecules of interest or drugs are encapsulated in the hydrophilic/aqueous compartment and the lipophiles are inserted into the membrane. Liposomes can be classified based on the size, a number of lamellae, and the surface charge. The liposomes are further classified based on the surface charge into, anionic, cationic, or neutral subcategories (Bonifacio et al. 2014). Liposomes have the property of encapsulating both hydrophilic and lipophilic materials, therefore, as a carrier, it can indiscriminately deliver molecules of interest through the cell membrane by increasing ingredient solubility and enhance intracellular uptake. Liposomal mode of drug delivery can maintain therapeutic concentrations of the drugs or other phytochemicals for prolonged periods of time, thus significantly improves the therapeutic activity, remedial effect and safety profiles. It releases herbal drugs/phytochemicals in a sustained release fashion with reducing peak-valley fluctuations and targeting into the desired area, by improving the solubility and bioavailability (Singh 2015; Abou ElWafa et al. 2003; Barragan-Montero et al. 2005; Weiss and Fintelmann 2000; Ajazuddin and Saraf 2010).

Liposomes were discovered in 1970 as drug delivery vehicles for targeting at the active site into desired concentration. The first successful example of a liposomal drug delivery system is the formulation of doxorubicin (anti-cancer drug) encapsulated in sterically stabilized liposomes (Doxil®). It was approved in 1995 by the FDA for clinical use in the US market (James 1995). Liposomes have been found to be a delivery system for vitamins and enzymes, small cytotoxic molecules as liposomes are biocompatible, nontoxic, and biodegradable in nature (Musthaba et al. 2009; Allen and Cullis 2013). Liposomal drug delivery systems play a vital role owing to easy preparation, and charged liposomes could enhance the percutaneous permeation through the skin, resulting in transdermal drug delivery. The applications of liposomes in herbal formulations have been investigated widely and it's evident from the latest researches that are more focused on enhancing the bioavailability of phytoconstituents (Musthaba et al. 2009; Ajazuddin and Saraf 2010). *Atractylodes macrocephala* Koidz essential oil entrapped into liposomes for the treatment of digestive diseases and tumors has displayed lesser side effects (Wen et al. 2010). *Tripterygium wilfordi* extract displayed better heat stability and lesser side effects on liposomal entrapment (Li et al. 2007).

Quercetin liposomes increased anxiolytic and cognitive effects with a significant reduction in dose when administered through oral and intranasal route (Priprem et al. 2008; Blumenthal et al. 2000). To improve the solubility of Silymarin in the gastrointestinal tract, it has been incorporated into liposomal dosage form which on oral administration improved its bioavailability. Soybean lecithin has been used to incorporate silymarin in liposomal form to improve the bioavailability in a stable buccal dosage form. Silymarin has also been encapsulated as hybrid liposomes (El-Samaligy et al. 2006) to prevent aggregation by maintaining liposomal stability. Commercially available liposome as a delivery system for herbal extracts is Liposomal based powder form Herbasec® by a Swiss-based company Cosmetochem International AG. It is available in the freeze-dried form which is reformed-encapsulating the concentrated plant extract on dispersion in water (Saraf 2010).

12.2.3 Ethosome

Ethosomes are the slightly modified un-shakable drug carrier liposome. It was developed by Touitou et al. (1997), as a non-invasive drug delivery carrier that facilitates drug delivery into the deep skin layers and/or into the systemic circulation through the stratum corneum barrier (Bendas and Tadros 2007). Ethosomes are malleable soft vesicles containing ethanol (20–45%),

phospholipids, and water customized for enhanced delivery of desired compounds. These phospholipids are mainly phosphatidylserine, phosphatidylcholine, phosphatidic acid (Merdan et al. 1998). Ethanol is added to make vesicular systems an elastic nanovesicle. The property of ethanol to disturb the skin lipid bilayer organization acts as a competent permeation enhancer and helps in penetration of stratum corneum by interacting with the hydrophilic polar part of the lipid molecules imparting lipid fluidity, and enhances cell membrane permeability as a result of a decrease in the melting point of the stratum corneum lipid. The addition of ethanol imparts high flexibility to the vesicular membrane making elastic enough to squeeze through the pores smaller than their size (Verma and Pathak 2010). Ethosomes can penetrate through the skin at a higher rate than liposomes, rendering them to replace liposomes. Ethosomes entraps phytochemicals and drug molecule with differing physicochemical properties i.e. hydrophilic, lipophilic, and also amphiphilic molecules like proteins and peptides. Herbal ethosome preparations have effectively enhanced the bioavailability of many medicinal plants including *Sophora alopecuroides*, *Cannabis sativa*, *Glycyrrhiza glabra*, etc. for various diseases (Pawar et al. 2015). These ethosomes are suitable for various applications in cosmeticeuticals, phyto-pharmaceuticals, pharmaceuticals, nutraceuticals, veterinary and biotechnology segments. Topical application of Vitamin E, exogenous lipophilic vitamin with antioxidant property reported to enhance the skin protection from exogenous oxidants and used widely in various dermatological preparations. Vit E addition decreases the production of lipid peroxides and protect against UV exposure, destructive chemicals, and physical agents as well. Antioxidants rapidly undergo degradation when exposed to light. Ethosomes have been reported to be an advantage in cosmeceuticals for topical administration of antioxidants to diminish oxidative injury in the skin. Koli and Lin (2009) developed antioxidant ethosomes using the synergistic properties of Vit A palmitate with Vit C for Vit E transport into the deeper layer of stratum corneum. An absolute protection of the ethosome formulations from the oxidation was observed due to the synergistic interaction of Vit C and Vitamin A and E in the aqueous core and lipid bilayer, respectively.

Ethosomes application in transcutaneous immunization of antigen against Hepatitis B showed superior entrapment efficiency when compared to conventional liposomes. *In vitro* assay in murine dendritic cells demonstrated an efficient uptake of HBsAg-loaded ethosomes. It also generated a robust systemic and mucosal humoral immune response on the topical application in mice in comparison with alum-adsorbed HBsAg suspension (i.m.), the topical application plain HBsAg solution, and the hydroethanolic (25%) HBsAg solution. HBsAg-loaded ethosomes were capable to produce a protecting immune response. It was further tested using human cadaver skin, which displayed a superior skin penetration of the antigen than the conventional liposomes and soluble antigen formulation (Mishra et al. 2007). The ethosomes may be used for the development of a Hepatitis B vaccine via a transcutaneous route due to its ability to transverse and target the immunological environment of the skin.

