

## Novel Drug Delivery System for Herbal Formulations: A Review

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Submitted: 15-04-2023

Accepted: 25-04-2023

**ABSTRACT:** From ancient times, herbal medicines are in use to cure the diseases due to their potential and less side effects. But difficulties in identification, processing, standardizing, extracting of herbal drugs, it rarely attracts scientists towards the development of novel delivery systems for herbal drugs. The reduced efficacy of herbal drugs is due to the traditional and out of date approach of administration to patients. To minimize these problems various novel drug delivery systems (NDDS) such as phytosomes, ethosomes, transfersomes, herbal transdermal patches and nanoparticles are used nowadays. Plants are nature's remedies and have been used by human beings on earth since ancient times for food and medicine. Today there are global movements towards finding of herbal medicaments in plants on lab scale and after successive preclinical and clinical trial to bring them in market via a suitable drug delivery system for mankind. The basic thought behind it is treatment of each disease is hidden in nature. Novel drug delivery technologies have gained the importance to achieve modified delivery of herbal drugs thereby increasing the therapeutic value as well as reducing toxicity. These techniques provide improved patient compliance, sustained release and targeted action of plant actives and extracts. This review summarizes the information of various novel techniques used for improving safety and efficacy of phytomedicines, type of active ingredients, biological activity and application of novel formulation of herbal drugs to achieve better therapeutic response.

**KEYWORDS:** Herbal drug, novel drug delivery system, natural products..

### I. INTRODUCTION

In the past few decades, considerable attention has been focused on the development of novel drug delivery system for herbal drugs. Herbal drugs are becoming more popular in the modern world for their application to cure variety of diseases with less toxic effects and better

therapeutic effects. Novel herbal drug carriers cure particular disease by targeting exactly the affected zone inside a patient's body and transporting the drug to that area. Novel drug delivery system is advantageous in delivering the herbal drug at predetermined rate and delivery of drug at the site of action which minimizes the toxic effects with increase in bioavailability of drugs. In novel drug delivery technology, control of the distribution of drug is achieved by incorporating the drug in carrier system or in changing the structure of the drug at molecular level. Incorporation of herbal drugs in the delivery system also aids to increase in solubility, enhanced stability, protection from toxicity, enhanced pharmacological activity, improved tissue macrophage distribution, sustained delivery and protection from physical and chemical degradation. For example, liposomes act as potential vehicles to carry anti-cancer agents by increasing amount of drug in tumor area and decrease the exposure or accumulation of drug in normal cells/tissues thereby preventing tissue toxicity effects.[1]

From time immemorial, it has been the endeavor of the doctor and the apothecary to provide patients with the best possible varieties of medications, so that recovery from disease is faster and more complete. The drugs are rendered in a suitable formulation keeping in view the safety, efficacy, and acceptability among other ingredients, and the preparation is usually known as dosage form or drug delivery system. With the progress in all domains of science and engineering, the dosage forms have developed from simple mixtures and pills to highly sophisticated technology, intensive drug delivery systems, which are known as NDDSs.[2] In the past few decades, considerable attention has been concentrated on the evolution of an NDDS for herbal drugs. Herbal drugs are getting more popular in the modern world for their diligence to cure a variety of diseases with less toxic effects and better therapeutic effects. Meanwhile, some limitations of herbal extracts/plant actives such as instability in highly

