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CRITICAL REVIEW ON NOVEL DRUG DELIVERY SYSTEM AND AYURVEDIC FORMULATIONS

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ABSTRACT

Ayurveda system of the medicine is an old as the Vedic age. In, *Ayurvedic* texts many different dosages forms are mentioned. From the ancient times the medicines are prepared in the different ways as per the requirement of the patient and disease. According to the condition of the patient, disease and action which we want from the drug, the *Acharays* has mentioned the different forms of the formulation from the same raw drugs like- *swarasa kalka, asava, arishta, bhasma*, etc. In the recent years, there were many of the development that are going on at medicinal dosage forms so as to enhance their solubility, bioavailability, pharmacological activity, stability, reduce their toxicity and increase the compliance, etc. The new advanced novel drug delivery system (NDDS) was designed now a day's to achieve the continuous delivery of the drug at their predictable and reproducible kinetics over an extended period of the time in the circulation. NDDS is a combination of both the advance techniques and new dosage forms. NDDS is referred as the formulation, systems and technologies for the transportation of the pharmaceutical compound in the body. But on comparing both this *ayurvedic* and NDDS system we found that there are many of the similarities between both of these systems. The facts governing the NDDS system are already mentioned in our *ayurvedic* texts. What new technologies they are trying to make are already somehow mentioned already. The difference is only that they are left unexplored. This paper presents the critical review of the traditional dosage form and novel drug delivery system and their correlation. We have tried to quote some of the examples of the *ayurvedic kalpas* which can be correlated with this new system of the medicine i.e. NDDS.

KEYWORDS: *swarasa kalka, asava, arishta, bhasma*, etc.

INTRODUCTION

In *Ayurvedic* texts there are different and numereous dosage forms mentioned as per the requirement of the condition. For different diseases, condition of the patients, palatability, stability and shell life of the formulation, they have made the different preparation of the same drugs. Like- if we take example of the *amalaki*(Emlica Officinalis) it is available in different dosage form such as *swarasa, kwatha, choorna, ghrita, etc.* It comes under different dosage forms even the drug is same but according to the requirement it is used in the different form and it acts differently on changing its form.

As there are many of developments going on at present scenario in the field of the medicines, the NDDS is also one of the result of the nowadays medicinal development. NDDS is combination of the advance techniques and the new dosage forms. NDDS refers to the formulation, systems and technologies for transporting a pharmaceutical compound in the body.[1] The method by which we delivered the drug in our body can have a significant effect on its efficacy. Some of the drugs have an optimum concentration range within which its maximum benefit are derived, and the concentrations above or below on the other hand, tends to have very slow progress in the efficacy of the treatment of severe diseases has suggest a growing need for the new dosage form. Thus different types of herbal NDDS is given- Liposomes, Microspheres, Nano particles, Phystosomes, Transferosomes, Polymeric Micelle Formulation, Transdermal system, Implants, Micropellets, Complexation.

On reviewing of the *ayurvedic* texts, we found that this new NDDS systems which is explained and are developed nowadays can be compared with the few examples of the *ayurvedic* formulations. The purpose for which NDDS is developed is tends to fulfilled by some

of the *kalpas* mentioned in the *ayurvedic* texts. *Ayurvedic* medicines are serving a range of the therapeutic objectives with inimitable approach on virtue of its unique structural specifications like those of the liposomes. The only difference is that they are left unexplored. So studies should also be done to explore the pharmacology of this different *ayurvedic* dosage forms to know the pharmacokinetics and pharmacodynamics of this drugs and how the *ayurvedic* formulations act in our body. Are these *ayurvedic* dosage form and NDDS working the same way, further studies have to be done on it.