Other applications of ethosome have been reported in the administration of hormones by Ainbinder and Touitou (2005). Paolino et al. (2005) investigated the anti-inflammatory ammonium glycyrrhizinate ethosomes for dermal delivery for various skin diseases. Lodzki et al. (2003) prepared a transdermal cannabidiol ethosomal formulation for the treatment of rheumatoid arthritis.

12.2.4 Phytosome

In most of the cases, biological activities are partially or totally lost during the isolation and purification process of the molecules having therapeutic potential. It has been observed that the bioavailability and biological activities of the active constituents is dependent on the complexity of the different ratios of the constituents present in the crude or partially purified extract. Extracts, when taken orally, may sometimes lead

to the destruction of active constituents in the gastric environment due to digestive secretions and gut bacteria. Therefore poor bioavailability hinders their effects. As most of the bioactive water-soluble phytochemicals like flavonoids, tannins, terpenoids, etc. have large molecular weight and this leads to poor absorption by passive diffusion, and possibly their poor lipid solubility also limits their ability to permeate through lipophilic biological membranes, thus results in poor bioavailability of these molecules (Manach et al. 2004; Kumar and Kesari 2011). Therefore, for such herbal extracts to be effectively utilized as herbal drugs is hugely dependent on the delivery to an effective level. Indena S.p.A. of Italy developed the Phytosome® technology which markedly enhanced the bioavailability of select phytomedicines. This technology involves incorporation of water-soluble phytoconstituents or standardized plant extracts or fractions into phospholipids molecular complexes; improves their bioavailability (Bombardelli et al. 1989; Manach et al. 2004).

Phytosomes display structural and functional differences from liposome as phytosomes are a molecular unit of few molecules bound together while the liposomes are made of several phospholipid molecules aggregating together to enclose the phytochemicals or drugs without specifically binding with them. The water-soluble active principles are hosted in the inner cavity of liposomes with limited interaction with surrounding lipid core. On the contrary, the phytosomes accompany their polyphenolic guest at their surface and the guest having polar functionalities via polar interactions with phospholipids bearing charged phosphate groups. The spectroscopic technique can evident these interactions. The topical application of phytosomes enhances the absorption of desired active compounds and oral administration significantly improves the systemic bioavailability and thus phytosomes are superior to liposomes in these modes of administration (Fry et al. 1978; El Maghraby et al. 2000; Jain 2005).

Phytosome being able to cross the lipophilic biological membranes to reach into systemic circulation results in higher plasma concentrations than the individual compounds (Mauri et al. 2001; Kidd and Head 2005; Rossi et al. 2009). The resulting higher plasma concentration ensure that more amount of the desired constituent is available at the site of action (liver, kidney, brain, heart, or another organ) at the same or even low dose. Therefore, the therapeutic action improves, prolongs and becomes detectable. Absorption of phytosome in gastro-intestinal tract can be favorably deployed in the treatment of acute hepatic disorders of metabolic and/or infective origin. Phosphatidylcholine can also be used as a hepatoprotective besides its use as a phytosome carrier, thus it may exert a synergistic effect as hepatoprotective (Saraf and Kaur 2010). The phytosomes can be used for various ailments including cardiovascular, anti-inflammatory, immunomodulatory, anticancer, antidiabetic, etc and also for prophylactic and health benefits as neutraceuticals.

Several therapeutically important phytochemicals developed in this form displayed excellent therapeutic activity in the animal and human models. Meriva®, a patented curcumin-soy phosphatidylcholine complex (Kidd 2009; Marczylo et al. 2007) demonstrated greater bioavailability in rats in comparison with standardized curcumin extract in rats. Indena complexed soyphospholipids exploiting the Phytosome® technology to defeat the poor bioavailability of silybin. Ginkgoselect® Phytosome® have been used in human trials for Raynaud's disease and the study exerted the usefulness of the phytosome in the reduction of Raynaud's attacks, both the frequency (56%) and severity (Muir et al. 2002).

12.2.5 Nanoemulsions/ Microemulsions

Emulsions are thermodynamically unstable formulations of oil and water phase, stabilized by a suitable emulsifying agent. Nano and micro emulsions O/W or W/O type emulsion possess the size range of several microns. These emulsions are widely used in drug delivery formulations to enhance the solubility of inadequately soluble drugs and possess various advantages such as

good thermodynamic stability, ease of manufacturing, fewer chances of drug degradation, etc. (Kumar et al. 2012; Mujaffar et al. 2013).

FDA approved surfactants, considered safe for human use, are utilized for the preparation of these emulsions. The higher surface area and lower size enable them to penetrate easily through the skin. Nanoemulsions can be prepared by various methods including the high-pressure homogenization and microfluidisation technique (Lieberman et al. 1998; Lachman et al. 1996) unlike to microemulsions which form spontaneously. The scope of microemulsions and nanoemulsions in herbal drug delivery is wide and has been used clinically as well as commercially (Goyal et al. 2011).

An enhanced anti-inflammatory activity of curcumin in O/W nanoemulsion was reported in 2008 (Wang et al. 2008). It was prepared by an optimized high pressure and high-speed homogenization method to achieve droplet sizes in the 618.6–79.5 nm range. 12-O-tetradecanoyl phorbol-13-acetate-induced edema of mouse ear was used to compare this formulation against 1% curcumin in 10% Tween 20 water solution and it was observed that high-pressure homogenization microemulsion showed improved activity compared to microemulsion prepared with the high-speed method; no activity was observed with 1% curcumin in 10% Tween 20 water solution. The eutectic properties of ubiquinone was utilized to develop a self nanoemulsion (Nazzal et al. 2002). This drug delivery system enhanced the solubility and bioavailability and reduced precipitation of the drug in the vehicle.

