International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1218-1227 www.ijprajournal.com ISSN: 2249-7781

Review: Recent Advancment in Nanoencapsulation

[1] Miss. JyotiUbale, [2] Miss. Pooja Zendekar, [3]Dr.Gajanan Sanap
[1] *Student,* [2] *Assistant professor,* [3] *Principal*
[1] *Department of Pharmacy*
[1] *Late Bhagirathi YashawantraoPathrikar College Of Pharmacy Pathri, Chh. Sambhajinagar, Maharashtra, India 431001*

Submitted: 01-04-2023 Accepted: 10-04-2023

ABSTRACT :
Nan encapsulation is a process of encapsulating substances in nanoparticles. These particles are typically composed of a polymeric or lipid matrix, and can range in size from 1–1000 nm. Nan encapsulation is used to modify the physical and chemical properties of the encapsulated substances, to improve their stability, solubility, and bioavailability, and to facilitate their delivery to a specific target area. Nan encapsulation is a method of encapsulating small molecules, such as drugs, within nanoscale capsules. The capsules are typically made of a biocompatible material and can be designed to release the molecules at a controlled rate. This method of drug delivery has potential applications in improving the efficacy of drugs, reducing their side effects, and increasing their stability. This paper provides an overview of the current state of nano encapsulation technology and discusses its potential applications in the pharmaceutical industry. Nan encapsulation is a process by which active ingredients are surrounded by a nanosized shell to improve the stability, solubility, bioavailability, and other physical and chemical properties of the active ingredient.. The review also examines the application of nanoencapsulation in the food, pharmaceutical, and cosmetics industries, and the potential future developments in the field of nano encapsulation. Nano encapsulation is a process of enclosing active ingredients in a nanoscale delivery system. This technique is used to improve the stability, solubility, and bioavailability of ingredients, and to protect them from the environment. It is also used to control the release rate of the active ingredients.

I. INTRODUCTION:

Nanoencapsulation is defined as the process of encapsulating substances with various coating material at the nano scale range. This technique is primarily used within the pharmaceutical, food and cosmetic industries. Encapsulation is allow to more active compounds are enclosed in an inert material. The substance which are encapsulated that are the core material, filler, internal phase where the encapsulation material is called as a external phase, shell, coating or membrane. (1)

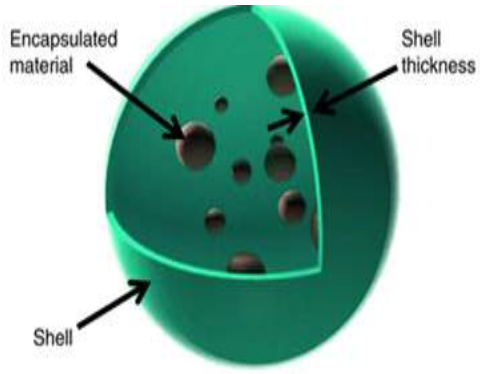

Fig.1 (2)

Nanotechnology has been touted as the next revolution in many industries, including agriculture and food industry. Nanotechnology has been revolutionizing the entire food system from production to processing, storage, and development of innovative materials, products, and applications. The application of nanotechnology to the food sector could generate innovation in the macroscale characteristics of food, such as texture, taste, other sensory attributes, coloring strength, processability, and stability during shelf-life, leading to a great number of new products. Moreover, nanotechnology can also improve the water solubility, thermal stability, and oral bioavailability of bioactive compounds (.(3,4)

Encapsulation: Encapsulation refers to any technological process that allows one or more active compounds to be enclosed within an inert material. Encapsulated substances are therefore protected against harsh environments, such as hydrochloric acid within the stomach, and can also offer a controlled release of drugs. The substance being encapsulated can be referred to as the internal phase, core material, filler or fill, whereas the

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1218-1227 www.ijprajournal.com ISSN: 2249-7781

encapsulation material is known as the external phase, shell, coating or membrane.(5)

Nanoencapsulation: It is a process by which small particles of core materials are packed within a wall material to form capsules. Encapsulation method was employed to protect bioactive compounds (polyphenols, micronutrients, enzyme, antioxidants, and nutraceuticals) and in the finished application to protect them from adverse environment and also for the controlled release at targeted sites (6)

Microencapsulation: Microencapsulation is a similar process to nanoencapsulation that only differs in the size of the particles, which typically range from 1 micrometer (µm) to 1 millimeter (mm), and the fact that it has been utilized for a longer period of time. Microencapsulation has been applied in almost all industrial sectors ranging from agriculture and environment to home and personal care.(7)

Nanocapsule Uniformity: The efficacy of many nanoencapsulated and microencapsulated processes often relies on uniformity in particle size and distribution. The use of supercritical carbon dioxide (CO_2) has shown promising benefits to ensure the optimal design of particle size in both microencapsulated and nanoencapsulated drugs, as well as the ability to control drug loading processes at various temperature, pressure and flow ratio ranges.(8)

Advantages of nanoencapsulation:

1. Nanoencapsulation is attributed to its ability to protect active pharmaceutical ingredients (API) from degradation.
2. Nanoencapsulation has also improved the precision of drug delivery targets by utilizing surface coating or conjugating that ensures adequate cell entry.
3. Nanoencapsulated drugs can be labeled with fluorescent probes for imaging purposes, which is particularly useful for evaluating drug efficiency during preclinical and clinical studies.(9)

Applications of nanoencapsulation: Nanoencapsulation is so widely used is its efficiency in protecting the core material and ultimately releasing the API when required.