Liposomes

These are the colloidal and spherical vesicles (0.05-5.0µm in diameter) which are composed of a bilayer membrane entrapping an aqueous core.[2] These are constructed with the polar lipids which are made up of the lipophilic and hydrophilic group on the same molecules. A liposome is a molecule which has an aqueous solution core surrounded by a hydrophilic membrane, in the form of the lipid bilayer; hydrophilic solutes dissolve in the core cannot readily pass through the layer. Hydrophobic chemicals associate with the bilayer. A liposome can be therefore loaded with the hydrophobic or hydrophilic molecules. To deliver the molecules to the site of their action, the lipid bilayer can fuse with other bilayers such as cell membrane, thus delivering the contents of the liposomes; this a complex and nonspontaneous events,[3] however by preparing the liposomes in the solution of DNA or drugs (which would normally be unable to diffuse through the membrane) they can be (indiscriminately) delivered past through the lipid bilayer, but are then typically distributed non homogeneously.[4]

Liposomes are used as models for the artificial cells. Liposomes can also be designed to deliver drugs in other ways. Liposomes that contain low (or high) ph can be constructed in such a way that dissolved aqueous drug will be charged in the solution (the ph is outside the drug's ph range). As the ph naturally neutralize within the liposomes (protons can pass through some membranes), the drug will also be neutralized, allowing it to freely pass through a membrane[5]. These liposomes work to deliver the drug by diffusion rather than by the direct cell diffusion. They are also widely used as drug carrier in topical treatment of diseases, especially in dermatology. They are capable to incorporate a variety of the hydrophilic and hydrophobic drugs, to enhance the accumulation of drug at the site of the administration, and to reduce the side effects. Liposomes help us in providing the sustained and/or controlled release of the entrapped drug. Liposomal system allows them for a high accumulation of this drug in the skin, with relatively low permeation flux if we compared it with the conventional dosage form.

In Ayurveda

There is very distinctive similarity between these liposomes and *sneha kalpana* on the account of their aqueous and oleaginous origin. *Sneha kalpana* is a unique dosage form mentioned in the *Ayurveda*. Aim of the arrangement of this *kalpana*, is the mass transfer of both the aqueous and lipid soluble active principles of all treated herbal drugs and materials of animal and mineral origin, if any in that drug to be delivered at the same time[6]. In this *sneha kalpana*, the drugs are processed with the *kalka, drava dravya, kwatha* and the lipid compound such as *ghrita* and *taila*.

On the other hand, in liposomes, the active compound can be locate either in the aqueous spaces, if it is water soluble, or in lipid membrane, if it is lipid soluble. The differences between both of them are – the less dosage of the liposome is required as compared to the *sneha* formulations but the liposomes have limitations of low encapsulation and rapid leakage of water soluble drug in the presence of blood components. The stability of the *sneha kalpanas* is much better than that of the liposomes.

In *Sharangdhar samhita, madhyam khand* chapter 5 phrase 7, one *kalpa* named as *Rasona kalka* is mentioned which is said to be used along with the *taila* and it is said to act on *vataj roga*. In Ayurveda *pakwashya* ~ intestines is said to be the main site of the *vata dosha*. The drug which we want to act upon the *vata dosha* must get absorbed through this site as the *rasona kalka* may get destroyed by the gastric juices so it is said to be coated by *taila* so that it is not destroyed by them and reach the intestines and show it action. In this way this *kalpa* is prepared to maintain its ph and a target action is achieved by it. This can also be compared with the liposomes as in its inner core we are taking hydrophilic molecule and in outer core we have lipid layers and also it's fulfilling the purpose of the liposomes of target delivery.