12.2.6 Microsphere

Microspheres are spherical particles having a diameter in the range of 1–1000 μm in which drug is dispersed in finely divided form or crystalline form and also referred to as microparticles. They can be prepared from various materials of natural and synthetic origin like albumin, gelatin, chitosan, polypropylene, polylactic acid, polyglycolic acid, modified starch, dextran, etc. The first order kinetics is followed by microsphere for the drug release and controlled by the matrix dissolution and disintegration. The drug release is majorly affected by the matrix type, size and concentration of the polymer (Brahmankar and Jaiswal 1998). Microspheres are having wide commercial applications including sustained drug delivery, they can be ingested or injected, overcome handling issues with potent molecules and improved targeting at the active site in desired concentration to maintain overall effective plasma concentration for a longer duration (Singh 2015; Varde and Pack 2004; Freiberg and Zhu 2004). Mucoadhesive microsphere has been prepared by evaporation technique and ionic cross-linking technique, etc. (Kanan et al. 2009; Das and Senapati 2008). In recent times, microspheres are widely used to enhance the therapeutic potential of various poorly soluble phytoconstituents.

Gastro-retentive floating microspheres of curcumin have been prepared with a prolonged gastric residence time in simulated gastric fluid for at least 20 h, resulting in increased drug bioavailability (Kumar & Rai 2012). Rutin-alginate-chitosan microsphere delivered rutin specifically to cardiovascular and cerebrovascular organelles (Xiao et al. 2008). *Piper sarmentosumn* extract encapsulated with calcium alginate beads used an industrially feasible process of adsorption (Chan et al. 2010a, b). Zedoary turmeric oil was microencapsulated to enhance bioavailability and sustained-release application. This was achieved by emulsion-solvent diffusion method (You et al. 2006). Turmeric oleoresin microspheres were prepared after emulsification of oleoresin followed by spray drying technique. The microspheres displayed an improved therapeutic effect and also protected the oleoresin from degradation when exposed to light, oxygen, heat, and alkali (Kshirsagar et al. 2009). Camptothecin was encapsulated in oxidized cellulose microspheres by spray drying process; enhanced its solubility and cytotoxicity (Chao et al. 2010).

12.2.7 Micelles

Micelles are lipid molecules organize themselves in a spherical shape in aqueous solutions.

Polymeric micelles are usually very small in size and range from 10 to 100 nm (Kataoka et al. 2001). Micelles protect the drug from its surrounding which may inactivate the drug and thus increases the drug bioavailability and retention (Kwon 2002). There are various factors which govern the drug release from micelles, such as micelle stability, drug diffusion rate, the partition coefficient, and the copolymer biodegradation rate (Kwon and Okano 1996). The drug release is also affected by its concentration and location inside the micelles, molecular weight and physicochemical properties (Teng et al. 1998). Targeted delivery of poorly soluble herbal drugs has been achieved by using polymeric micelles. Micelles formulations of poorly soluble drugs like Artemisinin and Curcumin with sodium dodecyl sulphate increased their solubility by 25-folds. The micellar formulation also increased the solubility of paclitaxel and has been used for the treatment of hormone refractory prostate cancer in LN Cap tumor model (Simon et al. 2000).

12.2.8 Transferosome

The transferosome concept was introduced in 1991 by Gregor Cevc. Transferosomes are phospholipid vesicles which can penetrate the stratum corneum to be used as potential transdermal drug delivery carriers (Pandey et al. 2009). Transferosomes exhibit better elasticity than the standard liposomes and thus more suitable for the transdermal drug delivery. Transferosomes squeeze themselves along the intracellular lipids of the stratum corneum and penetrate the skin (Eldhose et al. 2016). Hydration or osmotic force in the skin enhances the penetration through stratum corneum. They can be used as a potential carrier for drugs with a wide range molecular weights and different pharmacological actions including analgesic, sex hormones, anesthetic, anticancer, corticosteroids, and insulin, etc. They are biocompatible, biodegradable and have high entrapment efficiency (near to 90% for the lipophilic drug). They act as a depot for the encapsulated drug protecting from metabolic degradation, and release the drugs slowly and gradually. They are used in both systemic and topical drug delivery. The preparation of transferosomes is simple, short and do not involve pharmaceutically unacceptable additives (Cevc et al. 1998). Transferosomes are prepared using following: (a) phospholipids, a vesicle-forming material, (b) surfactant for providing flexibility, (c) alcohol as a solvent and (d) a buffering agent as a hydrating medium.

Curcumin is largely used as a potent anti-inflammatory herbal drug, but it has low bioavailability due to poor gastrointestinal absorption. Transferosomes encapsulating curcumin gel showed an increase in skin permeation compared with the plain gel containing curcumin, paving the transferosome as potential carriers for the curcumin transdermal delivery (Patel et al. 2009). High shear dispersion technique was used to prepare Capsaicin transferosomes and it showed better topical absorption compared to pure Capsaicin (Xiao-Ying et al. 2006). Colchicine transferosomes for topical delivery were prepared using handshaking method and prevented the GI side effects of oral absorption (Singh et al. 2009). Transferosomes encapsulating Vincristine sulfate were prepared by lecithin and sodium deoxycholate (70/20). The *in vitro* tests through mouse skin showed penetration through the skin at zero order rate (Lu et al. 2005).

12.2.9 Implants

Another approach of controlled drug delivery is to formulate into polymeric implants. Implants are polymeric devices which provide controlled drug delivery of wide variety of drugs. These are prepared using biodegradable polymers and can be directly placed at the site of action by a microsurgery for the insertion of these devices (Brahmankar and Jaiswal 1998). Two types of polymeric matrices are used for the preparation of Implants: Biodegradable and Nondegradable polymeric matrices. Nondegradable bio-matrices are made of either silicone or poly (ethylene-co-vinyl acetate) (Saltzman and Fung 1997). The Norplant system of contraception uses these non-biodegradable biomatrices for this type of drug

delivery (Darney 1994). Vadhanam et al. have delivered ellagic acid using this system of delivery in a mammary tumorigenesis model and observed tumor reduction with 130-fold less compound (silastic implants v/s dietary route) (Vadhanam et al. 2011). Although implant delivery system has the potential to deliver for a long duration, it has the risks of mechanical failure of implants that may lead to dose dumping. Another drawback of the system is the likelihood for fibrous growth in the region of the implants, which become difficult to remove after the treatment is over (Aqil et al. 2013). A biodegradable polymeric system can overcome those disadvantages of a nondegradable matrix system. A sustained-release implant containing plant extract has proved to be beneficial. An implant containing the extract of Danshen (*Radix Salvia miltiorrhiza*) using chitosan and gelatin was developed to support anastomosing and healing on muscles and tissues in abdominal cavities. The sustained delivery of the implant was observed for up to 28 days. The repairing of the wounds and tissues were healed better with this implant system and frequent dosing was reduced for the patient (Zhao et al. 2002).

