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Current Updates on Global Phytoceuticals and Novel Phyto Drug Delivery System in Herbal Medicine

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Abstract

The acceptance of the herbal drugs globally is increased in the modern era, is due to its potent active molecules and also its usage as excipients from natural origin in the pharmaceutical industries is remarkable. Due to complex structure, poor solubility, instability and lacuna in the standardization protocol, there is always a hindrance in the usage of herbal medicine at par with modern drugs. The formulation of phytomedicine in the area of Novel drug delivery system should be focused in basic research and also in the clinical trials, to overcome the solubility and bioavailability challenges in the phytoceuticals. This chapter gives the in-depth perception of phytomolecules, formulated in the domain of novel drug delivery system, especially in nano dosage forms in specific to nano-emulsion, methods of formulation, challenges in formulating nano-emulsion including characterization techniques, colon specific drug carriers and the usage of excipients from natural origin in formulation of modern drugs in the pharmaceutical industries globally.

Keywords: Phytomedicine, Phytoceuticals, Excipients, Colon specific drug delivery Nano phyto dosage forms

1. Introduction

The contribution of natural products to human kind is tremendous in modern drug discovery and its usage is well known before the era of Christ. Lead molecules from plants and microbial origin are significant [1]. In the global pharmaceutical industry, about 34% of the medicines originated from natural molecules. Among the 34%, 6% were natural products, 27.5% were natural products derivatives, thus played important source of lead molecules in manufacturing therapeutic agents in pharmaceutical industries globally [2, 3].

2. Remarkable contribution of Phytomolecules as API in pharmaceutical sector

Based on the survey in the dispensing area of union territory of Puducherry, India, the potent phyto molecules as Active Pharmaceutical Ingredient (API) is being prescribed by modern physicians, are

- Atropine, a tropane alkaloid (*Atropa belladonna* - Solanaceae) is a parasympatholytic drug with anticholinergic properties, prescribed for organophosphorous & carbamate poisoning, in bradycardia and as ophthalmic dosage form, administered for eye examination that produces mydriasis and cycloplegia. The formulations available are Atropine ointment USP & IP, Atropine eyedrops BP, Atropine sulphate tablets USP, Atropine dermal plasters, Atropine sulphate intravenous, intramuscular and subcutaneous injections.
- Pilocarpine, an imidazole alkaloid (*Pilocarpus jaborandi* - Rutaceae) is a cholinergic agonist used in the treatment of glaucoma. Pilocarpine hydrochloride tablets USP and pilocarpine ophthalmic solution USP available pharmaceutically.
- Morphine, a phenanthrene alkaloid (*Papaver somniferum* - Papaveraceae) is a narcotic analgesic used in the management of acute and chronic pain, in relief of dyspnoea of left ventricular failure and in pulmonary oedema. Morphine sulphate extended release tablets, morphine sulphate intramuscular injection available pharmaceutically.
- Codeine, a phenanthrene alkaloid (*Papaver somniferum* - Papaveraceae) is an antitussive agent– acts through brain and suppress the cough reflex. Codeine phosphates syrups and tablets are available.
- Digoxin, a cardiac glycoside (*Digitalis lanata* – Scrophulariaceae), is a cardenolide in the name of Lanoxin, used in the treatment of atrial fibrillation, atrial flutter & atrial tachycardia. Digoxin tablets USP, digoxin intramuscular injection, digoxin elixir for pediatric use is available.
- Vincristine sulphate, an indole alkaloid, (*Catharanthus roseus* - Apocynaceae), is an anticancer drug, used in the treatment of acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin's disease, neuroblastoma and small cell lung cancer and Vinblastine sulphate, an indole alkaloid, (*Catharanthus roseus* - Apocynaceae) used in the treatment of Hodgkin's lymphoma, non-small cell lung cancer, bladder cancer, brain tumor, melanoma, and testicular cancer. Vincristine & Vinblastine sulphate intramuscular and intravenous injections are available.
- Taxol, a diterpene alkaloid (*Taxus brevifolia* - Taxaceae) renamed to paclitaxel, is being used in the treatment of cancers for metastatic breast cancer, advanced ovarian cancer, non-small cell lung cancer and Kaposi's sarcoma, available as Paclitaxol injection IP.
- Caffeine, a purine alkaloid (*Coffea Arabica* - Rubiaceae) is an API finds important drug combinations with antihistamic drugs to counteract the sedative effect available as tablet in pharmaceutical market.
- Ergometrine, an indole alkaloid (*Claviceps purpurea* - Clavicipitaceae) used for uterus contraction in labour and in postpartum hemorrhage. Ergometrine maleate injections are available.
- Capsaicin, a pungent principle (*Capsicum annum* - Solanaceae) is used as counter irritant to relieve joint pain, stiffness and swelling caused by osteoarthritis of the knees. Pharmaceutically available as an ointment.
- β – Carotene, a tetraterpene (*Daucus carota* – Apiaceae) hydrolyses into two molecules of vitamin-A upon the action of the enzyme cholesterol ester

hydrolase and pancreatic lipase in duodenum thus serve as a precursor of vitamin –A. β – Carotene is available as a tablet pharmaceutically.

- Antibiotics - Penicillin from *Penicillium notatum* - Trichocomaceae, Streptomycin, macrolide antibiotics/aminoglycoside from *Streptomyces griseus* - Streptomycetaceae, Tetracyclins – broad spectrum antibiotics from *Streptomyces aureofaciens*, *S. rimosus* – Streptomycetaceae are active against communicable diseases.
- The important milestone of natural molecules in the time travel of drug discovery and also in global pharmaceutical market is, they act as precursors for some of the semisynthetic molecules [4–6].
- Chloroquine, semisynthetic derivative of quinine (*Cinchona species* – Rubiaceae, quinoline alkaloid) antimalarial drug active against *Plasmodium falciparum*.
- Diosgenin, a steroidal saponin (*Dioscorea deltoidea* - Dioscoreaceae) is used for the commercial synthesis of cortisone, pregnenolone, progesterone and other steroid products.

Table 1 gives the remarkable contribution of pharmaceutical phyto API, is being prescribed in modern medicine along with formulation.

