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Novel Drug Delivery System for Anticancer Drug: A Review

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Abstract: Novel drug delivery systems (NDDS) have many benefits, which include improved therapy by increasing the efficacy and duration of drug activity, increased patient compliance through decreased dosing frequency and convenient routes of administration and improved targeting for a specific site to reduce unwanted side effects. The challenge for both drug and drug delivery companies is to deliver both existing and emerging drug technologies in a manner that improves the benefits to the patients. Over the past several years, great advances have been made on development of novel drug delivery systems of anticancer drug (NDDS) .The variety of novel formulations like polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, hydrogels has been reported using bioactive and plant extracts. The novel formulations are reported to have remarkable advantages over conventional formulations of anticancer which include enhancement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. The present review highlights the current status of the development of novel formulations and summarizes their method of preparation, type of active ingredients, size, and entrapment efficiency, route of administration, biological activity and applications of novel formulations.
Key Words: Hydrogel, anticancer, drug delivery, nanoparticles, microspheres, liposomes.

INTERODUCTION:

In the past few decades, considerable attention has been focused on the development of novel drug delivery system (NDDS) for herbal drugs. The novel carriers should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity of herbal drug to the site of action. Conventional dosage forms including prolonged-release dosage forms are unable to meet none of these. In phyto-formulation research, developing nanodosage forms (polymeric nanoparticles and nanocapsules, liposomes, solid lipid nanoparticles, phytosomes and nanoemulsion etc.) have a number of advantages for herbal drugs, including enhancement of solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improving tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation etc [1].

Injectable polymers that have biocompatibility and biodegradability are important biomaterials for drug delivery system (DDS) and tissue engineering.

Multiple synthetic and natural biodegradable polymers have been investigated for these purposes, including polyesters, polyethers, poly amino-acids, polysaccharides, and proteins [2]. These polymers are employed as injectable drug delivery system, and especially as injectable drug delivery system for cancer chemotherapy, and have beeninvestigated actively so as to minimize the toxic side effects and increase the carcinostatic pharmaceutical effects [3].

Methods of local administration of drug delivery system, nanoparticles[4-6], microspheres[7, 8], polymeric micelles[9-11], liposomes[12-15], and hydrogel systems[16, 17] for targeting and controlled release have been investigated with nonand biodegradable polymers. However, the targeting drug delivery system has not been satisfactorily achieved. Accordingly, the injectable in situ forming drug delivery system with hydrogel system, that demonstrates a sol–gel transition in a physiological environment, has many uses[18,19]. For example, water-soluble polymers with stimuli-responsiveness have been widely used as injectable drug delivery system.

Furthermore, in situ gelling formulations derived from biopolymers that mimic the extracellular matrix such as collagen, gelatin, and hyaluronic acid are notable because biopolymers are generally more biocompatible and biodegradable than synthetic polymers. These polymers are generally cross-linked by noncovalent bonds such as ion bonds, electrostatic and hydrophobic interactions, or covalent bonds using cross-linking reagents such as glutaraldehyde and condensing agents such as carbodiimide[20]. For clinical usage, it is important that the in situ gelling formulations combine measurable stability and good biocompatibility. While noncovalent bonds are unstable in the body, cross-linking reagents have high toxicity.

We have recently developed novel tissue adhesives consisting of biomolecules such as collagen, gelatin, and human serum albumin, and organic acid derivatives with active ester groups[21-25]. These tissue adhesives are synthetically superior to commercially available surgical glues such as fibrin glue[26] and biomacromolecule–aldehyde glue[27] with regard to both bonding strength and biocompatibility.

Furthermore, the novel tissue adhesive possesses the potential to be a carrier of injectable in situ forming drug delivery system. An injectable in situ forming DDS using fibrin glue has been already reported, although it was not achieved for the long-term release of drugs[28-30].

DIFFERENT DELIVERY SYSTEM:

LIPOPROTEIN:

The changes in the drug discovery and development process over the last decade have been supplemented by corresponding changes in the area of pharmaceutical research and pharmaceutical biotechnology which resulted in the improvement of the field of drug delivery. For any ideal drug delivery system, a sufficient amount of active drug must be absorbed and transported to the site of action at the right time and appropriate rate of input. Also, it implies selective distribution with minimal uptake other than at the site of action, which is important when there is only a small of margin between effective and toxic concentration. Cancer chemotherapy and DNA based vaccine have been identified as special areas of need for improved drug delivery.