12.2.10 Cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides that contain six to eight dextrose units (α-, β-, and γ-cyclodextrins, respectively) connected through 1–4 bonds. The outer side of CDs is hydrophilic and the inner side is relatively lipophilic, enabling them to interact and entrap molecules forming noncovalent inclusion complexes (Challa et al. 2005). The application of cyclodextrins is also to enhance the drug bioavailability by enhancing the solubility, stability and overcoming the undesirable physiochemical properties of drugs (Le and Rysanek 1987; Szejtli 1982, 1988).

CDs enhance the permeability of hydrophobic drugs by increasing the availability of the drug on the surface of the biological barrier like skin and mucosa, where the drug partitions into the membrane and thus penetrating the lipid layers of these barriers. The optimum CDs should be used to solubilize the drug in the aqueous vehicle increasing the drug availability (Loftsson and Stefansson 1997).

Cyclodextrin scan be used for both oral and intravenous drug delivery and when used as vehicles/carriers for oral delivery they can increase the bioavailability of insoluble drugs by molecular dispersion, shielding it from degradation in different gastro intestinal tract pH, and increasing the availability at the intestinal wall. When it is used as parenteral vehicles, they solubilize the hydrophobic drugs without changing their pharmacokinetic properties (Thompson 1997).

Due to volatile properties, oxidation, photodegradation and/or polymerization, many naturally occurring compounds, like vanillin, cinnamaldehyde, essential oils and flavoring agents such as lemon and orange peel oil, tends to vanish from solid formulations. CDs formulation could overcome those problems up to an adequate level (Vyas et al. 2008).

High hydrophobicity and sensitivity to air, light and oxidative enzymes caused remarkable problem for resveratrol formulation. β-CD and G2 β-CD complexation with resveratrol reduced the oxidation as it is entrapped in the internal cavity of CDs (Lucas-Abellan et al. 2007).

CD complexation can stabilize many famous paramedical foul smelling and volatile products like cinnamon leaf oil and garlic oil (Ayala-Zavala et al. 2008). The glucopyranose rings of β-cyclodextrins are able to form inclusion complexes of small molecular weight with flavor substances. The stable β-cyclodextrin complexes have the advantages of persistent composition, macroscopic and microbiological purity, and reduced sensitivity to external factors (Lindner 2006).

12.2.11 Niosomes

Niosomes are vesicles composed of multiple lamellas and are non-ionic in nature. It consists of non-ionic surfactant and differs from liposomes which have phospholipids. Because of the similarity in structure with a liposome, niosome can be an alternative to liposomal drug carriers.

The properties of the niosomes are influenced by additives, mode of preparation, drug's physicochemical properties, surfactant's amount, structure and type, cholesterol content and resistance to osmotic stress (Rajera et al. 2011). Niosomes can enhance the therapeutic effect of drugs by targeted delivery as they are non-ionic in nature and are less toxic.

They can be prepared by any of the following methods—ether injection, sonication, reverse phase evaporation, extrusion, remote loading, hand shaking, and microfluidization. These vesicles act as a storehouse for the drug and release it in a controlled manner. They improve the stability of the entrapped drug molecule and thus enhance the oral bioavailability of poorly absorbed drugs. They cross the anatomical barrier of GIT via transcytosis of M cells of Peyer's patches in the intestinal lymphatic tissues (Jadon et al. 2009). Such highly contained drug accrual is beneficial in the treatment of diseases like leishmaniasis where parasites attack liver and spleen cells (Sheena et al. 1998; Baillie et al. 1986). Niosomes have been suggested for treatments of various diseases such as cancer and infection (Balasubramaniam et al. 2002), also as immunological adjuvants (Jain et al. 2005), as anti-inflammatory drug carrier (Shahiwala and Misra 2002) and also as a diagnostic imaging agent (Uchegbu and Vyas 1998). Niosomes can be administered through various routes and particular emphasis has been given for transdermal drug delivery systems. The evolution of niosomal drug delivery technology is in its formative years but it has displayed promising potential in cancer chemotherapy and anti-leishmanial therapy.

12.2.12 Transdermal Drug Delivery System (Transdermal Patches)

Delivery of phytochemicals via skin is widely investigated and an increase in interest for drug delivery through transdermal patch has been observed for enhancing permeation and therapeutic efficacy. The major advantages of topical delivery are an evasion of the first-pass metabolism, decrease adverse effects associated with oral and intravenous (IV) doses and improved therapeutic efficacy. Various strategies are used to enhance the transdermal permeation including transdermal patches, ethosomes, transferosomes, and SLNs (Prausnitz and Langer 2008; Benson and Watkinson 2011; Prausnitz et al. 2004). Ethosomes, transferosomes, and SLNs are already discussed in this chapter.

The medication delivery by transdermal patches is done through an adhesive patch which is attached to the patient's skin. The patch is made up of special membrane which can control the rate of drug release. Treatment through such patches is non-invasive and medication delivery is designed to release the active ingredient at a constant rate over a specific period ranging from several hours to days after application to the skin. It involves percolation of the drug from the surface of the skin passing through the layers of dermal tissue and finally into the circulatory system.

Transdermal patches are the novel approach which utilizes permeation enhancers (terpenes, ozones, and surfactants) for topical delivery. Various physical methods are used such as iontophoresis, sonophoresis, microneedles, and skin electroporation for delivery of the drug through a transdermal patch. The main limitation in transdermal patch approach is that it causes skin irritation or skin infection due to the high frequency applied through iontophoresis, which will overcome by the novel vesicular carriers such as transferosomes and ethosomes, which supplies essential nutrients results in maintaining the integrity of the skin.

