NANOENCAPSULATION TECHNIQUES IN PHARMACEUTICALS: REVIEW

Suhaila M.A*, K. Krishnakumar, B.Dineshkumar, Smitha K Nair*

Department of pharmaceutics, stJamesCollege of pharmaceutical sciences

St JamesCollege of pharmaceutical research center (DSIR recognized) chalakudy, Kerala

ABSTRACT

Encapsulation is the process of enclosing the substances within an inert material which protect from environment as well as control release .Nano encapsulation is the newly advanced technology having the feasibility to entrap bioactive compounds. Nano encapsulation shows site specific targeted drug delivery and efficient absorption through cells as a result of their controlled and sustained release properties, subcellular size and biocompatibility with tissue and cells.In this review,Nano encapsulationtechniques, characterization and various applications of Nano encapsulationsare also highlighted.

***Keywords*:**Nano encapsulation, bioactive compound,biopolymer.

No: of Tables: 1 **No: of Figues 5** **No: of References: 21**

INTRODUTION

Nano encapsulation is a type of microencapsulation; a technique for enclosing bioactive substance in nanoscale shell made from biodegradable polymers and lipids. Microencapsulation: it is the encapsulation of solids, liquids or gases in to micron size particles[1]. The typical size of Nano capsule ranges from 10-1000nm. However, depending on the preparation and use of the Nano capsule, the size will be more specific[2].

Nano capsule structure

It consist of Nano vesicular system that is formed in a core shell arrangements. The encapsulated material commonly known as internal phase, the core material, the filler or fill. Encapsulation material known as external phase. The shell of a typical Nano capsule is made of a polymeric membrane or coating [3].Nano capsulestructure shown in the figure 1.

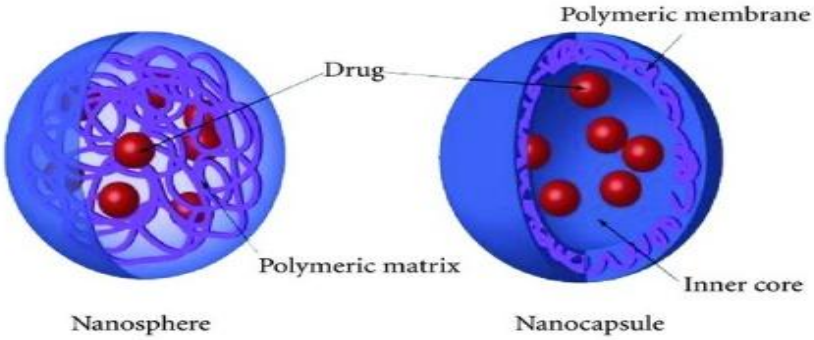

Figure 1: Nano capsule structure

Core material such as lipophilic and hydrophilic nutraceuticals compounds are used forNano encapsulation. Hydrophilic compounds are soluble in water but insoluble in lipids and organic solvents, whereas, lipophilic compounds are insoluble in water but soluble lipids and organic solvents [4].TheCore of a Nano capsule is composed of oil surfactant that is specifically selected to co-ordinate with the selected drug with in the polymeric membrane. The specific oil used mustbe highly soluble with the drug, and nontoxic when used in a biological environment [5].The oil-drug emulsion must have low solubility with the polymeric membrane to confirm that the drug will be carried throughout the system properly and be released at the proper time and location. Then the drug should be uniformly dispersed throughout the entire internal cavity of the polymeric membrane[6].

Coating material (polymers) used for the preparation of nanoparticles should be biodegradable and bio-compatible with the body in the terms of adaptability (non-toxicity and non-antigenicity). The polymers are listed in the table 1.

Table 1: polymers used in Nano encapsulation

Naturel polymers	Synthetic polymers
Chitosan Gelatin Sodium alginate Albumin	Poly lactide(PLA) Polyglycolides(PGA) Poly(lactide co-glycolides)(PLGA) Polyanhydrides Polyorthoesters Polycyanoacrylates Polycaprolactone Poly glutamic acid Poly mallic acid Poly(N-Vinyl pyrrolidone) Poly(methyl methacrylate) Polyacrylic acid Polyacrylamide Poly(ethylene glycol)

Mechanism of drug release[7]

The three mechanism by which the delivery of drug from the polymeric nanoparticles are follows:

1. Swelling of the polymeric nanoparticles by hydration and by diffusion release of drug takes place from the inner core.