For the last few years, advanced drug delivery systems have been investigated to overcome the limitations of the conventional systems. One of the leading approaches is the utilization of the plasma components as drug delivery systems such as lipoprotein, red blood cells, and albumin. Lipoproteins as drug delivery systems are becoming an attractive area of research and they are considered excellent candidates for targeted delivery of drugs to various tissues.

Lipoprotein as drug delivery system for cancer therapy:

a. Targeted drug delivery system in cancer treatment:

The development of novel drug delivery systems for cancer therapies that selectively deliver anticancer agents to tumor cells with limited toxicity to normal tissues is a challenge for oncology researchers[31]. A targeted drug delivery system offers the potential to enhance the therapeutic index of anticancer agents, either by increasing the drug concentration in tumor cells and/or by decreasing the exposure in normal host tissues. The success of cancer therapy, in many cases, is dependent on the possibility of utilizing biological differences between malignant and normal cells to selectively deliver anticancer agents to tumor cells. To deliver the anticancer agent to tumor tissue selectively, there are two ways: physical and biological targeting strategies[32]. Physical targeting is based on delivering anticancer agents directly to tumor tissue by physical implantation or injections of the agents precisely at the tumor site. The examples include intracerebral delivery of anticancer agents to brain tumor[33], implantation of anticancer agent loaded wafers[34], and intra-arterial drug delivery to liver cancer[35]. Biological targeting can be based on the following tactics. First, an anticancer moiety can be delivered by specific carriers such as liposomes, polymer conjugates[41], bacterial[31] and virus vectors[39]. Second, the development of targeted drug delivery systems to cancer can be based on the difference in substrate uptake between cancer cells and normal cells. Due to the high growth rate of cancerous

cells, they require more nutrient and various receptors, thus, are over expressed, such as folate receptors[36], transferrin receptors[37], growth factor receptors[38], and low-density lipoprotein receptors[42]. Drug delivery systems linked to ligands that target these receptors have been investigated[37,43]. The high requirement for LDL by malignant cells and thus the overexpression of LDL receptors can be utilized for developing a novel targeted drug delivery system. This strategy is attractive and promising. It will be discussed in this section and through various parts of the dissertation.

b. Low density lipoprotein for targeted delivery of anticancers:

Growing cells need cholesterol to construct cell membranes. They acquire cholesterol via *de novo* synthesis and high affinity receptor-mediated uptake of lowdensity lipoprotein (LDL). Many types of tumor cells display higher level of receptor mediated LDL uptakes compared to corresponding normal tissues. The increase in LDL receptor activity in cancer cells is suggested to be due to high cholesterol demand for cell growth and/or a mechanism directly linked to cell transformation[42]. LDL has therefore been proposed as a potential carrier for chemotherapeutic agents.

c. Our approach of targeting boron-containing compounds via the LDL pathway:

LDL is the endogenous carrier of cholesterol. The majority of cholesterol is obtained through the LDL receptor-mediated endocytosis mostly in the form of cholesterol ester. LDL particle is an oil droplet that is covered by a monolayer of phospholipid . The lipid core is made up mostly of triglycerides (20%) and cholesteryl esters (80%). Low-density lipoprotein particles are potential drug carriers, but only lipophilic drug species partition into the core of the system. Since cholesterol (in its ester form) is the native component of LDL, conjugation of an antitumor moiety with cholesterol facilitates the loading of these compounds into LDL. Synthesizing antitumor compounds that mimic native cholesteryl esters may result in successfully transferring these compounds into LDL. As these compounds share similar chemical and physical characteristics with native cholesteryl esters, they can interact well with LDL. They may transfer effectively into LDL in the physiological environment and, thus, utilize the elevated LDL receptor expression on tumor cells for targeted drug delivery.

d. Liposomes:

Liposomes, or phospholipid vesicles, have been recognized as a potential drug delivery vehicle for three decades[44]. Depending on the drug of interest, liposomes can serve as a controlled release carrier or simply as a biocompatible solubilizing vehicle for poorly soluble agents. Because of their size, which typically ranges in mean diameter from 50 to 250 nm for the systemically administered vesicles, liposomes display some unique pharmacokinetic characteristics. These include clearance via the reticuloendothelial system, which results in a relatively long systemic circulation time, and hepatic and splenic distribution. Furthermore, liposomes exhibit preferential extravasation and accumulation at the site of solid tumors due to increased endothelial permeability and reduced lymphatic drainage in these tissues, which has been defined as enhanced permeability and retention effect[45]. Liposomal delivery is therefore a means to modify the pharmacokinetic and pharmacodynamic properties of therapeutic agents. Such modifications can, in some settings, improve the therapeutic efficacy of anticancer drugs and reduce or modulate their toxicity profile. For example, long circulating polyethylene glycol-coated liposomal formulation of doxorubicin has been shown to exhibit increased solid tumor accumulation due to the enhanced permeability and retention effect and decreased dose-limiting cardiac toxicity relative to the free drug[46]. Development of liposomes as a drug carrier has been marked by a number of key innovations. These include the development of remote drug loading methodologies based on pH or ionic gradient[47], polyethylene glycol-coated long circulating liposomes[46], cationic liposomes for nucleic acid delivery[48], pH-sensitive liposomes for cytosolic drug delivery[49], temperaturesensitive liposomes for burst release in response to hyperthermia[50], and targeted liposomes for selective delivery to tumor cells or endothelium[51].

NANOPARTICLE:

There are numerous engineered constructs, assemblies, architectures and particulate systems, whose unifying feature is the nanometer scale size range (from a few to 250 nm). Materials at the nanometer scale often have different physical and biochemical properties from those of the same materials at bulk volume – properties that make nanostructures attractive for diagnostic and therapy applications. Since the size of the nanoparticles is significantly smaller than a cell, they can deliver a large payload of drugs, contrast agents or fluorescent probe onto the surface or interior of the cell, without disrupting its function. These particles are able to deep penetrate tissues, going through the fenestration of the small blood-vessel epithelial tissue. They can enter the systemic blood circulation without forming blood platelet aggregates. Their reduced particle size entails high surface area

and hence a strategy for faster drug release. Drug delivery rates and particle integrity can be modulated and controlled by engineering carriers in such a way that they can be activated by changes in the environmental pH, chemical stimuli by the application of a rapidly oscillating magnetic field, or by application of an external heat source. Among the engineered constructs investigated and developed for this specific target are: polymeric micelles, dendrimers, polymeric and ceramic nanoparticles, protein cage architectures, viral-derived capsid nanoparticles, polyplexes and liposomes. There are several techniques for producing *polymeric nanocarriers,* such as soft lithography, nanoimprinting and injection molding, which are capable of fabricating nanostructures with complicated patterns and other easier processing methods for producing *polymer membranes* with nanopores, nanofibers, nanotubes and multiple nanofilms/ layers[52] .

Natural polymers can also be used to manufacture nanocarriers for drug delivery. Among them the most utilized polymers are gelatin, dextran and chitosan. In general these nanoparticles have high encapsulation efficiency.

Gold nanoparticles represent a novel technology in the field of particle-based tumor-targeted drug delivery. Paciotti *et al.*[53] have reported an application of these carriers for the targeted delivery of tumor necrosis factor-alfa (TNF-·) to solid tumors.

Quantum dots have the potential to dramatically improve clinical diagnostic tests for the early detection of cancer. These engineered semiconductor particles combine cadmium with selenide in a tightly packed atomic structure that emits light in a spectrum of six colours, plus four near-infrared colours, as the dots decrease in size. By finely tuning the size of the dots, thousands of subtle colour variations could be created. These tiny glowing particles, when conjugated with anti-bodies, peptides, proteins, or DNA, form bioconjugated dots that can act as markers on cells and genes, giving scientists the ability to rapidly and differentially mark pathologic tissues.