acidic pH and liver metabolism have gone to attain the drug levels below to the therapeutic concentration in the blood resulting in less or no healing effect. Incorporation of novel drug delivery technology to herbal or plant actives minimizes the drug degradation or presystemic metabolism and serious side effects by accumulation of drugs to the nontargeted areas and improves the ease of administration in the pediatric and geriatric patients.[3] Conventional dosage forms, including prolonged- release dosage forms, are unable to fulfill the ideal requirements of novel carriers such as ability to deliver the drug at a rate directed by the penury of the body and to transmit the active entity of herbal drug to the site of activity. For good bioavailability, natural products must have a sound balance between hydrophilicity (for dissolving into the gastrointestinal fluids) and lipophilicity (to cross lipidic biomembranes). Many phytoconstituents such as polyphenolics have good water solubility, but are poorly absorbed either due to their multiple- ring large- sized particles which cannot be soaked up by simple diffusion or referable to their poor miscibility with oil and other lipids, severely restricting their power to reach across the lipid- rich outer membranes of the enterocytes of the little bowel. Thus, the nano- sized NDDSs of herbal drugs have a potential future for enhancing the natural process and overwhelming problems related with plant medicines. Novel herbal drug carriers cure particular disease by targeting just the affected zone inside a patient's body and transporting the drug to that region. NDDS is advantageous in giving up the herbal drug at predetermined rate and delivery of drug at the site of action which minimizes the toxic effects with an increase in bioavailability of drugs. In novel drug delivery technology, control of the dispersion of the drug is achieved by incorporating the drug in carrier system or in modifying the social organization of the drug at the molecular level. Incorporation of herbal drugs in the delivery system also aids to increase in solubility, enhanced stability, protection from toxicity, enhanced pharmacological activity, improved tissue macrophage distribution, sustained delivery, and protection from physical and chemical degradation. For example, liposomes act as potential vehicles to take anticancer agents by increasing amount of drug in tumor area and decrease the exposure or accumulation of drug in normal cells/tissues, thereby preventing tissue toxicity effects. The phytosomal carriers have been considered for effective delivery of herbal extracts

of ginseng (*Ginkgo biloba*), etc. Direct binding of phosphatidylcholine to herbal extract components led to better absorption characteristics as compared to conventional delivery of herbal infusions. Other vesicular assemblies such as microspheres, emulsions, and polymeric nanoparticles have been shown beneficial to carry herbal components. The present review article is directed to supply an overview of different cases of drug delivery systems incorporating active ingredients and potential advantages of such organizations. In the present study, an effort has been induced to touch on various aspects and applications related to novel herbal drug preparations.

#### Advantages of herbal drugs:-

1. **Low risk of side effects:** Mostly herbal drugs are well tolerated by the patient, having fewer unintended consequences and fewer side effects than traditional medicine, and may be safer to use.
2. **More Effectiveness:** Herbal drugs are more effective for long-standing health complaints that don't respond well to traditional medicine. One example is the herbs and alternative remedies used to treat arthritis. Vioxx, a well-known prescription drug used to treat arthritis, was recalled due to increased risk of cardiovascular complications. Herbal treatments for arthritis, on the other hand, have lesser side effects. Such treatments include dietary changes like adding simple herbs, eliminating vegetables from the nightshade family and reducing white sugar consumption.
3. **Lower cost:** Cost of herbal drugs is much less than prescription medications. Research, testing, and marketing add considerably to the cost of prescription medicines. Herbs tend to be inexpensive compared to drugs.
4. **Widespread availability:** Herbs are available without a prescription. Simple herbs, such as peppermint and chamomile, can be cultivated at home.

#### Importance of novel drug delivery systems in herbal medicines

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Our country has a vast knowledge base of Ayurveda whose potential is only being realized in the recent years. However, the drug delivery system used for administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. If the novel drug delivery technology is applied in herbal

medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. This is the basic idea behind incorporating novel method of drug delivery in herbal medicines. Thus it is important to integrate novel drug delivery system and Indian Ayurvedic medicines to combat more serious diseases. For a long time, herbal medicines were not considered for development as novel formulations owing to lack of scientific justification and processing difficulties, such as standardization, extraction and identification of individual drug components in complex poly herbal systems. However, modern phytopharmaceutical research can solve the scientific needs (such as determination of Pharmacokinetics, mechanism of action, site of action, accurate dose required etc.) of herbal medicines to be incorporated in novel drug delivery system, such as nanoparticles, micro emulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles and so on. Various drug delivery and drug targeting systems are currently under development to minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone.[4]