Microspheres

It consists of the spherical particles of size ideally from1-300µm. Each particle is a matrix of the drugs that are dispersed in the polymer and drug in it is released as a first order process. Polymers are used for the fabrication of micro particulate carriers such as albumin, gelatine, modified starch, resins, etc. Firstly the outer dissolution media will diffuse into the matrix and make the entrapped drug to solubilize in it and then the drug is released from this system- this is one type of the mechanism. Other type of the system constituting the polymer show surface erosion behaviour where the surface of it is eroded layer by layer and then the release of the drug occur[6,7]. There are varieties of the methods for the production of the microspheres which offers a myriad of opportunities to control the aspects of administration of the pharmaceutical compound. This focus facilitates its precise release in the desired amount at the site of action and its reduction at the non-target sites. Similarly, this factor provides us the protection of

the compounds before and after its administration. Plant active ingredients such as rutin, camptothecin, zedoary, oil, tetrandaine, quercetine, and cynra scolymus extract has been made into microspheres.[8]

There are two types of microspheres[9]

1. Microcapsule – are those in which entrapped substance is surrounded with the distinct capsule wall.
2. Micrometrics- are those in which the entrapped substance is allowed to disperse throughout the matrix. Microspheres play's an important role to improve bioavailability of the conventional drugs and minimize its side effects. It should have poses the ability of incorporating the reasonably high concentration of the drug. Stability of the preparation after synthesis with a clinical acceptable shelf life.

In Ayurveda

Guggul(Commiphora spp.) or Indian Myrrh is a yellowish colour gum-resin which is produced by the stem of the *guggul* tree. Resin is known to be a polymer. In Ayurveda there are various *kalpas* of the *guugul* mentioned such as *yoograj guggul*, *singhanad guggul*, etc which contain *guggul* and raw drugs along with it. As they contain polymers matrix we can compare them with the microspheres. The purpose of *guggul* formulation may be the same as that of the microspheres.

Nanoparticles

These are the colloidal systems which have particles size varying from 10nm-1000nm. The term nanoparticle is not usually applied to the individual molecule it is usually referred as inorganic materials. Nanoparticles are those materials which are confined to the nanoscale in all the 3 dimensions. It is a small object which behaves as a whole unit in the terms of its transport and the properties.[11]

In Ayuveda

Bhasma is an ancient nano particle. *Bhasma* means an ash obtained through incineration. The starter material undergoes an elaborated process of purification and this process is followed by reaction phase, which involves incorporation of some other minerals and/or herbal extract. The particle size is approximately upto1-2µ(1000nm-2000nm). The nano size of the particle not only increased the surface area but also the nano size helped the drugs to reach their target size efficiently., In the *ayurvedic* text, *bhasma* are said to have quick and more potent effect than other formulations in our body. Like of *bhasma*, nano particles can also be used to target the herbal medicines to individual organ which improves the drug for its selectivity, delivery, effectiveness and safety in the body. Nano particles have the capacity to deliver high concentration of the drugs to disease site because of their unique size and high loading capacities.

Phytosomes

They are the emerging trend in the delivery of the herbal drugs and nutraceuticals. It is a formulation in which standardized plant extracts or water soluble phyto-constituents were incorporated into phospholipids to produce the lipid compatible molecular complexes. It improves its absorption and bioavailability of herbals. It is useful as in the case of flavonoids, tannis and terpenoids. Most of the biologically active constituents of the plants are polar or water soluble molecules. However, water soluble phytoconstituents(like-flavonoids, tannis, etc) are poorly absorbed either because of their large molecular size which cannot absorb by passive diffusion or due to its poor lipid solubility, that severely limits its ability to pass across the lipid rich biological membranes, resulting into the poor bioavailability. It has often been observed that even after isolation and the purification of the extract, its lead to a loss of specific bio activity for the purified extract and when we take them orally some of the constituents may be destroyed in the gastric environment. It has also been observed that complexation with certain other clinically useful nutrients substantially improves its bioavailability of such extracts and their individual constituents. The nutrients which are helpful for the enhancement of the absorption are phospholipids. The only limitation of them is their bioavailability, when we administered them orally or topically.[12]

In Ayurveda

Triphala ghrita kalpana, as mentioned in the *Sharangdhar samhita, madhyam khand* chapter 9 can be compared with the phytosomes. As *triphal* have tannis present in it as a chemical composition and we prepare *ghrita* of *triphala*. In this *kalpana* we are converting the water soluble phyto-constituents of *triphala* into the phospholipids. As in both the same procedure is occurring we can compare the *triphala ghrita* with phytosomes.