Dendrimer-*based* drug delivery molecules have several potential advantages: dendrimers are comparable in size to proteins, being small enough (<5.0 nm in diameter) to escape the vasculature and target tumor cells, while also being below the threshold of renal filtration to allow urinary excretion. For instance, acetylated dendrimers have been conjugated to folic acid, methotrexate, tritium, fluorescein and 6- carboxytetramethylrhodamine, in order to allow simultaneous treatment and drug uptake monitoring in tumors[54].

Lipoproteins are another interesting type of vector for lipophilic drugs that can be incorporated into the apolar core without affecting lipoprotein recognition. They could be recognized and taken up *via* specific receptors and mediate cellular uptake of the carried drug. In addition, they are biodegradable. Although only low density lipoproteins have been explored intensively as drug carriers for cancer chemotherapy, new investigations are focused on the use of high density lipoproteins (HDL). Bin Lou *et al.*[55] have shown that a recombinant complex of HDL and aclacinomycin, prepared by co-sonication, is able to deliver a drug to hepatoma cells.

Magnetic-drug targeting can offer a unique opportunity to treat malignant tumors loco-regionally. Alexiou *et al.*[56] have treated squamous cell carcinoma *in vivo* with the injection of magnetic nanoparticles (ferrofluids) bound to mitoxantrone, as a chemotherapeutic agent, that was locally induced to concentrate by means of a magnetic field. The intra-tumoral accumulation of the particles can additionally be visualized by means of MRI.

NANOEMULSION:

Nanoemulsions can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500 nm. The particles can exist as water-in-oil and oil-in water forms, where the core of the particle is either water or oil, respectively. The terms sub-micron emulsion (SME) and mini-emulsion are used synonyms. Usually, SMEs contain 10 to 20 per cent oil stabilized with 0.5 to 2 per cent egg or soybean lecithin 8. The droplets are stabilized by surfactants. They are not formed spontaneously; their properties depend not only on thermodynamic conditions but on preparation methods and the order of addition of the components. On the other hand, nanoemulsions are equilibrium structures distinctly different from emulsions Nano-emulsions may possess high kinetic stability and optical transparency resembling microemulsions. Nanoemulsions can be used as micro reactors of controlled size for the preparation of monodisperse particles.

MICROCAPSULES:

Poor water solubility of many anticancer agents (such as paclitaxel, PCT; camptothecin, CPT; and certain porphyrins like meso tetraphenylporphine, TPP, used in photodynamic therapy, PDT) hinders their application and complicates direct parenteral administration. Various formulation strategies based

on the use of drug carrier systems have been suggested to overcome their poor solubility, low stability, and toxic side effects[57,58]. Among such systems, polymeric micelles have drawn much attention owing to their easily controlled properties and good pharmacological characteristics[59]. Micelles prepared from PEG-diacyllipids conjugates, such as PEGPE, are of particular interest[60]. Here, we describe the preparation, properties, and activity against cancer cells *in vitro* of PCT-, CPT-, and TPPloaded PEG-PE micelles as well as mixed micelles made of PEG-PE and D-α-tocopheryl polyetheyene glycol 1000 succinate (TPGS).

MICROEMULSION:

Microemulsions are liquid dispersions of water and oil that are made homogenous, transparent or translucent and thermodynamically stable by the addition of relatively large amounts of a surfactant and a co-surfactant and having diameter of the droplets in the range of 10 – 100 nm. Microemulsions have been widely studied for drug targeting to the brain and to enhance the bioavailability of the poorly soluble drugs. They offer a cost effective approach in such cases. Microemulsions have very low surface tension and small droplet size which results in high absorption and permeation. Interest in these versatile carriers is increasing and their applications have been diversified to various administration routes in addition to the conventional oral route. This can be attributed to their unique solubilization properties and thermodynamic stability which has drawn attention for their use as carrier for drug targeting to the brain. Intranasal drug delivery is one of the focused delivery options for brain targeting, as the brain and nose compartments are connected to each other via the olfactory route and via peripheral circulation.