3. Contribution of Phytomolecules as excipients in pharmaceutical industry

Excipients in formulating different dosage forms are pharmacologically inert thereby promotes the therapeutic activity of API. Bioavailability, safety, efficacy and stability of the dosage forms is depend on the nature of excipients. Excipients are classified as diluents, binders, surfactants, preservatives, sweeteners etc. [7]. The usage of herbal excipients as phytomolecules is veiled due to the popularity of synthetic molecules in the domain of pharmacy.

3.1 Advantage of phytomolecules as herbal excipients

- Natural excipients are biodegradable in nature
- As ecofriendly in the aspect of pharmaceutical effluents
- Most of the herbal excipients are carbohydrate in nature and hence they are non-toxic in nature
- Cost of the excipients are cheaper when compared to synthetic molecules
- Natural excipients are easily available from different natural sources.

Though natural excipients are advantageous, in some aspects they do possess some limitations, in the source of raw materials as herbal excipients. Possibility of attack of microbial contamination in contact with external environment, availability as raw material is varied depending upon climatic conditions and geographical origin, more importantly heavy metal contaminations. These are the challenges faced in herbal excipients as a source of raw materials in pharmaceutical industries.

S.No.	Name of pharmaceutical phyto API	Biological source & family	Formulation available in global market
1.	Atropine sulphate (Tropane Alkaloid)	<i>Atropa belladonna</i> -Solanaceae	Ointment USP Dermal Plaster
2.	Pilocarpine (Imidazole alkaloid)	<i>Pilocarpus jaborandi</i> -Rutaceae	Ophthalmic solution
3.	Morphine (Phenanthrene alkaloid)	<i>Papaver somniferum</i> -Papaveraceae	Extended release tablets

S.No.	Name of pharmaceutical phyto API	Biological source & family	Formulation available in global market
4	Codeine (Phenanthrene alkaloid)	<i>Papaver somniferum</i> -Papaveraceae	Syrup Tablets
5	Digoxin (Lanoxin - Cardiac glycoside)	<i>Digitalis lanata</i> –Scrophulariaceae	Lanoxin Pediatric Elixir
6.	Vincristine sulphate (Dimeric indole alkaloid)	<i>Catharanthus roseus</i> - Apocynaceae	Vincristine sulphate injection USP

S.No.	Name of pharmaceutical phyto API	Biological source & family	Formulation available in global market
7.	Vinblastine sulphate (Dimeric indole alkaloid)	<i>Catharanthus roseus</i> - Apocynaceae	Vinblastine sulphate injection USP
8.	Taxol (Diterpene alkaloid)	<i>Taxus brevifolia</i> - Taxaceae	Paclitaxel Injection IP
9.	Ergometrine (Indole alkaloid/amino alkaloid-Lysergic acid derivative)	<i>Claviceps purpurea</i> -Clavicipitaceae	Ergometrine maleate injection

Table 1.
Pharmaceutical phyto API in modern medicine.

The requirement of human community is the source of the drug should always from natural resources instead of synthetic origin not only the API but also the excipients.

4. Herbal excipients in pharmaceutical dosage forms

4.1 Acacia

Acacia Arabica – Leguminosae

Acacia tears

Acacia is the dried gummy exudation obtained from the stem and branches of wild *Acacia arabica*, *Acacia Senegal* (Leguminosae). It occurs as rounded or ovoid, colorless (the best grade) or amber tears, or as a white powder. The gummy exudation principally consist of arabin, is a complex mixture of calcium, magnesium and potassium salts of arabic acid. Arabic acid on hydrolysis gives L-arabinose, L-rhamnose, D-galactose and D-glucuronic acid. It also contains an enzyme oxidase and peroxidase [8].

Therapeutic indication: It is used as a demulcent, as a good protective colloid.

As an excipient: *Acacia* is compatible with hydrocolloids of other plants as well as starches and carbohydrates. *Acacia* is the suspending agent due to colloidal property and it is useful in the mixtures containing resinous tincture. It is used in the formulation of Lozenges, Pastilles and compressed tablets. It is a emulsifying agent for fixed oils, volatile oils and liquid paraffin. *Acacia* is the best emulsifying agent for the extemporaneous preparation of oral emulsions. Preparation of good quality, appearance and adequate stability, can be made with only a mortar and pestle. This is because the concentrated emulsion produced in the initial stage of preparation is very viscous and sticky and therefore, the oil cannot escape the vigorous sharing action of the pestle and is easily reduced to fine globules.

Because of the low viscosity of acacia emulsions, creaming occurs rather quickly and thickening agents tragacanth, sodium alginate and agar are used as stabilizers. *Acacia* emulsions are palatable and thereby are stable over a wide pH range (2–10), but they are too sticky for external use.

Compound tragacanth powder contains acacia (20%), tragacanth (15%), starch (20%) and sucrose. It is generally used in the form of compound powder (about 2 g per 100 ml of mixture) or as the mucilage (10 to 20 ml per 150 ml of product). The compound powder is always used as a vehicle other than water or chloroform water to avoid displacement of part of a medicinally active vehicle by the mucilage.

Novel drug dosage form: *Acacia* in combination with gelatin, used to form coacervates for microencapsulation of drugs.

4.2 Tragacanth

Astragalus gummifier (Leguminosae)

Tragacanth tears

Tragacanth is the dried gummy exudation obtained by incision from stems and branches of *Astragalus gummifer* (Leguminosae). It occurs as thin, white or yellowish white, ribbon like flakes or as a white powder. With water it forms viscous solutions or gels. It is much better thickener than acacia. It is used as a powder or mucilage or as compound tragacanth powder. It suspends heavy indiffusible powders. It is also useful for mixtures containing resinous tinctures.

As an excipient: Tragacanth produces less sticky mucilage than acacia and hence it is more suitable for external preparations. It is used in jellies, lotions, pastes and creams. Tragacanth is used as a emulsifying agent and is higher viscous in nature due to its mucilage. Due to coarse emulsion it is mainly used as an emulsion stabilizer. In industry hog and *Sterculia* gums are sometimes used as cheap substitutes for tragacanth.