Some examples of marketed preparations

(a) The virility patch: The RX male virility enhancement patch is an ultra-concentrated formulation infused in discreetly small patch containing a variety of herbs which exist to enhance male vigor. Other nicotine patch and diet patches are similar examples, where these products use advanced physiological technology to feed the formulation into the blood circulation of a patient in a timely manner. The effective mixture of ingredients

is right away absorbed into the skin from the patch. The major advantage of this product is that the formulation can bypass the digestive system and working mechanism of the formulation immediately fasten up and provides effective virility enhancement. This transdermal delivery system is approved by the FDA (Bayarski 2010).

(b) Transdermal slimming patch (Levin Health Care): This product is prepared on a soft patch embedded with formulation entirely made of natural herbs with the transdermal delivery system. It reduces the overburden to the vital organs and works for 24 h. Once applied it helps in the acceleration of the fat burning process, alleviating hunger pangs and provides the feeling of fullness, even when one has not eaten (Anonymous 2010).

12.3 Conclusion

Herbal drugs have the potential to treat all diseases with one or more active constituents present in them and they have been extensively used throughout the world since ancient times. With fewer side effects when compared with modern medicines, it's well-recognized between physicians and patients. Plant actives and extracts are now also been recognized for high therapeutic value in the new dimension of novel drug delivery and targeting. This change has been brought by the rising demand of herbal drugs in the market and also with the growth of awareness among people about the safety of plant origin drugs. NDDS for herbal drugs can bring down the repeatable dose administration to overcome noncompliance and elevate the therapeutic value increasing the bioavailability thus reducing toxicity and so on. This technology being an exploratory stage demands some more research, to resolve issues with production and application. The pharmaceutical companies have started focusing on adopting new drug delivery technology for existing drugs, for various reasons, such as reducing the dosing frequency to meet patient compliance, and these developed products are normally filed a new drug application (NDA) to capture the generic market because the development of investigational new drugs (IND) is slow and developing new drugs for specific diseases takes a long time. Several excellent phytochemicals have been successfully delivered using this technology. In years to come, there is definitely a great potential in the field of novel drug delivery systems for active phytochemicals.

References

Abou ElWafa AA, Mursi NM, El-Shaboury KM. A pharmaceutical study on certain ocular drug delivery systems. MS Thesis. Cairo University, Cairo (2003).

Ainbinder D, Touitou E. Testosterone ethosomes for enhanced transdermal delivery. Drug Deliv. 2005;12:297–303.

Ajazuddin, Saraf S. Applications of novel drug delivery system for herbal formulations. Fitoterapia. 2010;81:680–9.

Al-Farsi A, Ellis PM. Treatment paradigms for patients with metastatic non-small cell lung cancer, squamous lung cancer: first, second, and third-line. Front Oncol. 2014;4:157.

Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. Adv Drug Deliv Rev. 2013;65:36–48.

Anand P, Nair HB, Sung B, Kunnumakkara AB, Yadav VR, Tekmal RR, Aggarwal BB. Design of curcumin-loaded PLGA nanoparticles formulation with enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo. Biochem Pharmacol. 2010;79:330–8.

Anitha A, Maya S, Deepa N, Chennazhia KP, Naira SV, Tamurab H, Jayakumara R. Efficient water soluble O-carboxymethyl chitosan nanocarrier for the delivery of curcumin to cancer cells. Carbohydr Polym. 2011;83:452–61.

Anonymous. Transdermal patch. http://www.levinhealthcare.com. 2010.

Anuradha CA, Aukunuru J. Preparation, characterisation and in vivo evaluation of bis-demethoxy curcumin analogue (BDMCA) nanoparticles. Trop J Pharm Res. 2010;9:51–8.

Aqil F, Munagala R, Jeyabalan J, Vadhanam MV. Bioavailability of phytochemicals and its enhancement by drug delivery systems. Cancer Lett. 2013;334:133–41.

Ayala-Zavala JF, Soto-Valdez H, Gonzalez-Leon A, Alvarez-Parrilla E, Martın-Belloso O, Gonzalez-Aguilar GA. Microencapsulation of cinnamon leaf (cinnamomumzeylanicum) and garlic (Allium sativum) oils in β -cyclodextrin. J Incl Phenom Macrocycl Chem. 2008;60:359–68.

Baillie AJ, Coombs GH, Dolan TF, Laurie J. Non-ionic surfactant vesicles, niosomes, as delivery system for