Etoposide , an epipodophyllotoxin, is an anticancer drug useful for the treatment of small cell lung cancer and testicular carcinoma. Prior to administration, the drug has to be diluted in the infusion fluid; its low aqueous solubility thus acts as a constraint in the formulation of its parenteral dosage form. This attribute results in drug precipitation in the infusion fluid thereby proving detrimental to the health owing to the possibility of capillary blockade[61]

MICROSPHERES:

Microspheres are an example of a drug delivery system that has been evaluated extensively in cancer chemotherapy. They are essentially solid porous particles (1 - 100 μm diameters) which can both target their drug cargo by physical trapping in blood vessels (chemoembolisation) and sustain the action of a therapeutic agent through controlled release. Microspheres can be made from a broad range of polymeric materials, including proteins, polysaccharides, polyesters and lipids by a variety of different techniques (emulsification, heat stabilisation, coacervation and phase inversion technology). Their diversity identifies the microsphere as a drug delivery system with considerable flexibility. The present review develops the hypothesis that the matrix material and method of preparation are critical determinants in defining pharmaceutical characteristics, which in turn dictate biologic activity. Examples are cited of different approaches adopted with cytotoxic drugs (chiefly doxorubicin, mitomycin C, cisplatin and 5-fluorouracil) to achieve particular drug delivery profiles. However, it is clear that certain cytotoxic drugs are encapsulated in systems with pharmaceutical properties inappropriate for the particular mechanistic class. Also, studies demonstrating selective tumour targeting of cytotoxic drugs after systemic administration are rare. This review also focuses on the contribution that microspheres have made to delivery of immunomodulating cytokines, protein vaccines, antisense oligonucleotides and gene therapy. For these applications, new matrix materials such as bioadhesive polymers and more gentle methods of preparation have had to be developed to preserve the native conformation of these easily denatured biological molecules. Nevertheless, these systems require to be subjected to pharmaceutical characterisation and need further optimisation to overcome persistent instability problems. Microspheres are anticipated to contribute significantly in the future to the systemic, oral and loco-regional treatment of cancer with cytotoxic drugs and biological response modifiers.

DENDRIMERS:

Approaches to delivering unaltered natural products using polymeric carriers are of widespread interest[62,63]. Recently, dendritic polymers have been explored for the encapsulation of hydrophobic compounds and for the delivery of anticancer drugs. Dendrimers are globular, highly branched macromolecules possessing a well-defined core, an interior region, and a large number of end groups. The physical characteristics of dendrimers, including their monodispersity, water solubility, encapsulation ability, and large number of functionalizable peripheral groups, make these macromolecules ideal candidates for evaluation as drug delivery vehicles. Several previous reviews have covered the early work of drug delivery with dendrimers[64,65]. Currently, there are three methods for using dendrimers in drug delivery: (a) the drug is covalently attached to the periphery of the dendrimer to form dendrimer prodrugs, (b) the drug is coordinated to the outer functional groups via ionic

interactions, or (c) the dendrimer acts as a unimolecular micelle byencapsulating a pharmaceutical through the formation of a dendrimer-drug (i.e., host–guest) supramolecular assembly. The latter approach is of interest for multiple reasons and provides an opportunity to encapsulate pharmacologically active compounds and to study the supramolecular assemblies formed in these systems. For example, rose bengal and acetylsalicylic acid have been noncovalently encapsulated within poly (propylene imine) and poly(amidoamine) dendrimers. In the case of rose bengal, the internalized dye molecules were confined within the dendrimer as a consequence of steric congestion at the dendrimer periphery. Pyrene was encapsulated within both poly (propylene imine) dendrimers and unimolecular micelles based on PEGylated Fre´chet-type dendrites. Additionally, fluorescent dyes such as phenol blue and 4-(dicyanomethylene)-2-methyl-6-(4-dimethyl aminostyril)-4H-pyrane have been encapsulated. In a further example, poly (amidoamine) dendrimers have been used to enhance the delivery of ibuprofen to A549 lung epithelial cells.