2. Rupture or cleavage or degradation of the polymer occurred by an enzymatic reaction at site of delivery, there by releasing the drug from the entrapped inner core.

3. Dissociation of the drug from the polymer and it's de-adsorption or release from the swelled Nanoparticles.

Advantage [8, 9]

1. To increase the bioavailability of pharmaceutical agents
2. To increase the stability of pharmaceutical agents
3. To produce targeted drug delivery.
4. To decrease the evaporation rate of the core material.
5. We can easily and fastly delivers the pharmaceutical agent at a higher concentration to a diseased site at a desired rate.
6. To modify drug release from polymeric nanoparticles and the choice of polymer have made them ideal candidates for cancer therapy, delivery of vaccines.
7. Contraceptives and delivery of targeted antibiotics.
8. The properties of encapsulated material can also be modified (eg. Taste masking ,odour masking)
9. The industrial processes can be improved or facilitated(eg.transformation of liquid into solid

Disadvantages

1. It is an expensive process
2. Require skill
3. Difficult to obtain continuous and uniform film.

Techniques for the preparation of nanoparticles

Many methods have been developed for the preparation of nanoparticles. Depending on the physico-chemical characteristic of the drug, it is possible to select best method of preparation and best polymer to achieve an efficient entrapment of drug. In the case of Nano capsules it is a reservoir type system in which oily core surrounded by an embryonic polymeric shell. The physicochemical properties such as particle size, size distribution, surface area, shape, solubility, and encapsulation efficiency, and releasing mechanisms were reported to be altered by the encapsulation technique and delivery system. The selection of matrix (polymer) based on many factors including antigenicity of the final product, degree of biodegradability, drug release profile desired, and size of nanoparticle required, and surface characteristics.Nano encapsulationtechniques useeither top-down or bottom-up approaches for the developmentof nanomaterials. A top-down approach involves the application of precise tools that allow size reduction and structure shaping for desired application of the nanomaterial being developed. Techniques such as emulsification and emulsification –solvent evaporation are used under the top-down approach. In the bottom-upapproach, materials are constructed by self-assembly and self-organization of molecules, which were influenced by many factors including pH, temperature, concentration, and ionic strength. Supercritical fluid techniques, inclusion complexation, coacervation, and nanoprecipitation are used in the bottom – up approach. The nanoparticles are also obtained by polymerization reactions, these includes emulsion and interfacial polymerization, and ionic gelation or coacervation ofhydrophilicpolymers[10].

Solvent evaporation

Solvent evaporation was the first method developed to prepare nanoparticle (figure 2).It involves two steps. The first step involves emulsification of the polymer solution into an aqueousphase. In the second step polymer solvent is evaporated, inducing polymer precipitation as Nano spheres.This method is based on the solubility of the polymer and hydrophobic drug since both the polymer and hydrophobic drug are dissolved in an organic solvent like dichloromethane, chloroform, or ethyl acetate. (Organic solvent used for dissolving the mixture).Mixture obtained from polymer and drug solution is then emulsified in an aqueous solution. This aqueous solution contains surfactant or emulsifying agent to form oil in water emulsion. Once stable emulsion forms, the organic solvent is evaporated either by continuous stirring or by reducing the pressure. Then byultracentrifugationthe solidified nanoparticles are collected and washed with distilled water to remove any free drug or the stabilizer residue or and lyophilized for storage.

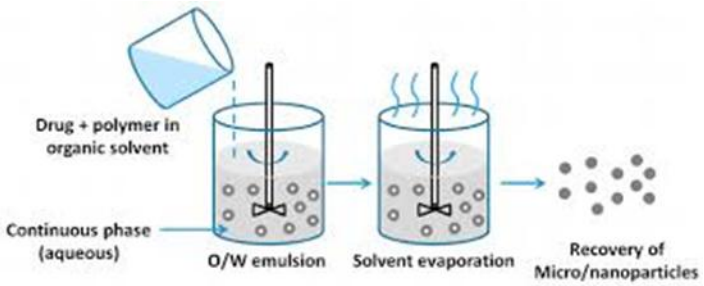

Figure 2: Solvent evaporation

Nanoprecipitation

Nanoprecipitation method otherwise called solvent displacement method involves, precipitation of a preformed polymer from an organic solution and diffusion of organic solvent in aqueous medium in presence or absence of surfactant. (Figure3.)The polymer dissolved in water-miscible solvent of intermediate polarity leading to precipitation of nanospherers.The Nao capsules are also formed when a small volume of non-toxic oil is incorporated in organic phase. Due to diffusion rate is enough to produce spontaneous emulsification, this technique is limited to water-miscible solvents. Acetone and dichloromethane are mainly used to dissolve and increase the entrapment efficiency of drugs. The nanoprecipitation method is basically applicable for lipophilic drugs because of the miscibility of the solvent with aqueous phase, and it is not suitable forencapsulating water soluble drugs.[11]