Transferosomes

It is a phospholipids vesicle which acts as powerful carriers. It is chemically unstable and its purity is under question and also they are very expensive.[8,13]

In Ayurveda

There is one *kalpa* named *vasantkalpa* mentioned in the *yoga ratnakar*, *ras* chandashu, in which fresh cream obtained from the cow milk was used as the *bhavana dravya* and this cream of cow milk contains phospholipids, so we can compare it with the transferosomes. As they both work in the same way by phospholipids vesicle. Also *mahamayur ghrita* and *aja ghrita* can be compared to it as they also show the same trend.

Ethosomes

Ethosomes are the vesicles, which are composed of the phospholipids and high concentration of the ethanol. It causes improved drug delivery to the deeper layer of the

skin and even to blood. It is useful for the topical delivery of alkaloids. The high concentration of the ethanol into the ethosomes makes them unique, as ethanol is known for its disturbance of skin lipid bilayer organization; therefore, when we integrated them into a vesicle membrane, it then gives that vesicle ability to penetrate into the stratum corneum. Also, because they have high ethanol concentration, the lipid membrane is packed less tightly than that of the conventional vesicles but has equivalent stability, allowing it a more malleable structure and improves the drug distribution ability in stratum corneum lipids.[14]

IN Ayurveda

In *ayurvedic* text *kalpana* such as- *asava* and *arishta* are mentioned in various places, they contain the alcohol content in it. But they are used internally. Also we had many external applications which show potent results but we have to rule out them for the ethanol contents if it present in it.

Nano/ Micro Emulsions

Nano or micro emulsions are the oil/water or multiple emulsions which have the size range of several microns which are useful in the transdermal delivery systems. They are said to be non-toxic and non-irritant. Nano emulsions are useful in delivering the drugs to cell culture, cancer therapy and as disinfectants. It used to increases the solubility and bio-avalibility of the drug[15]. Palatability and compatibility with other excipients is a limiting factor that is present in the case of oral drug therapy.

IN Ayurveda

We can compare it with the sarajrasa malahar mentioned in the Rasa Tantra and sikta taila mentioned in Rasa Tarangini. In sarajras malahar the oil is processed with the various drugs and then is poured into the water and are rubbed till the water is entrapped into it and emulsion of it form, it is used for the local application. And also sikta taila is prepared by using the oil and bees wax which is also a fat. We can compare sarajras malahar and sikta taila with the micro emulsion as they are also oil-water and oil-fat emulsions. Both of them have same method of preparations. Also they are used as a local application and possessed to work similarly like the nano/ micro emulsion.

Polymeric Micelle Formulation

Polymeric micelles are those which consist of an inner hydrophobic core that is capable of solubilizing lipophilic substance and an outer hydrophilic corona which serves as the stabilizing interference. They are used to carry a number of drugs like- Autemisinin from Artemisia annua l. and curcumin from the roots of curcuma longa l. are used as antimalarial drug. Polymer sodium doclecyl sulfate which led to 25 fold increase in their solubility. They have the limitation of the poor physical stability and potential for the embolism.[16]

In Ayurveda

In *ayurvedic text* many of the *leha kalpana* are mentioned at various places for the diseases such as- *kasa, swasa, amala pitta, sheetpitta*, etc. In these *leha kalpana*, if we talk about its method of preparation the general method of the preparation is- we fry the raw drug with the *ghrita* and when it gets completely fried and the *ghrita* enters into it completely and forms a different substance then the liquid medium in the form of *kwatha, paka*, etc is added into it and are prepared till it achieves the *leha* form. This *leha kalpanas* can be compared with the polymeric micelle formation as both have inner hydrophobic core that has lipid soluble content in it and is then micelle into hydrophilic core. Also they fulfill the target delivery action of the drugs. They should be also explored for exact chemical structure.