Some of the most common applications of nanoencapsulation therefore can be found in:

a. Targeted drug delivery systems that will only release drug upon its arrival at the correct location within the body
b. Nanoencapsulation gives a controlled release in a body. One example of this type of drug delivery system can be found in nasal drug delivery devices.
c. Embedded fragrances for perfumed garments
d. Food additions and enhancements
e. Increased shelf life and stability of over the counter pharmaceutical products, such as vitamins(10)

Techniques of nanoencapsulation:A multitude of techniques are used in nanoencapsulation and as the field is an emerging one, new techniques are constantly being developed. Nanoencapsulation techniques can be categorized as either top-down or bottom-up approaches. When the top-down approach is utilized, precise tools are used to accurately reduce the size and structure of the material, whereas the bottom-up approach involves the use of materials derived from either self-assembly and/or self-organization molecular processes.

Some of the most recent technologies utilized for nanoencapsulation purposes include

a. Nanoencapsulation
b. Nanoliposomes
c. Electrospray
d. Nanostructure Formation through the Use Of Cyclodextrins
e. Solid lipid Nanoparticles
f. Nanostructure Lipid Carriers(11)

II. METHODOLOGY:

Methods of Nanoencapsulation

a. Emulsification technique
b. Coaservation technique
c. Indusioncomplexation technique
d. Nanoprecipitation technique
e. Emulsificationsolvent evaporation technique
f. Supercritical fluid technique
g. Drying technique for producing nanoparticals
1. Spray drying
2. Freeze drying(12)

Emulsification Technique:

Emulsion technology is generally applied for the encapsulation of bioactive compounds in aqueous solutions through the production of nanoemulsions. Nanoemulsions are colloidal dispersions comprising two immiscible liquids, of which one is being dispersed in the other, with droplet sizes ranging from 50 to 1,000 nm (Sanguansri and Augustin 2006).(13)

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1218-1227 www.ijprajournal.com ISSN: 2249-7781

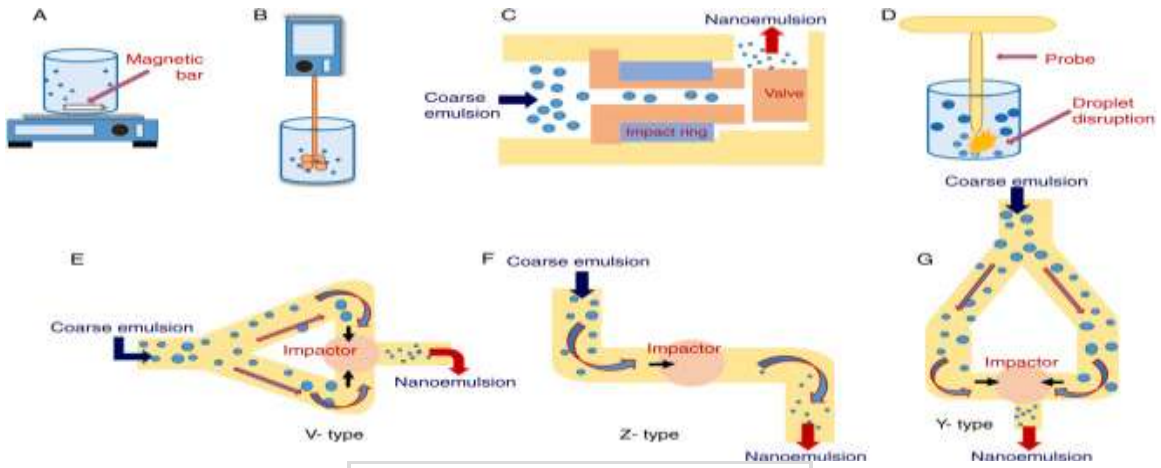

Fig. 2 Emulsification Technique (14)

Emulsification - solvent Evaporastion technique:

Emulsification–solvent evaporation technique is a modified version of solvent evaporation method. It involves emulsification of the polymer solution into an aqueous phase and evaporation of polymer solvent inducing polymer precipitation as nanospheres (Reis et al. 2006)(15). The drug is finely dispersed in the polymer matrix network. The size of the capsules can be controlled by adjusting the stir rate, type and amount of dispersing agent, viscosity of organic and aqueous phases, and temperature (Tice and Gilley 1985)(16). Frequently used polymers are PLA, PLGA, ethyl cellulose, cellulose acetate phthalate, PCL, and poly (h-hydroxybutyrate). In order to produce a small particle size, often high-speed homogenization or ultrasonication may be employed (Zambaux et al. 1998). Sowasod et al. (2008) encapsulated curcumin in chitosan by cross-linking with tripolyphosphate using multiple emulsion/solvent technique along with freeze drying technique. The obtained nanocapsules were spherical in shape and the particle sizes were ranging from 254 to 415 nm.(17)