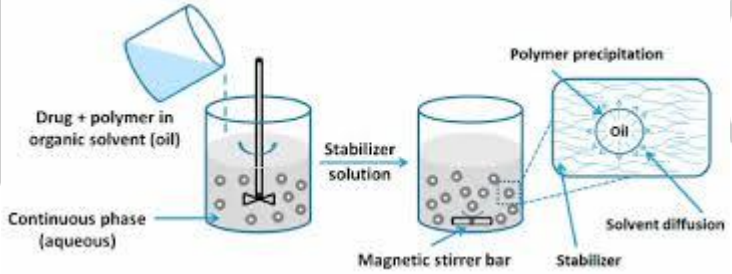

Figure 3: Nanoprecipitation

Emulsification or solvent diffusion

Solvent diffusion is a modified version of solvent evaporation method (Figure4).The encapsulating polymer is dissolved in partially water-miscible solvent such as (propylene carbonate, benzyl alcohol) and saturated with water to obtain the initial thermodynamic equilibrium of both liquids. When the organic phase is partly miscible with water, it is necessary to promote the diffusion of the solvent of the solvent of the dispersed phase by using excess of water and vice versa. The diffusion will leads to the formation of Nano capsule or Nano spheres. Finally, according to its boiling point solvent is eliminated by evaporation or filtration

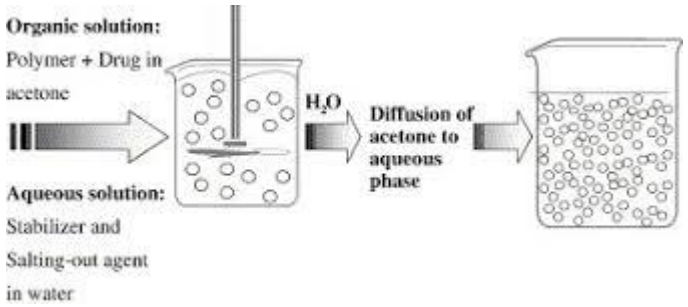

Figure 4: Emulsification or solvent diffusion

Salting out

It can be considered as the modification of emulsification or solvent diffusion methods. Here theseparation of water miscible solvent from aqueous solution via salting out effect have been occurred.. Initially drug and polymer are dissolved in a solvent such as acetone, which is then emulsified in to an aqueous gel containing the salting out agent (electrolyte such as magnesium chloride, calciumchloride, and magnesium acetate ornon-electrolyte such assucrose and) and a colloidal stabilizer such as polyvinylpyrrolidone or hydroxyl ethyl cellulose. This leads to the formation of oil/water emulsion which is further diluted with excess volume of water or aqueous solution to enhance the diffusion of solvent into the aqueousphase, thusinducing the formation of Nano spheres.By cross flow filtration both the solvent and salting out agent are then eliminated.

Advantages

Salting outdoes not require an increase of temperature and therefore, may be useful when heat sensitive substances have to be processed

Disadvantages

Limited application to lipophilic drug and the extensive nanoparticle washing steps[12].

Supercritical fluid technology

Above mentioned methods use organic solvents which are hazardous to environment as well as to physiological systems. Therefore it is necessary to obtain suitable technology to avoid the usage of organic solvents or any other ingredient hazardous to health. Since super-critical fluids are environmentally safe, therefore,the supercritical fluid technology has been investigated as an alternative to prepare biodegradable micro-and nanoparticles. Thistechnique uses environmentally friendly solvents with the potential to produce polymeric nanoparticles. Mainly it requires specially designed equipment and is more expensive. Supercritical fluids are those fluid which are at a temperature above its critical temperature remains in a single phase regardless of pressure. Supercritical fluids exhibit properties intermediate between those of liquid and gases such as low viscosity , low density, high solvating power, high diffusivities, and high mass transfer rates above the critical point. Some of the methods under supercritical fluid technology such as rapid expansion

from supercritical solution, gas supercritical anti -solvent precipitation, aerosol solvent extraction.