#### **Advantages of novel drug delivery systems :-**

1. Enhancement of solubility.
2. Increased bioavailability.
3. Protection from toxicity.
4. Enhancement of pharmacological activity.
5. Enhancement of stability.
6. Improved tissue macrophages distribution.
7. Sustained delivery.
8. Protection from physical and chemical degradation

**Herbal medicine:-** Herbal medicine may be defined as a dosage form consisting of one or more plant parts or processed plant parts provide specific or other benefits in the diagnosis, treatment and prevention of diseases in human or animals and also may have nutritional value.[5] Herbal drugs constitute found in a major contribution to all the officially renowned systems such as Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy. Herbal remedies are medicinal plants that contain as active ingredients plant materials such as juices, gums, fatty oils, essential oils and many other substances of these. They also include crude plant material such as leaves, fruit, seed, bark, root, stem, or other parts of the plants entirely or fragmented by using different local methods of

different countries like extraction, purification, fractionation etc.

#### **Scope of novel drug delivery systems for herbal drugs:-**

There is huge potential to utilize novel approaches of delivering herbal products, several researchers are working towards the development of novel drug delivery systems like Mouth dissolving tablets, sustained and extended release formulations, muco-adhesive systems, transdermal dosage forms, microparticles, microcapsules, nanoparticles, implants etc. of herbs. Many of them have already reached to market and some of them are at the laboratory stage. Many drug molecules such as Digoxin, Quinine, Morphine, Atropine, Colchicine, Bromelain, etc had been isolated from the plants as their active components for the treatment of various diseases. Many of the plant-based herbal formulations have the potential to provide remedy of cancer and inflammation such as Curcumin, Triphala, Pomegranate, Kalonji, Sariva, etc. [6] Novel drug delivery systems have gained the popularity and importance to achieve modified delivery of herbal drugs, thereby increasing the therapeutic effect with lowering toxicity. Lower bioavailability due to decrease drug absorption and lack of target specificity are the two major limitations of currently available formulations of herbal drugs. Novel herbal drug delivery systems are designed to subdue the limitations of the currently available herbal drug formulations due to its wide range of advantage to mankind can be summarized as follows:

1. The novel herbal drug delivery system can be used to achieve site specificity.
2. Novel drug delivery system enhances the surface area of the drugs, therefore allows quicker absorption and rapid onset of action.
3. The enhanced penetration of nanoparticles through Blood Brain Barrier (BBB).

#### **Types of Novel Herbal Drug Delivery Systems:-**

Several approaches in case of new herbal drug delivery system include different types of expressions such as mouth-dissolving tablets, liposomes, phytosomes, pharmacosomes, nanoparticles, microspheres, transfersomes, ethosomes, transdermal drug delivery system (TDDS), and proniosomes, niosomes, dendrimers are discussed.

## 1. PHYTOSOME

The term „Phyto“ means plant while „Some“ means cell-like. Phytosome is vesicular drug delivery system in which phyto constituents of herb extract surround and bound by lipid (one phyto-constituent molecule linked with at least one phospholipid molecule). Phytosome protect valuable component of herbal extract from destruction by digestive secretion and gut bacteria and because of which they show better absorption which produces better bioavailability and improved pharmacological and pharmacokinetic parameters than conventional herbal extract.[7]and the difference between phytosomes and liposome.

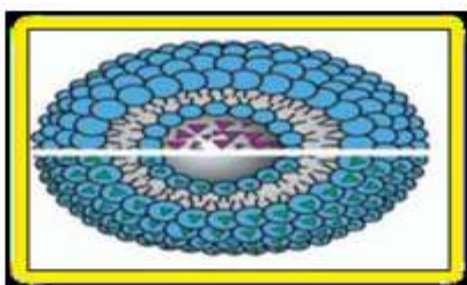


Fig 1:-Phytosome

### Advantages of Phytosomes

1. Increased bioavailability due to phospholipid complex.
2. Improved absorption in GIT.
3. Increased bioavailability causes improved therapeutic effect.
4. Less dose requirement due to high bioavailability.
5. Higher stability.
6. High lipophilicity causes high penetrability, hence forth used in cosmetics over liposomes
7. Greater clinical benefits.
8. Phosphatidylcholine acts as liver protective other than a carrier.