the anti-leishmanial drug, sodium stibogluconate. J Pharm Pharmacol. 1986;38:502–5.
Balasubramaniam A, Kumar VA, Pillai KS. Formulation and *in-vivo* evaluation of niosome encapsulated daunorubicin hydrochloride. Drug Dev Ind Pharm. 2002;28:1181–93.
Barragan-Montero V, Winum J, Moles J, Juan E, Clavel C, Montero J. Eur J Med Chem. 2005;40:1022–9.
Bayarski Y.. http://www.google.com/Transdermalpatches/NDDS/Herbal drugs.in. 2010.
Bendas ER, Tadros MI. Enhanced transdermal delivery of sulbutamolsulfate via ethosomes. AAPS Pharm Sci Tech. 2007;8:1–7.
Benson HE, Watkinson AC. Topical and transdermal drug delivery: principles and practice. New Jersey: Wiley Online Library; 2011.
Blumenthal M, Goldberg A, Brinkmann J. Herbal medicine. Newton: Integrative Medicine Communications; 2000.
Bombardelli E, Curri SB, Loggia DR, Del NP, Tubaro A, Gariboldi P. Fitoterapia. 1989;60:1–9.
Bonifacio BV, Silva PB, Ramos MA, Negri KMS, Bauab TM, Chorilli M. Nanotechnology-based drug delivery systems and herbal medicines: a review. Int J Nanomedicine. 2014;9:1–5.
Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics—a treatise. 1st ed. New Delhi: Vallabh Prakashan; 1998.. (reprint 2008):61:359–362
Cevc G, Gebauer D, Steiber J, Schatzlein A, Blume G. Ultraflexible vesicles, transfersomes, have an extremely low pore penetration resistance and transport therapeutic amounts of insulin across the intact mammalian skin. Biochem Biophys Acta. 1998;1368:201–15.
Challa R, Ahuja A, Ali J, Khar RK. Cyclodextrins in drug delivery: an updated review. AAPS Pharm Sci Tech. 2005;6:E329–57.
Chan ES, Yim ZH, Phan SH, Mansa RF, Ravindra P. Encapsulation of herbal aqueous extract throughabsorption with ca-alginate hydrogel beads. Food Bioprod Process. 2010a;88(40239):195–201.
Chan JM, Valencia PM, Zhang L, Langer R, Farokhzad OC. Polymeric nanoparticles for drug delivery. Methods Mol Biol. 2010b;624:163–75.
Chao P, Deshmukh M, Kutscher HL, Gao D, Rajan SS, Hu P, Laskin DL, Stein S, Sinko PJ. Pulmonary targeting microparticulate campothecin delivery system: anticancer evaluation in a rat orthotopic lung cancer model. Anticancer Drugs. 2010;21:65–76.
Cheson BD, Arbuck SG. Clinical trials referral resource. Clinical trials with topotecan. Oncology. 1993;7:49–51.
Costa G, Carbone PP, Gold GL, Owens AH Jr, Miller SP, Krant MJ, Bono VH Jr. Clinical trial of vinblastine in multiple myeloma. Cancer Chemother Rep 1. 1963;27:87–9.
Darney PD. Hormonal implants: contraception for a new century. Am J Obstet Gynecol. 1994;170:1536–43.
Das MK, Senapati PC. Furosemide loaded alginate microspheres prepared by ionic cross linking technique: morphology and release characteristics. Indian J Pharm Sci. 2008;70:77–84.
Das RK, Kasoju N, Bora U. Encapsulation of curcumin in alginate-chitosan-pluronic composite nanoparticles for delivery to cancer cells. Nanomedicine. 2010;6:153–60.
El Maghraby GM, Williams AC, Barry BW. Skin delivery of oestradiol from deformable and traditional liposomes: mechanistic studies. J Pharm Pharmacol. 1999;51:1123–34.
El Maghraby GM, Williams AC, Barry BW. Oestradiol skin delivery from ultradeformable liposomes: refinement of surfactant concentration. Int J Pharm. 2000;196:63–74.
Eldhose MP, Mathew F, Mathew NJ. Transfersomes – A Review. Int J Pharma Pharma Res. 2016;6:436–52.
El-Samaligy MS, Afifi NN, Mahmoud EA. Int J Pharm. 2006;319:121–9.
Frei E, Franzino A, Shnider BI, Costa G, Colsky J, Brindley CO, Hosley JF, Gold GL, Jonsson U. Clinical studies of vinblastine. Cancer Chemother Rep 1. 1961;12:125–9.
Freiberg S, Zhu XX. Polymer microspheres for controlled drug release. Int J Pharm. 2004;282:1–18.
Fry DW, White JC, Goldman ID. Rapid secretion of low molecular weight solutes from liposomes without dilution. Anal Biochem. 1978;90:809–15.
Fu RQ, He FC, Meng DS, Chen L. Taxol PLA nanoparticles. ACTA Academiae Medicinae Militaris Tertiae. 2006;28:1573–4.
Gera M, Sharma N, Ghosh M, Huynh DL, Lee SJ, Min T, Kwon T, Jeong DK. Nanoformulations of curcumin: an emerging paradigm for improved remedial application. Oncotarget. 2017;8:66680–98.
Goyal A, Kumar S, Nagpal M, Singh I, Arora S. Potential of novel drug delivery system for herbal drugs. Ind J Pharm Edu Res. 2011;45:3.
Jadon PS, Gajbhiye V, Jadon RS, Gajbhiye KR, Ganesh N. Enhanced oral bioavailability of griseofulvin via niosomes. AAPS Pharm Sci Tech. 2009;10:1186–92.
Jain NK. Liposomes as drug carriers, controlled and novel drug delivery. 1st ed: CBS Publisher; 2005. p. 321–6.
Jain S, Singh P, Mishra V, Vyas SP. Mannosylated niosomes as adjuvant carrier system for oral genetic immunization against Hepatitis B. Immunol Lett. 2005;101:41–9.
James JS. DOXIL approved for KS. AIDS Treat News. 1995;236:6.
Kanan K, Karar PK, Manavalan R. Formulation and evaluation of sustained release microspheres ofacetazolamide by solvent evaporation technique. J Pharm Sci Res. 2009;1:36–9.
Kataoka K, Harada A, Nagasaki Y. Block copolymer micelles for drug delivery: design, characterization and biological significance. Adv Drug Deliv Rev. 2001;47:113–31.
Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. Altern Med Rev. 2009;14:226–46.

Kidd P, Head K. A review of the bioavailability and clinical efficacy of milk thistle phytosome: a silybin-phosphatidylchoiine complex (Siliphos'). Altern Med Rev. 2005;10(3):193–203.

Koli JR, Lin S. Development of anti oxidantethosomes for topical delivery utilizing the synergistic properties of Vit A palmitate, Vit E and Vit C. AAPS Pharm Sci Tec. 2009;11:1–8.

Kshirsagar AC, Yenge VB, Sarkar A, Singhal RS. Efficacy of pullulan in emulsification of turmeric oleoresin and its subsequent microencapsulation. Food Chem. 2009;113:1139–45.

Kumar VS, Kesari A. Herbosome—a novel carrier for herbal delivery. Int J Curr Pharm Res. 2011;3:36–41.

Kumar K, Rai AK. Development and evaluation of floating microspheres of curcumin. Trop J Pharm Res. 2012;11:713–9.

Kumar R, Kumar MS, Mahadevan N. Multipleemulsions: a review. Int J Adv Pharm Res. 2012;2:9–19.

Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles based drug delivery systems. Colloids Surf B Biointerfaces. 2010;75:1–18.

Kwon GS. Block copolymer micelles as drug delivery systems. Adv Drug Deliv Rev. 2002;54:167.

Kwon GS, Okano T. Polymeric micelles as new drug carriers. Adv Drug Deliv Rev. 1996;21:107–16.

Lachman L, Lieberman HA, Kanig JL. The Theory and practice of Industrial Pharmacy. 3rd ed. Philadelphia: Lea & Febiger; 1996. p. 510–1.

Lasic DD. Liposomes: from physics to applications. Amsterdam/London, New York, Tokyo: Elsevier; 1993.

Le BG, Rysanek N. Cyclodextrins and their industrial uses. Duchene D Ed.; Editions de Santé. 1987.p.107–30.