Tragacanth jellies sometimes called bassorin pastes since the hydrophilic component of tragacanth that forms gels in water is been named bassorin. As a lubricant 2–3% is adequate, 5% is necessary for dermatological vehicle. Bassorin paste consist of tragacanth 5%, alcohol 10%, glycerol 2% and water made upto 100 ml, is been used as a vehicle for Ichthammol, resorcinol, salicylic acid and other medicaments. Tragacanth based catheter lubricants and electrode and contraceptives jellies have been developed.

The disadvantage of tragacanth jelly is

- I.They vary in viscosity, due to geographical origin of the gum and variations in milling and storage.
- II.It tends to flake when the film left on the skin.
- III.When the pH range alters from 4 to 5 to 7, the viscosity is lost.
- IV.They are susceptible to microbial degradation.

4.3 Agar

***Gelidium amansii* - Gelidiaceae**

Powdered agar

Agar is the dried gelatinous substance obtained from *Gelidium amansii* (Gelidiaceae). It is available as white powder or grayish white strips or shreds. Agar consist of two different polysaccharides agarose chemically D-galactose and 3, 6 unianhydro L- galactose units (responsible for gel strength) and agaropectin chemically believed to be a sulphonated polysaccharide in which galactose and uronic acid units are partly esterfied with sulfuric acid (responsible for viscosity).

As an excipient: It was used as an emulsion stabilizer in liquid paraffin emulsions prepared with acacia. The solubility is in boiling water, producing solutions of high viscosity. On cooling, it becomes thin gel with 0.5% mucilage. Only low concentration can be used if the product remains pourable.

Agar used as a gelling agent, thickening agent and stabilizer in liquid dosage forms. It is used as emulsifying agent and bulk laxatives. It is used in the manufacturing of jellies and confectionary items. In microbiology, it is used in the preparation of bacteriological culture medium.

4.4 Pectin

The source of pectin is from plants of different families. The important sources of pectin are *Citrus* (Rutaceae), *Malus domestica* (Rosaceae), *Daucus carota* (Apiaceae), *Helianthus annuus* (Asteraceae). Pectin is the purified carbohydrate product obtained by acid hydrolysis from inner portion of the rind of *Citrus limon* or *Citrus aurantium* (Rutaceae). Chemically pectin is a complex carbohydrate found in the middle lamella of plant cells. Pectin is a neutral methoxy ester of pectic acid. Pectins are polyuronides. Complete hydrolysis of pectin yields D-Galacturonic acid, methyl alcohol, small amount of galactose and arabinose.

Pectin is obtained from the inner rind of citrus fruits or from apple pulp remaining after cider making. It is extracted with dilute acid and purified. Pectin dissolves in about 20 parts of water, producing a viscous opalescent acid solution. It is good emulgent in acid media but degraded at alkaline pH.

Therapeutic indication: It is used as adsorbent in the treatment of diarrhea and as a haemostatic for internal or external hemorrhage. It is also used as a plasma substitute.

As an excipient: To replace acacia, it is been used in the proportion of 0.1 g per gram of acacia fully or partly in internal emulsions. It is used for the preparation or stabilizing pharmaceutical and cosmetic lotions and creams. Pectin is used as protective colloids. Pectin used as medical adhesive, as a demulcent and stabilizer. It is used as an emulsifying agent, a gelling agent in acid medium.

Novel drug dosage form: Pectin is used as a drug carrier in targeted drug delivery system. Pectin in combination with gelatin has been used as an encapsulating agent in pharmaceutical formulations to promote sustained release.

4.5 Lecithin

Lecithin is obtained from soybean oil *Glycine max* (Fabaceae). It is also available in several vegetable seeds, egg yolk, corn and from animal brain and nervous tissue. Chemically lecithin contains glycerol, fatty acids, phosphoric acids and choline. Lecithins contain a saturated fatty acid at α -position and an unsaturated fatty acid at β -position.

Therapeutic Indication: Lecithin with the combination of proteins, it forms lipoproteins of plasma and cells. Acetylcholine formed from choline part is responsible for transmission of nervous impulses across the synapses. It is a

lipoprotic agent and prevent formation of fatty liver and lowers the surface tension of lung alveoli.

As an excipient: In the formulation of pharmaceutical dosage forms it is used as an emulsifying agent, dispersing agent, wetting agent, penetrating agent, stabilizing agent.

Novel drug dosage form: It is employed in Encapsulation.

4.6 Gelatin

Gelatin

Soft gelatin capsules

Gelatin is a protein, extracted by partial hydrolysis of animal collagenous tissue such as skins, tendons, ligaments and bones with in boiling water. Chemically gelatin contains different amino acids in which lysine is major essential amino acid. It does not contain tryptophan, gelatin composed of gluten protein.

Therapeutic indication: Gelatin is used in the form of absorbable gelatin sponge as haemostatic. It is recommended for the treatment of brittle finger nails and non-mycotic defects of the nails.

As an excipient: Gelatin used in the manufacture of hard and soft capsule shells. It is used in preparing lozenges, pessaries, pastes, pastiles and suppositories. It is used as vehicle for injections like heparin in the form of Pitkin menstrum that contains dextrose, acetic acid and water.

Novel drug dosage form: Gelatin is employed for encapsulation of drugs.

In bacteriological culture media, gelatin is used in the form of absorbable gelatin sponge and gelatin film.

4.7 Lactose

Lactose

Structure of Lactose

Lactose is a natural disaccharide contains galactose and glucose obtained from milk of mammals. Chemically lactose monohydrate is monohydrate of O- β -D galactopyranosyl – (1-4)- α -D glucopyranose.

As an excipient: Lactose is widely used as filler and diluents in tablets, capsules. Fine grades of lactose are used in the preparation of tablet by wet granulation method. Direct compression grades of lactose are used in combination with micro-crystalline cellulose or starch and for tablet lubricant as 0.5% magnesium stearate.

Novel drug dosage form: Lactose is used as diluent especially in dry powder inhalations.

4.8 Mannitol

Sugary exudation from stem of *Fraxinus ornus* Oleaceae)

Structure of Mannitol

Mannitol is a hexahydric alcohol obtained by isolation from stem of *Fraxinus ornus* (Oleaceae). Chemically mannitol is a sugar alcohol.