## 2. LIPOSOME

Liposomes are concentric bilayered vesicle in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. The name liposome is derived from two Greek words: 'Lipos' meaning fat and 'Soma' meaning body. A liposome can be formed at a variety of sizes as uni-lamellar or multi-lamellar construction, and its name relates to its structural building blocks, phospholipids, and not to its size. A liposome does not necessarily have lipophobic contents, such as water, although it usually does. Liposomes are artificially prepared vesicles made

of lipid bilayer. Liposomes can be filled with drugs, and used to deliver drugs for cancer and other diseases. Liposomes can be prepared by disrupting biological membranes, for example by sonication. Liposomes are micro particulate or colloidal carriers, usually 0.05- 5.0  $\mu\text{m}$  in diameter which form spontaneously when certain lipids are hydrated in aqueous media. Liposomes are composed of relatively biocompatible and biodegradable material, and they consist of an aqueous volume entrapped by one or more bilayer of natural and/or synthetic lipids. Drug with widely varying lipophilicity can be encapsulated in liposomes, either in the phospholipids bilayer, in the entrapped aqueous volume or at the bilayer interface.[8] and the drug encapsulated in liposomes

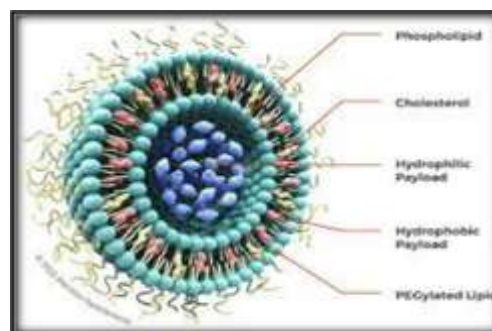


Fig 2:-Liposome

### Advantages of Liposome

1. Provides selective passive targeting to tumor tissues (Liposomal doxorubicin).
2. Increased efficacy and therapeutic index.
3. Increased stability via encapsulation.
4. Reduction in toxicity of the encapsulated agents.
5. Site avoidance effect.
6. Improved pharmacokinetic effects.

## 3. NIOSOMES

Niosomes are microscopic lamellar structures formed on admixture of a nonionic surfactant, cholesterol and a charge inducing agent with subsequent hydration in aqueous media. Niosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with a wide range of solubility's. Niosomes have been evaluated in many pharmaceutical applications. In such therapeutic applications, important advantages of using niosomes include their ability to reduce systemic toxicity by encapsulation of treatment agents and minimize clearance of such agents from

the body by slow drug release and the structure of niosome.

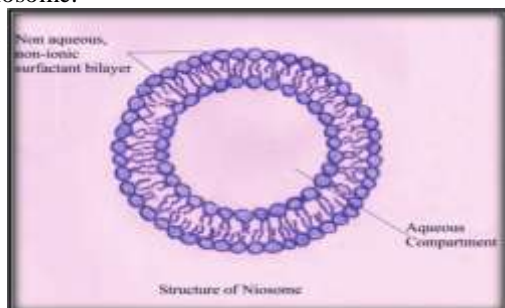


Fig 3:-NIOSOMES

#### Advantages of Niosome

1. Niosomes are biodegradable, biocompatible, non-toxic and non-immunogenic.
2. Niosomes are able to encapsulate large amount of materials in a small volume of vesicles.
3. Niosomes have better patient adherence and satisfaction and also better effectiveness than conventional oily formulations.
4. Niosomes can entrap wide range of chemicals (hydrophilic, lipophilic and amphiphilic drugs) due to its unique structure.