Legha SS, Tenney DM, Krakoff IR. Phase I study of taxol using a 5-day intermittent schedule. J Clin Oncol. 1986;4:762–6.

Leo E, Scatturin A, Vighi E, Dalpiaz A. Polymeric nanoparticles as drug controlled release systems: anew formulation strategy for drugs with small or largemolecular weight. J Nanosci Nanotechnol. 2006;6:3070–9.

Li HR, Li SF, Dua HQ. Preparation of liposomes containing extracts of Tripterygium wilfordii and evaluation of its stability. Zhongguo Zhong Yao Za Zhi. 2007;32:2128–31.

Lieberman HA, Rieger MM, Banker GS. Pharmaceutical dosage forms: disperse systems. 2nd ed. New York: Marcel Dekker Inc.; 1998. p. 339–44.

Lin J, Sahakian DC, de Morais SM, Xu JJ, Polzer RJ, Winter SM. The role of absorption, distribution, metabolism, excretion and toxicity in drug discovery. Curr Top Med Chem. 2003;3:1125–54.

Lindner K. Using cyclodextrin aroma complexes in the catering. Food Nahrung. 2006;26:675–80.

Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods. 2000;44:235–49.

Lodzki M, Godin B, Rakou L, Mechoulam R, Gallily R, Touitou E. Cannabidiol-transdermal delivery and anti-inflammatory effect in a murine model. J Control Release. 2003;93(3):377–87.

Loftsson T, Stefansson E. Effect of cyclodextrins on topical drug delivery tothe eye. Drug Dev Ind Pharm. 1997;23:473–81.

Lu Y, Hou SX, Chen T, Sun YY, Yang BX, Yuan ZY. Preparation of transferosomes of vicristine sulfate and study on its precutaneous penetration. Zhongguo Zhong Yao Za Zhi. 2005;30:900–3.

Lucas-Abellan C, Fortea I, Lopez-Nicolas JM, Nunez-Delicado E. Cyclodextrins as resveratrol carrier system. Food Chem. 2007;104:39–44.

Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79:727–47.

Marczylo TH, Verschoyle RD, Cooke DN, Morazzoni P, Steward WP, Gescher AJ. Comparison of systemic availability of curcumin with that of curcumin formulated with phosphatidylcholine. Cancer Chemother Pharmacol. 2007;60:171–7.

Mastropaolo D, Camerman A, Luo Y, Brayer GD, Camerman N. Crystal and molecular structure of paclitaxel (taxol). Proc Natl Acad Sci U S A. 1995;92:6920–4.

Mathew A, Fukuda T, Nagaoka Y, Hasumura T, Morimoto H, Yoshida Y, Maekawa T, Venugopal K, Kumar DS. Curcumin Loaded-PLGA nanoparticles conjugated withTet-1 peptide for potential use in Alzheimer's disease. PLoS One. 2012;7(3):e32616.

Mauri P, Simonetti P, Gardana C. Liquid chromatography/atmospheric pressure chemical ionization mass spectrometry of terpene lactones in plasma of volunteers dosed with Ginkgo biloba L. extracts. Rapid Commun Mass Spectrom. 2001;15:929–34.

Mei Z, Chen H, Weng T, Yang Y, Yang X. Solid lipid nanoparticle and microemulsion for topical delivery of triptolide. Eur J Pharm Biopharm. 2003;56:189–96.

Merdan VM, Alhaique F, Touitou E. Vesicular carriers for topical delivery. Acta Techno Legis Medicament. 1998;12:1–6.

Mishra D, Mishra PK, Dubey V, Nahar M, Jain NK. Systemic and mucosal immune response induced by transcutaneous immunization using Hepatitis B surface antigen-loaded modified liposomes. J Control Release. 2007;33:424–33.

Muir AH, Robb R, McLaren M, Daly F, Belch JJ. The use of *Ginkgo biloba* in Raynaud's disease: a double-blind placebo-controlled trial. J Vasc Med. 2002;7:265–7.

Mujaffar F, Singh UK, Chauhan L. Review of microemulsion as futuristic drug delivery. Int J Pharm Sci. 2013;5:39–51.

Musthaba SM, Baboota S, Ahmed S, Ahuja A, Ali J. Status of novel drug delivery technology for phytotherapeutics. Expert Opin Drug Deliv. 2009;6:625–37.

Nazzal S, Smalyukh II, Lavrentovich OD, Khan MA. Preparation and in vitro characterization of a eutectic based semisolid self nanoemulsified drug delivery system of ubiquinone: mechanism and progress of emulsion formation. Int J Pharm. 2002;235:247–65.

Orlikova B, Diederich M. Power from the garden: plant compounds as inhibitors of the hallmarks of cancer. Curr Med Chem. 2012;19:2061–87.

Overby A, Zhao CM, Chen D. Plant phytochemicals: potential anticancer agents against gastric cancer. Curr Opin Pharmacol. 2014;19C:6–10.

Pandey S, Goyani M, Devmurari V, Fakir J. Transferosomes: a Novel approach for transdermal drug delivery. Pharm Lett. 2009;1:143–50.

Paolino D, Lucania G, Mardente D, Alhaique F, Fresta M. Ethosomes for skin delivery of ammonium glycyrrhizinate: in vitro percutaneous permeation through human skin and in vivo anti-inflammatory activity on human volunteers. J Control Release. 2005;106:99–110.

Patel R, Singh SK, Singh S, Sheth NR, Gendle R. Development and characterization of curcumin loaded transferosomes for transdermal delivery. J Pharm Sci. 2009;1:71–80.

Pawar P, Kalamkar R, Jain A, Aberkar S. Ethosomes: a novel tool for herbal drug delivery. IJPPR Human. 2015;3:191–202.

Pimple S, Manjappa AS, Ukawala M, Murthy RS. PLGA nanoparticles loaded with etoposide and quercetin dihydrate individually: in vitro cell line study to ensure advantage of combination therapy. Cancer Nanotechnol. 2012;3:25–36.

Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26:1261–8.

Prausnitz MR, Langer R, Mitragotri S. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov. 2004;3:115–24.

Priprem A, Watanatorn J, Sutthiparinyanont S, Phachonpai W, Muchimapura S. Anxiety and cognitive effects of Quercetin liposomes in rats. Nanomedicine. 2008;4:70–8.