Preparation of nanoparticles by polymerization

Emulsion polymerization

It is one of the fastest methods for nanoparticle preparation. The core material is dissolved into polymerization solution. The monomers are polymerized to form capsules in an aqueous solution. Polyacrylamide Nano spherescan be produced by this method. The main advantages of this method is nanocapsles with narrow size distribution can be obtained. The main disadvantages of this method is it require toxic organic solvent, surfactant, and difficulty in controlling the capsule formation (polymerization process) [13].

Interfacial polymerization

It is one of the widely used method for the preparation of polymeric nanoparticles. It involves polymerization of two reactive monomers or agents which are dissolved respectively in two phases(continuous and dispersed phase). The reaction takes placeat the interface of the two liquids. Nanomer sized hollow polymer particles were

synthesized by employing interfacial cross-linking reactions as poly-addition and poly-condensation or radical polymerization. To promote Nano capsule formation, the use of aprotic solvents, such as acetone and acetonitrile was used.Protic solvent such as ethanol, n-butanol and isopropanol were found to induce the formation of Nano spheres in addition to Nano capsules[14]

Ionic gelation or cocervation of hydrophilic polymers

This method is used for the preparation of hydrophilic polymer based nanoparticles. Biodegradable hydrophilic polymers include chitosan, gelatin and sodium alginate. Coating material with dissolved core material is extruded as drops within an ionic solution.This method is based on the strong electrostatic interaction to form coacervates with a size in the range of nanomer. This strong electrostatic interaction between two aqueous phase results in the formation of coacervate. In ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature (Figure5)

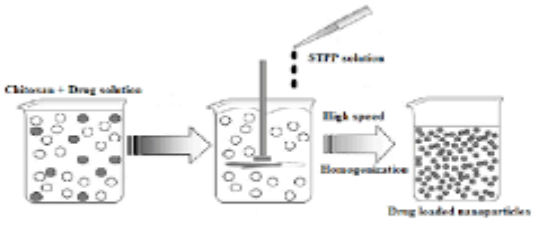

Figure 5: Ionic gelation method

CHARACTERIZATION OF NANOPARTICLES

Characterization of nanoparticles are primarily evaluated by the particle size and morphology, surface charge, release profile, drug stability.[15]

1. Particle size and morphology

It is the most important parameters of nanoparticles. Smaller the particle size of nanoparticles, larger the surface area and hence faster the drug release.

Photon correlation spectroscopy/dynamic light scattering analysis

It is the most commonly used to analyse the nanoparticles. In this teqnique solution of spherical particles in Brownian motion causes a Doppler shift when they are exposed against shining monochromatic light (laser).Such monochromatic light exposure hits the moving particles which results in change in wavelength of incominglight. Extent of this change in wavelength determines the size of the particles.

Electron microscopy

Scanning electron microscopy (SEM)

It is the type of electron microscope that images a sample by scanning it with high energy beam of electron in faster scan pattern .the electron interact with the atom that make up the sample producing a signal that contain information about the samples, surface topo graph, composition and other properties. During the process of SEM characterization, solution of nanoparticles should be initially converted into dry powder. The particles based on organic and non-conductive material they require gold coating (thickness-30-50 nm).Thus determined size should be denoted as gold coated particle size rather than as particle size.

Transmission electron microscopy (TEM)

The crystalline sample interacts with the electron being mostly by diffraction rather than by absorption. The intensity of the diffraction depends on the orientation of the plain of atoms in crystal relative to the electron beam. A high contrast image can be formed by blocking deflected electron intensity that reveals information on the crystal structure. This can generate both bright and light field images. Transmission electron microscopy techniques can provide imaging, diffraction and spectroscopic information, either simultaneously or in a serial manner, of the specimen with an atomic or a sub-nanometer special resolution.[16]

2. Surface charge

The nature and intensity of the surface charge determines the interaction of nanoparticles with the biological environment as well as their electrostatic interaction with bioactive compound. Stability of colloidal material usually analyzed through zeta potential of nanoparticle.Zeta potentialis used to measure the surface charge on nanoparticles. The storage stability of colloidal dispersion depends on zeta-potential values. High zeta potential value (either +ve or-ve) are achieved in order to make sure the stability and avoid aggregation of particles. Zeta potential values can be used in evaluating surface hydrophobicity and the nature of material

encapsulated with in the Nano capsule or coated onto the surface.