**4.TRANSFERSOME:-** The term and concept of Transfersome were introduced in 1991 by Gregor Cevc. The name means “carrying body”, and is derived from the Latin word 'transferre', meaning „to carry across”, and the Greek word „soma”, for „body”. A Transfersome carrier is an artificial vesicle which resembles the natural cell vesicle. Thus it is suitable for targeted and controlled drug delivery. Transfersome is a highly adaptable and stress-responsive, complex aggregate. It is an ultra-deformable vesicle which possesses an aqueous core surrounded by the complex lipid bilayer. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and self-optimising. This enables the Transfersome to cross various transport barriers efficiently, and then act as a drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents. These self-optimized aggregates, with the ultra-flexible membrane, are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency. These vesicular transfersome are several orders of magnitudes more elastic than the standard liposome and thus well suited for the skin penetration. Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of

the stratum corneum. Flexibility of transfersome membrane is achieved by mixing suitable surface-active components in the proper ratios.[9] structure as shown in the fig

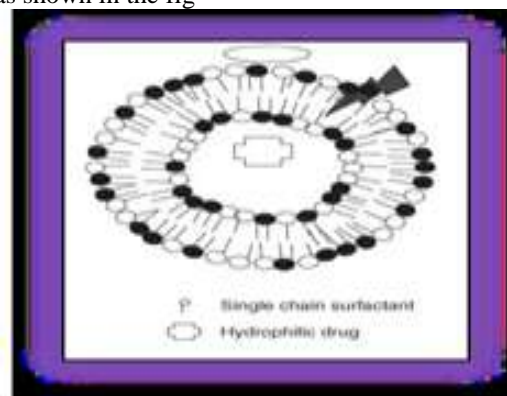


Fig 4 :- Transfersome

#### Advantages of Transfersomes

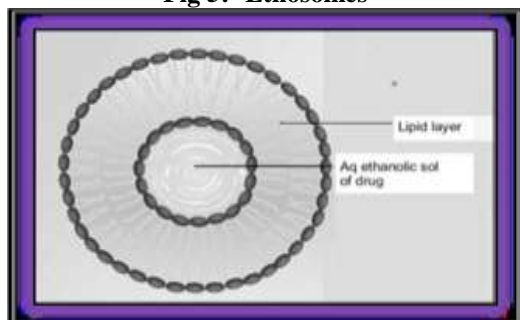
1. Transfersomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss.
2. They have high entrapment efficiency, in case of lipophilic drug near to 90%.
3. This high deformability gives better penetration of intact vesicles.
4. They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin.

#### 5.ETHOSOMES:-

Newer advancements in the patch technology have led to the development of ethosomal patch, which consists of drug in ethosomes. Ethosomal systems are made up of soya phosphatidylcholine, ethanol and water. Ethosomes are the slight modification of well established drug carrier liposome. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. Ethosomes are soft vesicles made of phospholipids and ethanol (in higher quantity) and water. The size range of ethosomes may vary from tens of nanometers (nm) to microns ( $\mu$ ) ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux. Ethosomes are a sac-like system composed of a high concentration of ethanol and phospholipids. High concentration of ethanol in the sac enhances their permeability through the. Ethosomes

delivered the drug in the form of a cream, gel for patient comfort.[10]

**Fig 5:- Ethosomes**

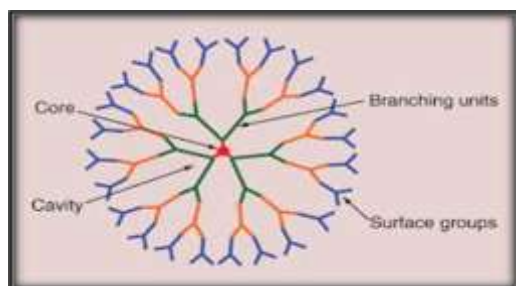


**Advantages of Ethosomes**

1. Delivery of large molecules (peptides, protein molecules) is possible.
2. It contains non-toxic raw material in formulation.
3. Enhanced permeation of drug through skin for transdermal drug delivery.
4. Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.