Rajera R, Nagpal K, Singh SK, Mishra DN. Niosomes: a controlled and novel drug delivery system. Biol Pharm Bull. 2011;34:945–53.

Rao JP, Geckeler KE. Polymer nanoparticles: preparation techniques and size-control parameters. Prog Polym Sci. 2011;36:887–913.

Riondel J, Jacrot M, Picot F, Beriel H, Mouriquand C, Potier P. Therapeutic response to taxol of six human tumors xenografted into nude mice. Cancer Chemother Pharmacol. 1986;17:137–42.

Rossi R, Basilico F, Rossoni G, Riva A, Morazzoni P, Mauri PL. J Pharm Biomed Anal. 2009;50:224–7.

Russo GL. Ins and outs of dietary phytochemicals in cancer chemoprevention. Biochem Pharmacol. 2007;74:533–44.

Saltzman WM, Fung LK. Polymeric implants for cancer chemotherapy. Adv Drug Deliv Rev. 1997;26:209–30.

Saraf S, Kaur CD. Phytoconstituents as photoprotective novel cosmetic formulations. Pharmacogn Rev. 2010;4:1–11.

Shahiwala A, Misra A. Studies in topical application of niosomally entrapped Nimesulide. J Pharm Pharm Sci. 2002;5:220–5.

Shaikh J, Ankola DD, Beniwal V, Singh D, Kumar MN. Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer. Eur J Pharm Sci. 2009;37:223–30.

Sheena IP, Singh UV, Kamath R, Uma Devi P, Udupa N. Niosomal with a ferin A, with better tumor efficiency. Indian J Pharm Sci. 1998;60:45–8.

Simon YL, Jackson J, Miyake H, Burt H, Gleave ME. Polymeric micellar paclitaxel phosphorylates Bcl-2 and induces apoptotic regression of androgen-independent LNCaP prostate tumors. Prostate. 2000;44:156–63.

Singh D. Application of novel drug delivery system in enhancing the therapeutic potential of phytoconstituents. Asian J Pharm. 2015;9(4):S1–S12.

Singh HP, Utreja P, Tiwari AK, Jain S. Elastic liposomal formulation for sustained delivery of colchicine: in vitro characterization and in vivo evaluation of anti-gout activity. AAPS J. 2009;11:54–64.

Szejtli J. Cyclodextrins and their inclusion complexes. Budapest: AkadémiaiKiadó; 1982. p. 296.

Szejtli J. Cyclodextrin technology. Dordrecht: Kluwer Academic; 1988. p. 450.

Teng Y, Morrison ME, Munk P, Webber SE, Prochazka K. Release kinetics studies of aromatic molecules into water from block polymer micelles. Macromolecules. 1998;31:3578–87.

Thamake SI, Raut SL, Ranjan AP, Gryczynski Z, Vishwanatha JK. Surface functionalization of PLGA nanoparticles by non-covalent insertion of a homobifunctional spacer for active targeting in cancer therapy. Nanotechnology. 2011;22(3):035101.

Thompson DO. Cyclodextrins—enabling excipients: their present and future use in pharmaceuticals. Crit Rev Ther Drug. 1997;14:1–104.

Touitou E, Alkabes M, Dayan N, Eliaz M. Ethosomes: the novel vesicular carriers for enhanced skin delivery. Pharm Res. 1997;14:305–6.

Uchegbu IF, Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm. 1998;33:172–6.

Vadhanam MV, Ravoori S, Aqil F, Gupta RC. Chemoprevention of mammary carcinogenesis by sustained systemic delivery of ellagic acid. Eur J Cancer Prev. 2011;20:484–91.

Varde NK, Pack DW. Microspheres for controlled release drug delivery. Expert Opin Biol Ther. 2004;4:35–51.

Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: an overview. J Adv Pharm Technol Res. 2010;1:274–82.

Vyas A, Saraf S, Saraf S. Cyclodextrin based novel drug delivery system. J Incl Phenom Macrocycl Chem. 2008;62:23–42.

Wall JG, Burris HA, Von Hoff DD, Rodriguez G, Kneuper-Hall R, Shaffer D, et al. A phase I clinical and pharmacokinetic study of the topoisomerase I inhibitor topotecan (SK&F 104864) given as an intravenous bolus every 21 days. Anticancer Drugs. 1992;3:337–45.

Wang X, Jiang Y, Wang YW, et al. Enhancing anti-inflammation activity of curcumin through O/W nanoemulsions. Food Chem. 2008;108:419–24.

Weiss R, Fintelmann V. Herbal medicine. 2nd ed. Stuttgart, New York: Thieme; 2000.

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;88:1102–7.

Wiernik PH, Schwartz EL, Strauman JJ, Dutcher JP, Lipton RB, Paietta E. Phase I clinical and pharmacokinetic study of taxol. Cancer Res. 1987;47:2486–93.

Xiao L, Zhang YH, Xu JC, Jin XH. Preparation of floating rutin-alginate-chitosan microcapsule. Chin Trad Herb Drugs. 2008;2:209–12.

Xiao-Ying L, Luo JB, Yan ZH, Rong HS, Huang WM. Preparation and in vitro-in vivo evaluations of topically applied capsaicin transferosomes. Yao Xue Xue Bao. 2006;41:461–6.

Yallapu MM, Gupta BK, Jaggi M, Chauhan SC. Fabrication of curcumin encapsulated PLGA nanoparticles for improved therapeutic effects in metastatic cancer cells. J Colloid Interface Sci. 2010;351:19–29.

You J, Cui FD, Han X, Wang YS, Yang L, Yu YW, Li OP. Study of the preparation of sustained releasemicrospheres containing zedoary turmeric oil by the emulsion solvent diffusion method and evaluation of theself emulsification and bioavailability of the oil. Colloids Surf B Biointerfaces. 2006;48:35–41.

Zhang J, Jasti B, Li X. Formulation and characterization of silibinin-loaded sterically stabilized solid lipid nanoparticles. Drug Deliv. 2007;15:381–7.

Zhao HR, Wang K, Zhao Y, Pan LQ. Novel sustained release implant of herbal extract using chitosan. Biomaterials. 2002;23:4459–62.