3. **Surface hydrophobicity**

The surface hydrophobicity of nanoparticles has an important influence on the interaction of colloidal particles with the biological environment. Techniques such as hydrophobic interaction chromatography, biphasic-partitioning,adsorption of probes, contact angle measurements can be utilized for the determination of surface hydrophobicity. Recent advancement in research offers several sophisticated analysis tools for surface property analysis of nanoparticles. Modern techniques such as X-ray photon correlation spectroscopy not only determines surface hydrophobicity but also permit the identification of specific chemical group on the surface of nanoparticles.

4. **Drug release**

It is very essential to determines extend of the drug release and in order to obtain such information most release method require that the drug and its delivery vehicle be separated. Drug loading capacity of the nanoparticle is defined as the amount of the drug bound per mass of polymer or another term it is the moles of drug per mg polymer or mg drug per mg polymer or it could also be given as percentage relative to the polymer. UV spectroscopy or High performance liquid chromatography (HPLC) after ultracentrifugation, ultrafiltration, gel filtration or centrifugal ultrafiltration are used to determine this parameter.[17]

5. **Stability study**

The stability studies are done to evaluate the effect of storage conditions on various physicochemical parameters of Nano encapsulatedformulations. These studies are helpful in determining the suitable storage conditions .The selected Nano encapsulated formulations are subjected to both room temperature and refrigerated temperature for about 6 months and they are assessed for changes in physicochemical parameters.

6.**Encapsulation efficiency**

It is determine indirectly by measurement of the amount of free drug in the supernatant after ultracentrifugation and was calculated according to following equation.

Encapsulation efficiency = amount of total drug – amount of free drug in supernatant *100

Amount of total drug

PHARMACEUTICAL APPLICATIONS

1**. Controlled drug delivery**

Time release drug delivery where the Nano encapsulation material slowly allows the drug to be released into body. The coating material can be customized to determine the rate of delivery. Eg: gelatin nanoparticles are able to encapsulate water soluble protein drug for the prolonged drug release in a controlled manner.[18]

2**. Targeted drug delivery**

Nano encapsulation of drug or small molecules in Nano carriers is a very promising approach for nanomedicine. Modern drug encapsulation methods allow efficient loading of drug molecules inside the Nano carriers there by reducing the systemic toxicity associated with drugs. Targeted drug delivery systems that release the drug only when the drug has arrived at the site in the body when it is required. Targeting ofNano carriers can enhance the accumulation of Nano encapsulated drug at the diseased site.

3.Nano encapsulation in food industry

The Nano encapsulation is rapidly expanding technology in the food industry. The encapsulating layer forming a protective layer on the food or flavor molecules. An increase in surface area leads to the enhancement of bioavailability of food and flavors which have low solubility. It also improving the solubility of poorly water soluble ingredients. They are optically transparent and are useful in beverage applications.[19]

4. Pestcontrol

The Nano encapsulation technology aim to reduce the direct usage of pesticides, and ensure their safe application. The Nano pesticides shows increased solubility of poorly soluble ingredient and release the active ingredient in slow and targeted manner and also protect the active ingredient in premature degradation.eg: nanohexaconaxole is 5 times more effective in controlling pathogen as compared to water dispersible powdered form.[20]

5. Nano encapsulation for nutrient delivery

Nutraceuticals are substance that are placed in food to enhance nutrition.Nano encapsulation technology select the nutrient based on the less solubility in water which includes vitamins and antioxidants such as omega-3-ftty acids,carotenoids,curcumin, green tea ,polyphenols are used for nanoencapsulation.The Nano encapsulation technology could make the delivery of vitamins and other nutrients to the body much more efficient effectively by adding tiny vitamin tablets to our food. These must prevent the chemical degradation or oxidation and it can easily incorporated in to food products without changing the texture, flavor and appearance and shows targeted and controlled release properties.Eg:Nano capsule containing tuna oil incorporated in to bread products which avoid the unpleasant taste of tuna oil.

6. Ethyl alcohol absorption

It involves the encapsulation of digestive enzymes within a non-toxic polymer shell. The enzyme filled Nano shell has been proven in lab mice to absorb ethyl alcohol from the blood stream, therefore resulting in reduced blood alcohol levels .It has been concluded that the particle act as organells,which proposes other benefits to enzyme therapies.[21]

7. Anticanceractivity

Nano encapsulated compounds are used for anticancer activity, since they can target the tumor cells.The water soluble polymer shell are mainly created to deliver a protein, apoptin into cancer cells. The protein goes into the nucleus of the cancer cells alone, unlike other therapies as

chemotherapy and genetherapy.They are having the capacity to target the tumors within a healthy tissue.