**6. DENDRIMERS:-**

Dendrimers are spheroid or globular nanostructures of polymeric materials. They are highly branched, monodisperse nanoparticles that bind the drug at the surface or entrap within their inner cores. There is a unique property of branching around the inner space that has huge effect on physical and chemical properties. Preparations of these particles are either by divergent or convergent methods. The size grows linearly while the number of surface groups put in. They have very low poly disparity index and ranging dimension increment by stepwise from 1-10 nm. The performance and individual properties of dendrimers can be at variance deeply from their linear complements. [11]



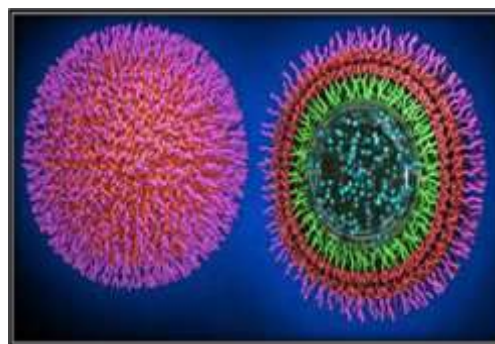
**Fig 6 :Dendrimers**

**Advantages of Dendrimer**

1. Medication to the affected part inside a patient's body directly.
2. In target drug delivery: Dendrimers are suitable for targeting solid tumors due to increased permeability, limited drainage in tumour vasculature which will lead to accumulation of macromolecules in tumor (enhanced permeation rate). There is also reduction in amount of drug used via targeted delivery (attaching site specific ligands at surface or magnetic guidance) and thus reduction in systemic toxicity.
3. Controlled and sustained release of drugs can also be obtained.

**7.NANOPARTICLES:-**

Nanoparticles are efficient delivery systems for the delivery of both hydrophilic and hydrophobic drugs. Nanoparticles are the submicron- sized particles, ranging 10–1000 nm. The major goal behind designing nanoparticle as a delivery arrangement is to control particle size, surface properties, and release of pharmacologically active agents in order to achieve the site- specific action of the drug at the therapeutically optimal rate and dose regimen. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices.[12]



**Fig 7 :Nanoparticles**

**Advantages Of Nanoparticles**

- Due its small size than microspheres and liposome's they can easily pass through the sinusoidal spaces in the bone marrow and spleen as compared to other systems with long circulation time
- Nanoparticles increases stability of drug/proteins against enzymatic degradation
- They offer a significant improvement over traditional oral and intravenous (IV) methods of administration in terms of efficiency and effectiveness

### 8. PRONIOSOMES:-

Proniosome gel system is step forward to niosome, which can be utilized for various applications in delivery of actives at desired site. Proniosomes are vesicular system in which the vesicles made up of non-ionic based surfactants, cholesterol and other additives. Proniosomes prepared by dissolving the surfactant in a minimal amount of an acceptable solvent, namely ethanol and then hydration with the least amount of water to form a gel. These structures are liquid crystalline compact niosomes hybrids that can be converted into niosomes immediately upon hydration or used in topical/ transdermal applications. The use of proniosome gel in topical/dermal delivery does not require hydration before application. It can be applied as such or loaded on a base material of emulsion, gel, ointment before application. Base helps in the application and dilution of active material on the skin. Proniosomes used to enhance drug delivery in addition to conventional niosomes. [13]