Therapeutic indication: Mannitol is a diuretic and isotonic agent. Mannitol does not metabolized and is eliminated by glomerular filtration and hence used as diagnostic and as an osmotic diuretic.

As an excipient: Mannitol used as a diluent, tonicity agent, stabilizer, as cryoprotectant and excipient for chewable tablets.

4.9 Starch

***Zea mays*
(Graminae)**

***Oryza sativa*
(Graminae)**

***Triticum aestivum*
(Graminae)**

***Manihot esculenta*
(Euphorbiaceae)**

***Solanum tuberosum*
(Solanaceae)**

Starch is a polysaccharide granules obtained from grains of maize (*Zea mays* Linn.), rice (*Oryza sativa* Linn.) or wheat (*Triticum aestivum* Linn.) belongs to Graminae, tapioca (*Manihot esculenta*) family Euphorbiaceae and from the tubers of potato (*Solanum tuberosum* Linn.) family solanaceae. Starch contains chemically two different polysaccharides. Amylose (β -amylose, water soluble) and amylopectin (α -amylose in water, soluble but swells responsible for gelatinising property) in the proportion of 1:2.

Therapeutic indication: starch is used as a nutritive, demulcent, protective and as an absorbent. In talcum powder starch is one of the ingredient for application over skin. It is used as an antidote in iodine poisoning.

As an excipient: Starch used as a disintegrant, diluent, binder and lubricant in the formulation of solid dosage forms. Glycerin of starch is used as an emollient and as a base for suppositories.

Sometimes starch is used with other suspending agents because of the high viscosity of the mucilage. It is an ingredient of compound tragacanth powder. Starch is a poor emulsifying agent. Its emulsions are suspensions of large globules prevented from coalescing by the high viscosity of mucilage. It is occasionally used for preparing enemas containing oils.

4.10 Bees wax

Yellow Bees wax

***Apis mellifera* (Apidae)**

Yellow bees wax is purified wax obtained from the honey comb of bees *Apis mellifera* and other species of *Apis* (Apidae). It occurs as yellow or white discs or blocks. The yellow beeswax is used in the preparation of dark colored ingredients. The white beeswax is bleached and preferred when the ingredients are colorless, white or like calamine a pastel shade.

Chemically bees wax is the esters of straight chain monohydric alcohols with straight chain acids. The chief constituent of the bees wax is myricyl palmitate (about 80%). In addition cerotic acid (15%), small quantity of melissic acid and aromatic substance cerolein present along with chief constituent.

Beeswax contains sterol containing substances. Higher alcohols (eg., cetyl and steary) form w/o emulsion. The chief constituent of beeswax is myricyl palmitate, is a ester of higher alcohol and responsible for emulsifying properties partly. In addition, beeswax contains small amounts of esters of cholesterol (a sterol producing w/o emulsions) and free cerotic acid ($C_{25}H_{51}COOH$) reacts with borax producing soap used as an emulgent in cold creams.

As an excipient: Bees wax is not a very good emulgent but is useful stabilizer for w/o creams in facilitating incorporating water. Pharmaceutically it is used as an ingredient of Paraffin ointment IP. It is used as an stiffening agent and ointment base in semisolid dosage forms.

4.11 Lanolin/wool fat

Lanolin Wax

Ointment

Lanolin is a waxy substance secreted by sebaceous glands of wool bearing animals. Hydrous wool fat is the purified fat like substance obtained from the wool of the sheep *Ovis aries* Linn. (Bovidae). It is a pale yellow, greasy, sticky material with 36–42°C melting point. Wool fat will be deposited onto the wool fibers. Chemically hydrous wool fat is the complex mixture of esters and polyesters of 33 molecular weight alcohols and 36 fatty acids. It contains mainly esters of cholesterol and ischolesterol with carnaubic, oleic, myristic, palmitic, lignoceric and lanopalmitic acids. It also contains 50% of water.

As an excipient: It is poorly absorbed by skin but along with soft paraffin or vegetable oils produce creams that penetrate well and assist absorption of medications. It absorb 50% of water but when mixed with other fatty substances, it emulsify several times on its own weight of aqueous or hydro alcoholic liquid and the emulsions are w/o in type.

It is too sticky in nature to use alone and generally mixed with hydrocarbons as in the official eye ointment base and simple ointment B.P. The above products absorb appreciable amount of aqueous liquids. Example is the B.P alkaloidal eye ointments are prepared by incorporating aqueous solution of the alkaloidal salt into base thus forming a stable semi-solid emulsion.

It does not rancidify readily. It is used in creams and ointments and as an emulsion stabilizer and in lotions. Retaining its properties and to improve the physical characteristics and stability of wool fat, the following process can be done

I. Hydrogenation: Hydrogenated wool fat is a white, odorless and non-sticky in nature and spreads easily on skin and absorbs 50% of water.

II. Fractionation: They are viscous liquids consist of esters and called as liquid lanolins. They are used as emulgents and emulsion stabilizers and they are virtually free from stickiness.

III. Treatment with ethylene oxide: The polyoxyethylene derivatives are known as water soluble lanolins are non – ionic, water soluble and promote the formation of o/w emulsions.

Pharmaceutically in semi-solid dosage form, lanolin is used as water absorbable ointment base. It is a common ingredient and base for many water soluble creams and cosmetic preparations. It is used in topical liniments, as a lubricant and employed in rust preventive coatings.

Wool alcohols are obtained by crude fractionation of wool fat. Small amounts upto 2.5% used as a stabilizer in o/w emulsions. High concentrations cause phase inversion.

4.12 Theobroma oil (cocoa butter)

Cacao Butter

***Theobroma cacao* Sterculiaceae**

Theobroma oil or Cacao butter is the fat obtained from roasted seeds of *Theobroma cacao* family Malvaceae. It is yellowish white solid with chocolate like odor. Chemically *Theobroma* oil consists of stearic 34%, palmitic 25%, oleic 37% acids along with small amount of arachidic and linoleic acid. The non greasiness of the fat is due to glyceride structure. Melting point range is 30–36°C, hence it is solid at room temperature but melts in body. Readily liquefy on warming and rapid setting on cooling.

As an excipient: *Theobroma* oil is a suppository fatty base and ointment base, used in manufacturing creams and toilet soaps.