Eg:anticancer activity of fucoidan nanoparticles

Nano encapsulation of curcumin nanoparticles

CONCLUSION

Nano encapsulation is the coating of various substances within another material at size on the nanoscale. Different methods are available for nanoencapsulation.Among these polymerization method is most commonly used. The polymer, encapsulated drugs and any adjuvant substances used for Nano encapsulationhave a great influence on the drug absorption, biodisrtibution pattern and elimination. Thus Nan encapsulation shows better drug delivery system as a result of their sustained and controlled release properties subcellular size, and biocompatibility with tissues and cells

REFERENCES

Suganya V,anuradha V. Microencapsulation and Nano encapsulation-A review. International journal of clinical research. 2017; 9(3):233-239.

Lopez A,Gavara R and Lagaron J .Bioactive packaging: turning food in to healthier foods through biomaterial. Trends in food science and technology. 2006; 17(10):567-575.

Ezhilarasi P, P Karthik, chhanwalN, chinnaswamy A .Nano encapsulationtechniques for food bioactive components' review.Food and bioprocess technology. 2013; 6(3):628-647.

Jafari S. Nano encapsulation technologies for the food and nutraceutical industries.Journal of nutrition. 2017; 1(3):623-636.

Kumari A, single R, Guliani A and kumarYadav S .Nanoencapsulation for drug delivery.Excli journel.2014; 1(3):265-286.

Reis CP,Neufeld R J, Ribeiro AJ ,Veiga F. Nanoencapsulation – method for preparation of drug loaded polymeric nanoparticles. Nanomedicine. 2006; 2(1):8-21.

Abhilash M. Potential applications of nanoparticles, Int J Pharm Bio Sci. 2010; 1(1):1-11.

Kayser OA, Lernke and trejo NH. The impact of Nano biotechnology on the development of new drug delivery systems.Current pharmaceutical biotechnology.2005; 5(3):16-20.

Augustin MA and Sanguansri P. Nanostructured materials in food industry.Advances in food and nutrition research. 2009; 58(4):183-213.

Sanguansri P and Augustin M A.Nanoscale materials development-a food industry perspective, Trends in food science and technology, 2007; 17(10):547-556.

Mishra B,Patel B B and Tiwari S , Colloidal nanocarriers :a review on formulation technology- types and applications towards targeted drug delivery. Nanomedicine: nanotechnology, biology and medicine. 2010; 6:9-24.

Chong G H,Yunus R,Abdullah N , Choong T S and spotarS.Coating and encapsulation of nanoparticles using super critical antisolvent.American journal of applied sciences.2009;6:1353-1358.

Puglisi G,Fresta M ,Giamonna G ,Ventura CA. Influnece of preparation conditions in poly(ethyl cyanoacrylate) Nano capsule formation .Int J Pharm.1995;125:283-7.

Dustgania A Farahania EV Imanib M Preparation of nanoparticles loaded by dexamethasone sodium phosphate, Iranian J Pharma sci. 2008; 4(2):111-114.

Stoica R, Somogia, RM. Preparation of chitosan tri polyphosphate nanoparticles for the encapsulation of polyphenol extracted from rose hips. Digest material of nanomaterial and biostructure.2013; 8(3):955-963.

Nelson G. Application of microencapsulation in textiles. International Journal of pharmaceutics. 2002; 4(3):55-62.

Kumar A, Singla R, Guliani A, and Kumar Yadav S .Nanoencapsulation for drug delivery. Excli Journal.2014; 13:265-286.

Javier Paredes A, Mariana Asencio C, Juan Manual L, Alberto D, Daniel P.Nano encapsulation in the food industry: Manufacture, applications, and characterization.Journal of food bioengineering and bioprocessing.2016; 1(1):56-79.

Ragaeis M, Hassan Subra A. Nanotechnology for insect pest control. InternationalJournal of science environment and technology.2014; 3(2):528-545.

Nair HB,Yadav VR,Kannapan R,,Chaturvedic MM,,Aggarwal BB. Delivery of Anti-inflammatory nutraceuticals by nanoparticles for the prevention and treatment of cancer. Biochemical pharmacology.2010; 80(12):1833-1843.

Kawasaki EPlayer A.Nanotechnology, nanomedicine, and the development of new effective therapies for cancer.Nanomedicines.2005; 1(1):101-109.