ABSTRACT

A novel drug delivery system has been emerging by combining herbal medicine with nanotechnology to administer drugs encompassing the enhancement of compatibility and efficacy. The herbal phytoconstituents are compatible compared to the chemical active pharmaceutical ingredients (APIs). But the therapeutic consequence of the phytoconstituent is limited due to poor aqueous solubility. Therefore, the demand to develop a system which improves the solubility of the phytopharmaceuticals mounting rapidly. Nanotechnology plays a vital role in increasing the solubility, enhancing the bioavailability, and improving the drug specificity of bioactive constituents. Nanosystems such as ethosomes, nanoparticles, phytosomes, liposomes, and solid lipid nanoparticles are used to deliver bioactive constituents at an adequate dose to the site of action.

INTRODUCTION

Plants have long been recognized for their therapeutic properties. For centuries, aboriginal cultures around the world have used traditional herbal medicines to treat a myriad of diseases [1]. The demand for herbal medicines has surged recently due to the ability to treat diseases with negligible or lesser side effects [2]. There has been a chief concern using modern medicines in treating diseases like cancer using chemotherapy, hormone-blocking therapy, monoclonal antibodies, and their kinds. They create the aftermaths and adverse effects in addition to the therapeutic complications and cost. Ethnopharmacological medicines are an ideal alternate to these concerns.

Some major water-insoluble phytoconstituents like flavonoids and tannins suffer from confines like poor water solubility, lipophilicity, and inappropriate molecular size consequential in poor absorption and bioavailability [3]. But the technique by which a drug is transported can have a substantial consequence on its efficacy [4]. Hence, the research across the globe has begun to ponder on formulating the delivery system without having to change the nature of the phytoconstituents of the herbs.

Various drug delivery systems and drug targeting approaches are now under progress to curtail drug deprivation, prevent destructive side-effects and increase drug bioavailability [5, 6]. Some of the novel drug delivery approaches are effectual in improving the dissolution properties of poorly water-soluble drugs in accomplishing controlled drug delivery systems which delivers the drug at a rate dictated by the need of the body over a period of treatment at the site of action. Carrier-mediated drug delivery systems can be applied for herbal drugs to safe, effective and time-tested products [7]. The carriers can be made gradually degradable, prompt reactive and even targeted. Different types of nanomaterials are used as nanocarriers which permit hydrophobic and hydrophilic drugs to deliver throughout the body which can be either dissolved, entrapped or encapsulated to the polymer matrix to intensify the solubility, sustained release effects, can be protected from degradation and can even be targeted to the site of action [8, 9]. Therefore, various types of nanocarriers can be made up of natural and synthetic polymers, polysaccharides and lipids such as polymeric nanoparticles, solid lipid nanoparticles, liposomes and phytosomes for better therapeutic responses by integrating with traditional medicine system (fig. 1). These types of novel drug delivery systems enhance the solubility, bioavailability, stability, pharmacological activity of the drug molecule and also protect it from physical and chemical degradation.

Search criteria

The sources and range of years used to write this review articles are Pubmed, Google scholar, Science direct and 2014–2018 respectively.

Drug delivery systems are based on interdisciplinary approach, that slowly delivers drug at a controlled rate. They amend drug release profile, absorption, distribution and elimination thereby improving the product efficacy as well as the pharmacokinetic and pharmacodynamic characteristics of various drug molecules to potentially overcome the limitations of conventional therapeutics [10].

Nanoparticles

Nanoparticles are colloidal systems whose particle size ranges from 10 to 100 nm [11]. It has numerous advantages which includes enhanced solubility and bioavailability, size reduction and better absorption of herbal medicine [12].
tissues. They are also capable of releasing biologically active constituents to the site of action at a therapeutically optimal rate in a dose-dependent manner [13]. There are different biological and non-biological methods of nanoparticle synthesis which is economical, eco-friendly and also cost-effective [14-16].

Raksha et al. formulated paclitaxel loaded nanoparticulate system which appears to be capable in carrying as well as targeted delivery of paclitaxel with enhanced therapeutic efficacy and safety thereby minimizing the adverse effects [17]. Khair et al. developed novel chitosan-modified polymeric nanoparticles by double emulsion solvent evaporation technique which proficiently encapsulated anticancer drugs, and sustained the release, enhanced oral bioavailability, and improved tumour cellular uptake of the drugs [18]. Patricia et al. developed three different lignin nanoparticles which show better stability, biocompatibility, uniform dispersity, ability to load poorly soluble drugs, good cellular interaction and sustained drug release for disease diagnosis and therapy [19]. Jignas et al. reported a novel method to synthesise methionine mediated super paramagnetic Cobalt ferrite nanoparticle linked with gold quantum dots which has promising application in targeted drug delivery [20]. Chen et al. inspected a pH-sensitive drug release system for targeting CD44 receptor using doxorubicin conjugated mesoporous silica nanoparticles which exhibited improved drug effectiveness and better stability at functional pH for novel preparation of drug delivery systems [21]. Villaret et al. Silver nanoparticles act as a potential antibacterial agent for treating human infectious disease i.e specifically influenza virus infection. It enhanced chemokine (C-C motif) 5 and interferon beta cytokines that might have practical implication in clinical application [22].