4.13 Sodium carboxy methyl cellulose / sodium cellulose glycosallate

Sodium carboxy methyl cellulose

**Wood and cotton fibre
Gossypium hirsutum (Malvaceae)**

Sodium carboxy methyl cellulose is the sodium salt of poly carboxy methyl ether of cellulose from wood and cotton fiber *Gossypium hirsutum* (Malvaceae).

As an excipient: Sodium carboxy methyl cellulose used as a protective colloid, film forming agent, stabilizing agent, suspending agent, thickening agent and binding agent. It is used in concentrations from 0.25 to 1% for suspending powders in parenteral, oral and external products. Autoclaving at 125°C for 15 minutes reduces the viscosity by about 25% and allowance for this must be made when it is used in heat sterilized injections. It can be sterilized by dry heat at 160°C but this reduced the viscosity.

4.14 Sodium alginate /Algin

Sodium alginate

Brown sea weeds

Sodium alginate is the sodium salt of alginic acid, a polyuronic acid obtained from the algal growth of the species of family Phaeophyceae. The common algae are *Macrocystis pyrifera*, *Laminaria hyperborean*, *Laminaria digitata* and *Ascohyllum nodosium*. It occurs as a white or buff powder. Algin is purified carbohydrate extracted from brown sea weed (algae) by treatment with dilute alkali.

Alginic acid present in cell wall. The algae are harvested, dried, milled and extracted with dilute sodium carbonate solution results in a pasty mass. It is diluted to separate insoluble matter. Only soft water is used for extraction process. Further it is treated with calcium chloride or sulfuric acid for converting into calcium alginate. Purification can be done through washing. The next step is treating with hydrochloric acid. Alginic acid collected is treated with sodium carbonate for neutralization and conversion into sodium salt.

Sodium alginate is used as a stabilizing agent for emulsion, in the formulation of buccal tablets, as a cross linking polymer in enzyme immobilization. It is employed as a binding and disintegrating agent in tablet and lozenges, thickening and suspending agent in liquid dosage forms.

Novel drug dosage form: In the formulation of microspheres.

4.15 Chondrus (Irish Moss, carrageen)

Carrageenan Powder

Irish Moss

Irish moss is dried seaweed, red algae *Chondrus crispus* family Gigartinales. It occurs as yellowish, horny masses. Chemically carrageenan is sulfated galactans. Sodium alginate is a linear polysaccharide derivative of alginic acid comprised of 1,4-β-d-mannuronic (M) and α-l-guluronic (G) acids. It is a cell wall component of marine brown algae, and contains approximately 30 to 60% alginic acid.

As an excipient: Sodium aliginate is used as an emulsifying agent. For small scale emulsification it is not suitable because preparation of mucilage is time consuming and the emulsification must be homogenized. Mucilage is prepared by washing the

seaweed. Digesting it with boiling water for 15 minutes, staining while hot through cotton wool in a hot jacketed funnel and adjusting to volume and mixed. 3% solution produces a gel on cooling and 2–5% mucilage will emulsify an equal volume of fixed oil. Very stable emulsions can be made by mechanical methods and *Chondrus* has been used industrially as an inexpensive emulgent for fixed oils, particularly for cod liver oil. It is also a useful emulsion stabilizer.

4.16 Peppermint oil

Mentha piperita (labiatae)

Peppermint oil

Peppermint oil is obtained by steam distillation of fresh flowering tops of *Mentha piperita* (Labiatae). To isolate the oil, the air dried material is packed into galvanized iron or mild steel still. The still designed for this purpose has a false perforated bottom. The steam under pressure, generated with the help of boiler, is then passed through the drug. It takes about 3-4 hours for distillation. More than 80% of the oil is distilled off during the first half of distillation. Distillation should be completed carefully, as menthol of medicinal and commercial uses comes later part of distillation process. The condenser should be made up of either aluminum or stainless steel and should be coiled because of increase in the area of condensation. The mentha oil is insoluble in water and having lower density than water can be easily decanted and filtered.

As an excipient: Aromatic waters are used mainly for their flavoring properties although some are mildly therapeutic and or preservative in action. For peppermint aromatic water the dilution in parts by volume is 1 ml with 39 ml of water. Used as flavor, carminative and weak preservative.

4.17 Liquorice liquid extract

Liquorice root

Liquorice liquid extract

Liquorice liquid extract is obtained from the dried, unpeeled, roots and stolons of *Glycyrrhiza glabra* Linn., (Fabaceae). The solvent used for extraction process is hydroalcohol. The chief constituent of liquorice is a triterpenoid saponin glycyrrhizin.

Therapeutic indication: Traditionally liquorice is being used as an expectorant and demulcent. It is used in the treatment of peptic ulcer due to presence of yellow colored flavonoids liquiritin and isoliquiritin. It is used in cough mixtures.

As an excipient: Used as a flavoring agent and for disguising the taste of saline ingredients, such as ammonium salts and alkali iodides in cough mixtures.

4.18 Lemon spirit

***Citrus limonis* (Rutaceae)**

Lemon spirit

Lemon spirit is obtained by maceration of lemon peel which is the outer part of the pericarp of ripen fruits of *Citrus limonis* family rutaceae, in alcohol. Lemon peel consists of volatile from 2 to 4%, hesperidin, pectin, calcium oxalate and bitter substances. The chief constituents of volatile oil are limonene 90%, citral 4%, geranyl acetate and terpineol.

As an excipient: Pharmaceutically lemon oil is used as flavoring agent and lemon spirit is used to mask the taste of alkaline citrates.

4.19 Orange syrup and compound orange spirit

***Citrus aurantium* (Rutaceae)**

compound orange spirit

Orange syrup and compound orange spirit is prepared from fresh or dried outer peel of the ripen or nearly ripen fruits of *Citrus aurantium* family Rutaceae. Outer peel consists of 2.5% of volatile oil, hesperidin, isohesperidin, neohesperidin, vitamin C and pectin. Aurantiamarin and aurantimaric acid are glycosidal compounds responsible for bitter taste.

Therapeutic indication: Orange peels are used as stomachic, aromatic and carminative.

As an excipient: It is used as a flavoring agent in oral liquid preparations and to disguise the metallic and astringent tastes of iron salts in childrens mixture.