PHYTOSOMES:

Over the past century, phytochemical and phytopharmacological sciences established the compositions, biological activities and health promoting benefits of numerous plant products. Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, terpenoids, etc.) are poorly absorbed either due to their large molecular size which cannot absorb by passive diffusion, or due to their poor lipid solubility; severely limiting their ability to pass across the lipid-rich biological membranes, resulting poor bioavailability[66]. It has often been observed that the isolation and purification of the constituents of an extract may lead to a partial or total loss of specific bio-activity for the purified constituent — the natural constituent synergy becomes lost. Very often the chemical complexity of the crude or partially purified extract seems to be essential for the bioavailability of the active constituents. Extracts when taken orally some constituents may be destroyed in the gastric environment. As standardized extracts are established, poor bioavailability often limits their clinical utility due to above said reasons. It has been observed that complexation with certain other clinically useful nutrients substantially improves the bioavailability of such extracts and their individual constituents. The nutrients so helpful for enhancing the absorption are the phospholipids. Phytosome is a patented technology developed by a leading manufacturer of drugs and nutraceuticals, to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, called as phytosomes and so vastly improve their absorption and bioavailability[67]. In liposomes no chemical bond is formed; the phosphatidylcholine molecules surround the water soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water soluble compound. In contrast, with the phytosome process the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substance (s) complexed, involving chemical bonds. Phospholipids are complex molecules that are used in all known life forms to make cell membranes. In humans and other higher animals the phospholipids are also employed as natural digestive aids and as carriers for both fat-miscible and water miscible nutrients. They are miscible both in water and in lipid environments, and are well absorbed orally. Phytosomes are more bioavailable as compared to conventional herbal extracts owing to their enhanced capacity to cross the lipoidal biomembrane and finally reaching the systemic circulation.

TABLE-1: PHYTOSOMAL HERBAL FORMULATIONS

Formulations	Active Ingredients	Applications of phytosomal formulations	Biological activity	Method of preparation	Ref.
Ginkgo biloba Phytosomes	Flavonoids	Flavonoids of GBP stabilize the ROS	Cardio-protective, antioxidant activity	Phospholipids complexation	68
Ginkgoselect Phytosome	Flavonoids	Inhibits lipid peroxidation (LPO), stabilize the ROS	Hepatoprotective, antioxidant	Phospholipids complexation	69
ybin Phytosome	Flavonoids	Absorption of silybin phytosome from silybin is approximately seven times greater	Hepatoprotective, antioxidant for liver and skin	Silybinphospho lipid complexation	70
Ginseng Phytosome	Ginsenosides	Increase absorption	Nutraceutical, Immunomodulator	Phospholipids complexation	71
Green tea Phytosome	Epigallocatechin	Increase absorption	Nutraceutical, Systemic antioxidant, anticancer	Phospholipids complexation	71
Grape seed Phytosome	Procyanidins	The blood TRAP n Total Radical-trapping Antioxidant Parameter) were significantly elevated over the control	Systemic antioxidant cardio-protective	Phospholipids complexation	71
Hawthorn Phytosome	Flavonoids	Increase therapeutic efficacy and absorption	Cardio-protective and antihypertensive	Phospholipids Complexation	71
Quercetin Phytosome	Quercetin	Exerted better therapeutic efficacy	Antioxidant, Anticancer	Quercetin–phospholipid complexation	82
Curcumin Phytosomes	Curcumin	Increase antioxidant activity and Increase bioavailability	Antioxidant, Anticancer	Curcumin–phospholipid complexation	73
Naringenin Phytosomes	Naringenin	Prolonged duration of action	Antioxidant Activity	Naringenin–phospholipid complex	74

HYDROGELS:

Hydrogels are three-dimensional, cross-linked networks of water-soluble polymers. Hydrogels can be made from virtually any water-soluble polymer, encompassing a wide range of chemical compositions and bulk physical properties. Furthermore, hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. As a result, hydrogels are commonly used in clinical practice and experimental medicine for a wide range of applications, including tissue engineering and regenerative medicine[75], diagnostics, cellular immobilization, separation of biomolecules or cells, and barrier materials to regulate biological adhesions[76].

Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration. Several terms have been coined for hydrogels, such as 'intelligent gels' or 'smart hydrogels'[77]. The smartness of any material is the key to its ability to receive, transmit or process a stimulus, and respond by producing a useful effect[78]. Once acted on, stimuli can result in changes in phases, shapes, optics, mechanics, electric fields, surface energies, recognition, reaction rates and permeation rates. Hydrogels are 'smart' or 'intelligent' in the sense that they can perceive the prevailing stimuli and respond by exhibiting changes in their physical or chemical behavior, resulting in the release of entrapped drug in a controlled manner.