**Liposomes**

Liposomes are lipid bilayers of 50-1000 nm in diameter that act as convenient vehicles to deliver biologically active agents [23]. They are usually made up of phospholipids which can incorporate both hydrophilic and lipophilic molecules [24, 25]. They improve drug solubility, bioavailability and stability. They can even combine with site-specific ligands to attain active targeting. They also enhance the therapeutic activity and safety of drugs chiefly by delivering them at the site of action and by sustaining the therapeutic levels of drug for a prolonged period of time [26, 27].

Hadis et al. reported that the liposomes are one of the most advanced and reliable techniques for the progress of useful bioproducets particularly in medical diagnostics [28]. Maussang et al. formulated PEyolated liposomes conjugate with glutathione for safely deliver the encapsulated drugs to the brain which serve as promising drug delivery technology for the treatment of CNS disorders [29]. Xiao et al. developed sorafenib and gudelumina co-loaded liposomes to improve the sparingly water soluble sorafenib and to screen its distribution and the early response on its in vivo treatment in a precise manner and found that this could be a promising nano-carrier for the MRI-guided in vivo visualization of the delivery and Hepatocellular carcinoma treatment [30]. Sharma et al. proposed an advanced approach to target C-type lectin receptor through nanoliposome by mannane surface modification for active targeting which is a promising system for effective cancer immunotherapy [31]. Abraham et al. prepared a safe and efficient nanoliposome for the proper delivery of therapeutic mRNA for treating various diseases such as cancer, inflammatory as well as cardiovascular diseases [32]. Ju et al. studied octreotide altered daunorubicin conjugated liposomes loaded with dihydroartemisinin that showed improved cellular uptake and cytotoxicity while evaluated on breast cancer cells and xenografts nude mice models [33]. Tatodeet al. used response surface methodology to formulate paclitaxel-loaded liposomes by thin film hydration method which demonstrates better enhancement of in-vitro drug release [34].

**Nanoemulsions**

Nanoemulsions are also called as oil-in-water emulsions composed of oil droplets and stabilized by surfactants [35, 36]. The average size of the oil droplet in nanoemulsion is between 100 and 500 nm. It is prepared by mixing oil phase with an aqueous phase under high mechanical extrusion process [37, 38]. Both hydrophilic and lipophilic molecules can be efficiently incorporated. This is one of the efficient systems for enhancing drug delivery. Zheng et al. integrated nanoemulsions into hydrogels which shows great potential for therapeutic purposes through topical or systemic administration. They also claimed that the prepared nanoemulsion is more stable and safe [39]. Mou et al. developed nanoemulsion gel-based topical delivery of Amphotericin which is an economic approach for enhanced and sustained permeation of drug against fungal infection [40]. Primo et al. demonstrated magnetic nanoemulsion which enhances the diffusion of the drug when associated with Foscarnet the application of photodynamic therapy [41]. Mahato et al. reported that nanoemulsions serve as the effective drug delivery as a carrier of nucleic acids, drugs as well as imaging agent which has been widely used for disease diagnostics, imaging and therapy [42]. Jasmina et al. prepared nanoemulsions by both higher energy and lower energy emulsion methods and concluded that low energy methods are greatly recognized by the manufacturers as they do not require any expensive equipment [43]. Wu et al. determined the absorption mechanism ofBaiclairin mediated nanoemulsion by in situ preparation method and chylomicron-blocked rat model for effectual oral delivery [44]. Gueitin et al. evaluated erythromycin loaded nanoemulsion by high pressure homogenization method which increases the stability of erythromycin in an acidic condition as it acts as a suitable system for Helicobacter pylori treatment [45].

**Phytosome**

Phytosome is also known as phytolipids delivery system which forms a bridge between the conventional drug delivery system and novel drug delivery system. The polyphenolic phytoconstituents are complexed with phospholipid to produce lipid compatible molecular complexes in the equimolar ratio [46]. They improve the absorption of poorly water-soluble drugs through various routes of administration thereby increasing the bioavailability and therapeutic index when compared to traditional drug delivery systems [47, 48]. They also enhance the capacity of drugs to cross the lipid bilayer thereby reaching the systemic circulation [49].