5. Novel phyto drug delivery system (NPDDS) in herbal medicine

Earth is gifted by creator with rich heritage of botanicals in terms of natural products. Some of the natural products are potential in its therapeutic action for the betterment of mankind. Exploring the unexplored potential phytomolecules and converting it into novel formulation is the need of the hour to combat the challenging diseases and disorders.

Novel drug delivery in modern phytoceutical research can pave a way to determine its pharmacokinetic property, mechanism and site of action, accurate dose required to exert the desired therapeutic action. Phytomolecules can be incorporated into novel drug carriers as nanoparticles, nano and micro emulsions, matrix

systems, solid dispersions, liposomes, solid lipid nanoparticles and the like. Improving phytodrug delivery to the receptor target improves the efficacy thereby minimize the toxicity due to delivery of precise dose at the site of action.

6. Challenges in formulating novel phyto drug dosage form

Exploring the novel phytomolecules as pharmacophores to combat various diseases and disorders is been realized due to resentment on synthetic molecules. The limited clinical usage of herbal medicine is due to hydrophobic nature of phytomolecules results in poor absorbable nature thereby leads to low bioavailability [9] and lower lipid solubility results in increased systemic clearance. In other fringe at the site of administration, the phytomolecules are not stable at acidic pH in stomach, results in degradation leads to loss of desired therapeutic action [10].

In order to overcome these challenges, developing novel phyto dosage forms will pave a way to deliver the potent phytomolecules at receptor target with improvement in bioavailability, specificity, efficacy and stability and to control the rate of release of phytodrug thereby reduction in dosage frequency, enhances solubility as well as absorption of phytomolecules.

Novel drug delivery strategies include modified drug in terms of sustained and controlled release (polymers, miscelles, liposomes, ethosomes, and nanotechnology), prodrugs, transdermal drug delivery systems, ocusert, insulin jet and micropump, patient controlled analgesia, drug eluting stents, gene therapy and personalized medicine.

Phytometabolites also act as carriers to deliver the drug into different sites (Brain, stomach, colon, lungs, etc.). The aim of this chapter is to articulate the current updates in the area of drug carriers in specific to colon target and the data mining on the nano engineered phytomolecules in pharmaceutical research in the area of phytopharmaceuticals.

7. Natural polysaccharides based colon-specific drug delivery

The delivery of drugs into gastrointestinal tract is difficult due to physiological challenges like motility, hepatic clearance, acidic degradation, efflux mechanism, mucous turnover etc. Localizing orally administering drugs into the colon is complicated due to prediction of exact residence time of solid dosage forms in the stomach and small intestine. Also the residence time of the drugs depends on fed/ fasted patterns, meal compositions and intensity of peristalsis. Solid dosage form may stay few minutes to 8 hour in stomach and 3 to 5 hour in bowel. Hence the colonic route of drug delivery can be used for systemic administration of drugs. Various approaches can be exploited to target the release of drug to colon by coating the drug with pH sensitive polymers, biodegradable polymers, embedding in biodegradable matrices and hydrogels, timed release systems, osmotic systems and bio adhesive systems [11].

Drug delivery systems targeted to colon by using natural polysaccharides finds superior over other systems. Moreover the uniqueness of polysaccharides are, retains their integrity and prevent the release of drug during its travel through GI tract and finally when it come in contact with colonic fluid it is digested by micro-organism thereby the entrapped drug will be liberated. The polysaccharides been explored in colon specific drug release from plant origin are amylose, pectin, guar gum, alginates from algal origin, inulin, locust bean gum and pectin.

7.1 Amylose

Amylose is a component of starch, a polysaccharide obtained from plant source. Chemically amylose is glycopyranose residues linked by α -(1–4) bonds. It is a poly (1–4- α -D-glucopyranose).

Chemical structure of amylose.

Natural polysaccharide	Reference
<i>In-vitro</i> potential of Amylose-Ethycel (1:4) coated 5-aminosalicylic acid pellet is prepared for colon targeted delivery, to protect drug release in stomach and intestine	[12]
Amylose & Ethecol (1:4) coated pellets containing 300 mg (¹³ C) glucose is developed for colonic drug delivery	[12]
Epichlorhydrin treated crosslinked amylase investigated for colon target drug delivery	[13]

7.2 Guar gum

Guar gum is the powdered endosperm of the seeds of *Cyamopsis tetragonolobus* Linn, family Fabaceae. Chemically guar gum consist of linear chain of β -D-mannopyranosyl units linked (1 $\rightarrow$ 4) with single member α -D-galactopyranosyl units occurring as side branches having molecular weight of approximately 1,000,000 giving it a high viscosity in solution.

Natural polysaccharide	Reference
Matrix tablet of guar gum with dexamethasone & budesonide investigated for colon targeted drug delivery.	[14]
Matrix tablet containing various proportions of guar gum is prepared by wet granulation technique using starch as a binder and colecoxib as a drug	[15]

7.3 Alginates

Alginates are natural hydrophilic polysaccharide derived from seaweeds. Chemically aliginates are 1 → 4 linked D-mannuronic acid and L-glucuronic acid residues.

Alginates

Natural polysaccharide	Reference
Calcium alginate beads prepared as cores and 5-amino salicylic acid coated on them, act as controlled drug release.	[16]
Calcium alginate coated with Aquacoat®, a pH independent polymer followed by 2% w/w coating of Eudragit® resisted the release of drug in acidic media and drug release triggered at alkaline pH, act as sustain release in colon.	[17]

When drug coated with calcium alginate beads swells due to osmotic gradient and the film bursts and release the drug. The delivery of the drug will be to the distal intestine with minimum initial leak and thus provides sustained release in the colon.

7.4 Inulin

Inulin is a polysaccharide which is a chemotaxonomic marker of the plants belongs to compositae family. Chemically inulin is β 2–1 linked D-fructose having glucosyl unit at the reducing end. Mostly fructose chains have glucose unit as the initial moiety.

Structure of Inulin.