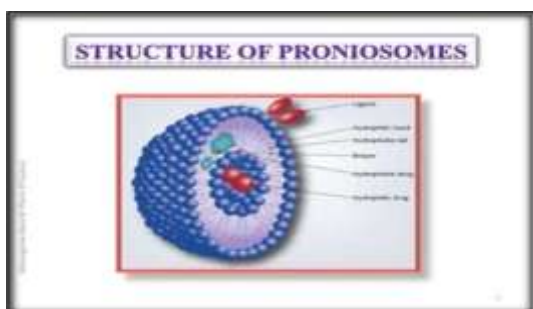


Fig 8 . Proniosomes

### 9. MICROSPHERES:-

Microspheres are discrete spherical particles ranging in average particle size from 1 to 50  $\mu$ . Microparticulate drug delivery systems are studied and taken on as a reliable one to rescue the drug to the target site with specificity, to assert the desired concentration at the situation of interest without untoward effects. Microencapsulation is a useful method which extends the duration of drug effect significantly and improves patient compliance. Finally, the entire dose and few adverse reactions may be thinned out since a steady plasma concentration is kept. So far, a series of active ingredients of plants, such as rutin, camptothecin, zedoary oil, tetrandrine, quercetine, and Cynara scolymus extract, has been made into microspheres. In addition, reports on immune microsphere and magnetic microsphere are also usual in recent years. [14]

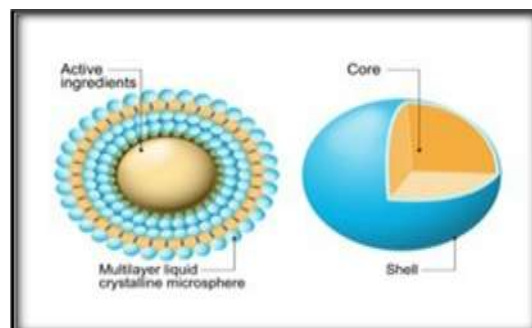


Fig 9 :-Microspheres

### Advantages of microsphere

Administration of medication via microparticulate system is beneficial as they can be taken orally or injected and release profiles can be controlled and can even provide site targeted release. Zedoary oil and Quercetin microspheres therapeutic effectiveness are reported in the literature.

### 10. MOUTH-DISSOLVING TABLETS:-

Asoka Lifescience Limited launched Res- Q, the world's first polyherbal mouth-dissolving tablet, fast mouth-dissolving drug. It induces a new drug delivery system that imparts increased efficacy. In the Ayurvedic medicine segment, this is the inaugural attempt to make medicines more effective in managing chronic ailments. Res- Q is a polyherbal medicine highly effective for lung problems and other respiratory ailments such as asthma. This unique mouth-dissolving drug delivery system ensures that the drug reaches the blood right away and the first-pass metabolism is bypassed. It dissolves in mouth by mixing with the saliva and get absorbed. This Res- Q provides relief from respiratory distress within 15 min. Hence the product shows a great resemblance with the efficacy of Sorbitrate, a revolutionary mouth-dissolving drug used in cardiac distress. [15]



Fig 10:- Mouth-Dissolving Tablets

### Advantages of mouth dissolving tablets:

1. Administration to the patients who cannot swallow, such as the elderly, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
2. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients
3. No need of water to swallow the tablet

### Future Prospective

The widespread uses of natural products with medicinal properties are obtained from commonly used herbs and medicinal plants. Herbal medicines have been used vastly by the major part of the population for curing ailments. All over the world, the exploration has been going on herbal remedies. The development of herbal medicine in the drug delivery system in a number of organizations is being performed at basic and clinical trial levels. Though the herbal formulations are unexpected to cure diseases fully but they can assist in the better regulation of diseases by the patient himself. Besides, it can also improve the quality of life by giving nutritional supplement as well.

## II. CONCLUSION:-

Many therapeutic potentials are there in herbal medicines or plant extracts, which should be investigated using cutting-edge drug delivery technology. This review provides information on the varieties, formulations, applications, and innovative drug delivery systems of herbal medicines as well as on the state of the market at the time of writing. This knowledge is helpful for future research projects, chemical entity isolation from novel herbal drug delivery systems, and novel herbal drug delivery system development. The therapeutic potential of herbal medicines should be examined using some value-added drug delivery technologies. Utilizing the cutting-edge drug delivery technology, many of the great phyto components have been successfully released. As a result, there is great potential for developing new medicine delivery methods for plant extracts and active ingredients. Compared to their synthetic cousin, herbal excipients are less expensive, easily accessible, and non-toxic. Medical professionals and individuals around the world have long recognised the benefits of using herbal remedies. because they are more effective therapeutically and

have fewer side effects than contemporary medications.

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