Chetan et al. reported that phytosome shows improved pharmacokinetic and pharmacodynamic effect than conventional botanical extracts which can be utilized for treating various diseases [50]. The prepared phytosome using sinigrin shows higher efficiency than control to release the compound in a slow and controlled manner into the stratum corneum for wound healing [51]. Abdelkader et al. formulated L-carnosine phytosome by combining hydrogel and lipid-based carrier which shows sustained drug pervasion and inhibits the browning of the lens and protects from cataract formation [52]. Dami et al. focused on encapsulating orange peel and liquorice extracts into phospholipid complex which exhibited as a better topical dosage delivery towards skin that ensured high cutaneous absorption of phytoconstituents in the skin for long period of action in contradiction to skin ageing [53]. Das et al. proposed the synthesized rutin-phytosome complex increases the transdermal absorption rate to treat various diseases such as arthritis, rheumatism, etc. with controlled and sustained drug release [54]. The lyophilized technique was found to be more efficient to deliver disomin when compared to other methods (solvent evaporation, salting out) of phytosomal preparation as it enhances the absorption and permeation of the drugs across the lipid bilayer as described by May et al. [55]. Telange et al. conjugated apigenin, a low aqueous soluble compound with phospholipid which act as an excellent potential to improve the in vivo antioxidative activity, solubility, bioavailability and pharmacological properties compared to free apigenin [56].

**Ethsosomes**

Ethosomessare non-invasive lipid vesicular carrier system in which it composed of phospholipid increased the concentration of alcohol (mostly ethanol) and water [57]. High concentration of alcohol makes this system more unique. They effectively incorporate the delivery of hydrophilic, hydrophobic and amphiphilic molecules to the body [58]. They promote high entrapment efficiency, better stability and controlled release of drugs through transdermal route to the
systemic circulation [59]. They tend to be more superior than liposomes as it delivers drug through the skin in terms of quantity and level of penetration [60].

Sharma et al. developed phospholipid-based carrier systems for the effective delivery of Aceloflacen and found that ethosome prepared by cold method offers high vesicle density and drug loading efficiency as compared with elastic membrane vesicles [61]. Shelke et al. optimized Zolmitriptan loaded ethosomal intranasal gel by three-level factorial design which could aid as an effective therapy for the recurrence of a migraine with controlled release and permeability [62]. Sujatha et al. observed the release of flasteride ethosome was first order kinetics compared with elastic membrane vesicles [61]. Shelke et al. developed ethosomal loaded with Carbopol as hydrogel and evaluated the in vitro permeation studies using rat skin which facilitate effective carrier for the transdermal route of drug administration [64]. Ahmed et al. aimed to optimize the ethosomal formulation made up of glimepiride and integrating them into transdermal films can reduce side effects and prolong the drug release [65]. Shaik et al. explored Aceloflacen loaded ethosome increases the transdermal flux and serve as an effective vehicle for the sustained release of the drug. They also optimized the ethanol and lecithin concentration to improve the skin permeability and concluded that increased ethanol enhances the drug diffusion [66]. Milind et al. developed ethosome for topical delivery of rizatRIPTAN benzolate as site-specific approach and optimized for maximum entrapment efficiency [67].

**Solid lipid nanoparticles**

Solid lipid nanoparticles are spherical lipid particles remains in a solid state at room temperature [68]. Their size ranges from 50-1000 nm and are dispersed in aqueous surfactant solution [69]. Lipids used in the preparation of solid lipid nanoparticles can be stabilized by adding a biocompatible surfactant in the proper ratio [70]. They are generally made up of the hydrophobic core to which a monolayer of phospholipid is coated [71]. They have a tendency to carry both the hydrophilic and hydrophobic drugs for therapeutic purposes.

Kotmak et al. synthesised small solid lipid nanoparticles below 100 nm by modified microemulsion method which exhibits lower toxicity on L929 cells for effective drug delivery [72]. Bhupinder et al. developed Acyclovir Solid Lipid Nanoparticles by high-pressure hot-homogenization technique were found to the average size in nano range. It exhibited better entrapment efficiency and drug loading capacity in drug distribution pattern [68]. Thakkar et al. combined aspirin and curcumin with free sulforaphane entrapped in nano range. It exhibited better entrapment efficiency and drug distribution pattern [68]. Thakkar et al. combined aspirin and curcumin with free sulforaphane entrapped in nano range. It exhibited better entrapment efficiency and drug distribution pattern [68].

**CONCLUSION**

Nanotechnology has been recognized for natural bioactive compounds to safely transport drugs into systemic circulation through various novel drug delivery systems. They have a tendency to exploit various biological compounds which have poor solubility, permeability and bioavailability. Hence, novel drug delivery systems can be used to improve the potency of biological compounds thereby avoiding the first pass effect, dose frequency and side effects at low cost. Thus, the progress of nanotechnology clutches the great potential to improve the therapeutic approach in the development of novel drug delivery system.

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**AUTHORS CONTRIBUTIONS**

All the author has contributed equally

**CONFLICT OF INTERESTS**

Declared none

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