Natural polysaccharide	Reference
Inulin incorporated into Eudragit® RS films resist degradation in the upper GI tract and digested in human fecal medium	[18]
Inulin reacted with glycidyl methacrylated in N,N-dimethyl formamide in presence of dimethylaminopyridine as catalyst results in formation of hydrogel, degraded by inulinase enzymes causes bulk degradation.	[19]

7.5 Locust bean gum

Carob gum is the synonym of Locust bean gum obtained from seeds of *Ceratonia siliqua* family Fabaceae. Chemically locust bean gum is β -1,4-D-galactomannan units. It requires heat to achieve full hydration and maximum viscosity.

β -o-Manp- β -o-mannopyranosyl unit.
 α -o-Galp- α -o-galactopyranosyl unit.
 Polysaccharide units of locust bean gum.

Locust bean gum and chitosan (2:3, 3:2 & 4:1) in combination used as a polymer for colon specific drug delivery. Invitro drug release and invivo studies revealed the core tablet is capable of protecting the drug release in stomach, small intestine. Further susceptible to colonic bacterial enzyme results in drug release [20].

7.6 Pectin

Pectin is obtained from *Citrus* (Rutaceae), *Malus domestica* (Rosaceae), *Daucus carota* (Apiaceae), *Helianthus annuus* (Asteraceae). Chemically pectin is a polysaccharide consist of α -1,4 D-galacturonic acid and 1,2 D-rhamnose with D-galactose and D-arabinose side chains with average molecular weight between 50,000-1,50,000. Depending on the plant source and preparation they contain varying degree of methyl ester substituents.

Structure of Pectin.

Natural polysaccharide	Reference
Coating with pectin in presence of additives and hydrophobic polymers remains unaffected in gastric and small intestinal enzymes and digested in presence of colonic bacterial enzymes	[21]
Insoluble salt of calcium pectinate by deesterification is utilized for the preparation of matrix tablets and incorporating indomethacin as water insoluble drug marker in the invitro release experiments. The release of indomethacin is significantly increased in rat caccal contents.	[22]

Natural molecules other than plant source also plays important role in pharmaceutical sector. Chitosan high molecular weight polycationic polysaccharide obtained from chitin (Cuticles of various crustaceans, principally crabs and shrimps), chondroitin sulphate, a mucopolysaccharide consist of D-glucuronic acid linked to acetyl D – galactosamide obtained from extracts of cartilaginous cow and pig tissues and other sources such as shark, fish, and bird cartilages, cyclodextrins, an enzymatic conversion of starch, dextrans, a colloidal, hydrophilic and water soluble linear chains of α -D- glucose molecules obtained from microorganisms of the lactobacillus *Leuconostocmesenteroides* are being used as natural polysaccharides based colon specific drug delivery.

Colon based drug delivery strategies are exploited to target the drug release to the colon. Several approaches is been and being investigated to achieve site specificity to colon. In this context, the presence of polysaccharides in the colon provides platform for the delivery of drugs to the colon. Specifically the natural polysaccharides remains intact in the pH condition of stomach and small intestine and when reaches the colon, the drug loaded natural polysaccharides are cleaved by polysaccharidases enzymes, due to presence of large number of derivatizable groups, wide range of molecular weights, varying chemical compositions, low toxicity and high stability. Challenges faced in use of polysaccharides as drug carriers ishydrophilicity that results in drug release slowly in upper GI tract. This can be overcome by crosslinking of the polysaccharides with epichlorhydrin, glutaraldehyde and STMP. In this aspect the crosslinking agents should not alter the biodegradability of the polysaccharide matrix in colon.

8. Phytomolecules in nano dosage form

Phytomolecules are complex in structure contributes to its polarity. Non polar phytoconstituents are steroids, terpenoids, volatile oils, alkaloids and fixed oil, flavonoids are moderate polar constituent, alkaloidal salt, tannins, glycosides, phenols, gums, resins, mucilage are highly polar constituents. Employing novel drug delivered strategy for varied polar Phytoconstituents illuminate the focus of phytodrug in the global pharmaceutical sector. The advantage of converting phytomolecules into nano size results in increase in solubility in the systemic circulation thereby increase in bioavailability, physical stability, improving tissue macrophage distribution, protection from physical and chemical degradation, dose proportionality, smaller dosage form, smaller particle size with greater surface area provides higher absorption rate including lipophilic non polar phytomolecules, as a substitute for liposomes and vehicles. More importantly the nano sized phytomolecules potentially enhances the therapeutic action that ends in innovative therapeutic strategies for herbal medicines.

Nanotechnology is the engineered technology applied for the drug molecules at the nano size of 1-100 nm.Designing of drugs especially phytodrugs in nano dosage

forms offers greater efficacy and cell specificity. Nanodosage forms are one of the significant novel drug delivery systems.

9. Nanoemulsions

Plants containing volatile oils can be easily formulated into nanoemulsion. Nanoemulsions constitute vehicles for volatile oil with sizes ranging from 20 to 200 nm. Nanoemulsions are colloidal dispersion system mixed with emulsifying agents, surfactants and co-surfactants to form single phase. Nanoemulsions are classified into o/w type (oil dispersed in aqueous phase), w/o type (water dispersed in oil phase) and bicontinuous (microdomains of water and oil are interdispersed within the system). Multiple emulsion is also included in the types of nanoemulsion wherein both o/w and w/o emulsion present in one system. Hydrophobic and lipophilic surfactants are used for stability.

Following is the perception of phytonanoemulsion, formulation methods (Table 2), characterization techniques (Table 3).

S.No.	Method	Type	Principle
1	Low energy emulsification	Phase inversion method	Using low temperature and high temperature
		Phase inversion composition method	Magnetic stirring and evaporation of the water miscible solvents under vacuum
		Solvent displacement method	Membrane contractor liquid phase forced through membrane pores leads to formation of droplets
2	High pressure emulsification	Ultrasonication	Sonicator probe contacts the liquid and it generates mechanical vibration leads to Cavitation
		High Pressure homogenization	500-5000 psi
		Microfluidiser	500–20,000 psi

Source: (Sunil [23–26]).

Table 2.
Formulation methods in nanoemulsion.