Transdermal Systems

In transdermal system, a transdermal patch which is a medicated adhesive patch is placed on the skin to deliver a specific dose of the medication through the skin and then into the bloodstream. An advantage of this delivery route over the other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch used to provides a controlled release of the medication into the patient, usually through either a porous membrane which is covering a reservoir of medication or through the body heat melting thin layers of medication embedded in the adhesive. These are the devices in which the drug present in the formulation permeates into systemic circulation by the method of the diffusion into the stratum corneum and further to the effected organs. These devices make uses of polymer matrix, adhesive bandage and permeation enhances. There limitation is they first pass metabolism through hepatic and maintenance of steady state concentration in the serum.[17]

In Ayurveda

In *Ayurvedic* texts, we found out many references of the *lepa* such as *vrishchakdansh hara lepa, sunthi lepa, dashang lepa*, etc. These *lepas* are applied on the skin in the form of the patch and left out there for some time the active principles of them get absorbed through skin and then reaches the circulation and shows it actions locally and systematically. We can compare this with the transdermal systems as both possess the same mode of the action. More studies should e done on its pharmacokinetics and pharmacodynamics to know the proper pharmacology of these *ayurvedic lepas.*

Implants

Implants are used for the controlled and sustained action of drug. Devices are directly placed into the body fluids/ cavities by means of some kind of microsurgery. They are fabricated by using biodegradable polymers for examples- chitoran and gelatin. Non-biodegradable polymers may sometimes cause irritation. This activity may last for 28 day's which prevent the patients from frequent dosing.[18]

In Ayurveda
In Ayurveda, *suchika bharan* rasa as mentioned in the, can be compared with the implants, as that *kalpa* is told to be used in the unconscious patients by making a small incision on the head of the unconscious person.

Micropellets
These are used for the delivery of drug's having size 1-1000µm to their specific sites and for the extended period of the time. It is used for the delivery of two incompatible drugs simultaneously. Pallets are done for the coating and taste masking of the formulations. HPMC coated curcumin pellets were prepared for delivering of the curcumin in the colon to treat the inflammatory disease. Pectinolytic enzyme helps in releasing drug in the colon and avoids vomiting, loss of appetite and nausea. Its limitations are –bioavailability and site specific drug delivery[19].

In Ayurveda
There are many references of *vati* in which *bhavana* of different liquids are said to be given like in *shanka vati* the *bhavana* of *nimbu swarasa* is said to be given, the reason for it would be that it changes it ph to acidic which permits it to get absorb through the stomach and show its action. We can compare this with the micropellets as in both of them they are coated with a required solution according to the situation needed.

Complexation
Complexation is association between the two or more molecules which form a non bonded entity with well-defined stoichiometry. There are various complexing agents such as EDTA, cyclodextrim and polymers which have been used for the complexation. The solubility of the circumin was increased by the formation of the circumin soya lecithin complex and evaluated for its hepatoprotective study.[8]

In Ayurveda
There are many *Vati kalpana* which are mentioned in *ayurvedic* texts we can compared them with the complexation as more molecules are presented in it which are non-bonded.

CONCLUSION

1. The NDDS can actually be compared to the traditional dosage form. The novel drug delivery system discovered now a day's are already mentioned by our *ayurvedic* texts.
2. *Ayurvedic* formulations are already well furnished so instead of searching for the new systems we have to evaluate the already existing forms.
3. Studies should be conducted out on the unexplored *ayurvedic* formulations to know their pharmacodynamics, pharmacokinetics and other actions.
4. These *ayurvedic* preparations should also be evaluated for their chemical structure if they are equivalent
5. Also these preparations should be evaluated for their efficacy in comparison with that of the new system.

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