The unique physical properties of hydrogels have sparked particular interest in their use in drug delivery applications. Their highly porous structure can easily be tuned by controlling the density of cross-links in the gel matrix and the affinity of the hydrogels for the aqueous environment in which they are swollen. Their porosity also permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of the small molecule or macromolecule through the gel network. Indeed, the benefits of hydrogels for drug delivery may be largely pharmacokinetic e specifically that a depot formulation is created from which drugs slowly elute, maintaining a high local concentration of drug in the surrounding tissues over an extended period, although they can also be used for systemic delivery. Hydrogels are also generally highly biocompatible, as reflected in their successful use in the peritoneum and other sites *in-vivo*. Biocompatibility is promoted by the high water content of hydrogels and the physiochemical similarity of hydrogels to the native extracellular matrix, both compositionally (particularly in the case of carbohydrate-based hydrogels) and mechanically. Biodegradability or dissolution may be designed into hydrogels via enzymatic, hydrolytic, or environmental (e.g. pH, temperature, or electric field) pathways; however, degradation is not always desirable depending on the time scale and location of the drug delivery device. Hydrogels are also relatively deformable and can conform to the shape of the surface to which they are applied. In the latter context, the muco- or bioadhesive properties of some hydrogels can be advantageous in immobilizing them at the site of application or in applying them on surfaces that are not horizontal. Despite these many advantageous properties, hydrogels also have several limitations. The low tensile strength of many hydrogels limits their use in load-bearing applications and can result in the premature dissolution or flow away of the hydrogel from a targeted local site.

In situ gel:

Recent advancement in hydrogel engineering has led to the development of *in-situ* hydrogel formation for drug delivery applications. The *in-situ* sol-gel transition enables the surgery or implantation procedure to be performed in a minimally invasive manner. Various physical and/or chemical cross linking mechanisms have been used for *in-situ* network formation. Physical phenomenon involved in the formation of in-situ hydrogels are as follows

1. Hydrogen bonding
2. Hydrophobic – hydrophobic interactions.
3. Electrostatic interactions.

For example, sodium alginate hydrogels are formed physically by cross-linking due to addition of calcium ions but are unstable and disintegrate rapidly and unpredictably distinguishing from preformed hydrogels, in situ forming gels are formulations, applied as a solution, which undergoes gelation after instillation due to physicochemical changes inherent to the biological fluids. In this way, the polymers, which show sol-gel phase transition and thus trigger drug release in response to external stimuli, are the most investigated. In-situ hydrogels are providing such 'sensor' properties and can undergo reversible sol-gel phase transitions upon changes in the condition. These "intelligent" or "smart" polymers play important role in drug delivery since they may dictate not only where a drug is delivered, but also when and with which interval it is release.

CONCLUSION:

For the last few years, advanced drug delivery systems have been investigated to overcome the limitation of the conventional systems. Cancer chemotherapy and DNA-based vaccines have been identified as special areas of need for improved drug delivery. Lipoproteins as drug delivery systems have become an attractive area of research and they are considered excellent candidates as novel drug delivery systems. Herbal drugs have enormous therapeutic potential which should be explored through some value added drug delivery systems. Lipid solubility and molecular size are the major limiting factors for drug molecules to pass the biological membrane to be absorbed systematically following oral or topical administration. Several plant extracts and phytomolecules, despite having excellent bio-activity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility

or improper molecular size or both, resulting poor absorption and poor bioavailability. Standardized plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, xanthones when administered through novel drug delivery system show much better absorption profile which enables them to cross the biological membrane, resulting enhanced bioavailability. Hence more amount of active constituent becomes present at the site of action (liver, brain, heart, kidney, etc.) at similar or less dose as compared to the conventional plant extract or phytomolecule. Hence, the therapeutic action becomes enhanced, more detectable and prolonged. Several excellent phytoconstituents have been successfully delivered using NDDS. Hence there is a great potential in the development of novel drug delivery systems for the plant actives and extracts.

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