S.No	Parameters	Characterization method
1.	Droplet size analysis	Diffusion method using light scattering particle size analyzer
2.	Viscosity	Brookfield viscometer
3.	Dilution	The Nanoemulsion is diluted with water and observed for phase inversion
4.	Drug content	HPLC method
5.	Poly dispersity	Photon correlation spectroscopy
6.	Refractive index	Refractometer
7.	Dye test	The water soluble dye is added in an o/w type nanoemulsion and it takes up the color uniformly. Similarly, the emulsion is w/o type and the water soluble dye being added and the emulsion is not uniformly colored.
8.	pH	pH meter
9.	Zeta potential	Zeta sizer / zeta analyzer
10.	Fluorescence test	Many oils exhibit fluorescence when exposed to UV light

S.No	Parameters	Characterization method
11.	Percentage transmittance	UV visible spectrophotometer
12.	Conductance measurement	Conductometer
13.	Filter paper test	Nanoemulsion dropped onto filter paper and observed for migration
14.	Morphology and structure	TEM (Transmission Electron Microscopy)
15.	Invitro skin permeation studies	Kesharychien-diffusion cell
16.	Stability studies	Heating cooling cycle (the formulation were subjected to refrigerator (six cycles) at the temperature 4 °C and 45°C) stable formulation subjected to centrifugation test& Centrifugation (stable formulation were centrifuged at 3500 rpm)
17.	Interaction study	Fourier transform infrared spectroscopy spectral analysis
18.	Surface morphology	Atomic force microscope
19.	Invitro drug release study	Dissolution test apparatus

Source: [27].

Table 3.
Characterization parameters for formulated Nanoemulsion.

10. **Phytomolecules in novel drug dosage form**

Phytomolecules is been formulated as novel dosage forms and over two decades it is been concentrated in scientific research. The plant actives and extracts are formulated into polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microspheres, transferosomes, and ethosomes. Secondary metabolites formulated as novel phyto drug nano dosage forms (**Table 4**) and **Table 5** gives the insight view of plant actives and extracts formulated into various novel dosage forms [48].

S.No	Phytomolecules	Biological source & Family	Formulation Method & Pharmacological action
1	Paclitaxel (alkaloid)	<i>Taxus brevifolia</i> (Taxaceae)	Nanoprecipitation Acts against several tumors, ovarian and breast cancer [28, 29]
2	Camptothecin (Quinoline alkaloid)	<i>Camptotheca acuminata</i> (Nycaceae)	Encapsulation Potent anticancer [30]

S.No	Phytomolecules	Biological source & Family	Formulation Method & Pharmacological action
3	Berberine (Isoquinoline alkaloid)	<i>Berberis vulgaris</i> (Berberidaceae)	Emulsion, ionic gelation. Inflammation and several cancers [25]
4	Curcumin (Polyphenol)	<i>Curcuma longa</i> (Zingiberaceae)	Wet-milling technique Potent anticancer and antitumor [31, 32]
5	Triptolide (Diterpenoidtrioxide)	<i>Tripterygium wilfordii</i> (Celastraceae)	Nanoencapsulation In inflammation and autoimmune diseases, especially for rheumatoid arthritis [30, 33]
6	Naringenin (Flavonone)	<i>Vitis vinifera</i> (Vitaceae)	Nano precipitation Acts against several tumors and Hepatoprotective [34]
7	Silymarin (Flavonolignans)	<i>Silybum marianum</i> L. Gaertner (Asteraceae)	Cold homogenization In several liver diseases, breast cancer [35]
8	Genistein (Isoflavone)	<i>Genista tinctoria</i> (Fabaceae)	Nanoemulsion and chitosan microsphere Used in cardiovascular diseases, breast and uterine cancer also in osteoporosis [36]

S.No	Phytomolecules	Biological source & Family	Formulation Method & Pharmacological action
9	Breviscapine (Flavonoid)	<i>Erigeron breviscapus</i> (Asteraceae)	Lipid encapsulation In cerebrovascular and Cardiovascular diseases also against pulmonaryfibrosis [37]
10	Quercetin (Flavonol)	<i>Sambucus nigra</i> (Adoxaceae)	Gelatin and chitosan loaded Potent anticancer and antioxidant [38]
11	Crude extract of <i>Ginkobiloba</i> (Ginkgoaceae)- Terpenic lactones	<i>Ginko biloba</i> (Ginkgoaceae)	Combination of dryand wet process.(Gas phase andliquid phasegrinding) Acts against loss ofmemory, thinking, language [39]

Table 4.
 Secondary metabolites formulated as novel phyto drug nano dosage form.

S.No	Formulation	Method	Pharmacological action	Reference
1	Liposome encapsulated Silymarin	Reverse evaporation technique	Hepatoprotective	[40]
2	Breviscapine liposome	Sustained delivery of breviscapine	To treat ischemic cerebrovascular and cardiovascular diseases	[41]
3	Paclitaxel liposome	Thin film hydration method	Anticancer	[42]
4	Berberine-loaded nanoparticles	Ionic gelation method	Anticancer	[43]
5	Glycyrrhizic acid-loaded nanoparticles	Rotary-evaporated film ultrasonication method	Anti-inflammatory & antihypertensive	[44]
6	Taxal loaded nanoparticles	Emulsion solvent evaporation method	Anticancer	[45]
7	Silybin phytosome	Silybin-phospholipid complexation	Hepatoprotective, antioxidant for liver and skin	[46]
8	Berberine nanoemulsion	Drawing ternary phase diagram	Hypolipidemic agent	[47]

Table 5.
 Phytomolecules in novel dosage forms.

11. Conclusion

Natural products either as a drug or pharmaceutical substance played vital role in the treatment and prevention of diseases in humans. Pharmacognosy is the established pharmaceutical science and is a mother of pharmacy wherein, phytochemistry and molecular pharmacology, is the heart of the drug discovery process. Investigation of plant products will give a way to enter as a lead molecule as pharmacophores in drug discovery process or as a drug carrier to receptor target rather than placing the herbs in traditional pharmacognosy.

Today pharmacognosy discipline is the carrier of potent traditional herbs that acts as a bridge and as a vehicle that transports to the site of modern drug discovery. Focusing pharmacognosy research not only identifies new chemical entities (NCE's), but also exploring the biomolecules from natural sources as drug carriers, in formulating novel phyto drug dosage forms equivalent to the synthetic drug dosage forms in the area of pharmaceutical sciences.

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