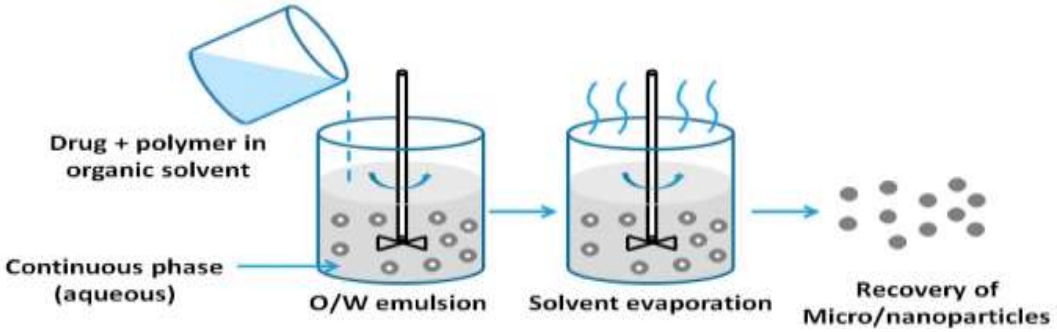

Fig. 3 Emulsification solvent evaporation (18)

Coacervation Technique :

Coacervation The coacervation technique involves the phase separation of a single or a mixture of polyelectrolyte from a solution and the subsequent deposition of the newly formed coacervate phase around the active ingredient. Further, a hydrocolloid shell can be cross-linked using an appropriate chemical or enzymatic cross-linker such as glutaraldehyde or transglutaminase, mainly to increase the robustness of the coacervate (Zuidam and Shimoni 2010)(19). Based on the number of polymer type used, the process can be termed as simple coacervation (only one type of polymer) and complex coacervation (two or more types of polymer)(20). Many factors including the biopolymer type (molar mass, flexibility, and charge), pH, ionic strength, concentration, and the ratio of the biopolymers affect the power of the interaction between the biopolymers and the nature of the complex formed (Tolstoguzov 2003; De Kruif et al. Turgeon et al.(21)

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1218-1227 www.ijprajournal.com ISSN: 2249-7781

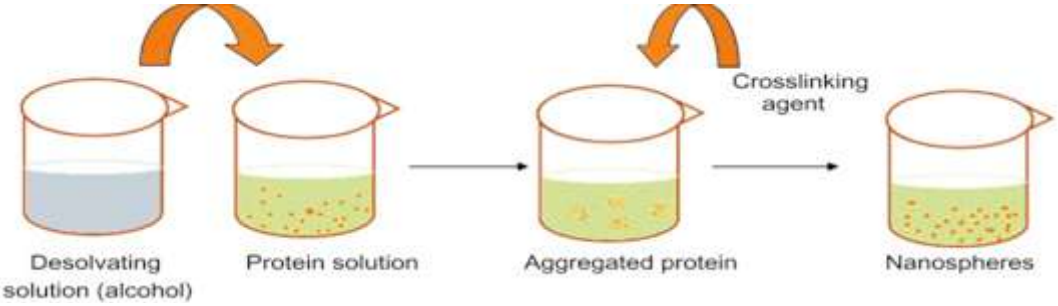

fig. 4coaservation technique : (22)

Nanoprecipitation technique :

Nanoprecipitationcoacervation involves aqueous solvents and gentle processing conditions and therefore is ideal for maintaining the stability of proteins and peptides. This method utilizes the physicochemical property of polysaccharides. Chitosan is insoluble in alkaline pH medium, however, it precipitates coacervates when it comes in contact with an alkaline solution. Particles are produced by blowing chitosan solution into an alkali solution like sodium hydroxide, NaOH-methanol, or ethanediamine using a compressed air nozzle to form coacervate droplets.

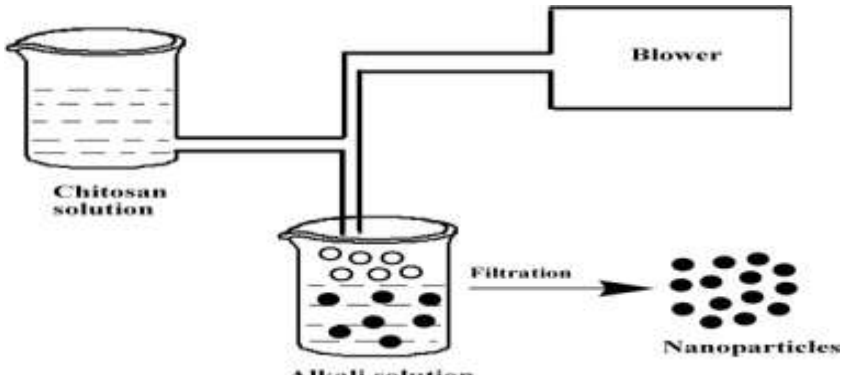

Fig. 5 Nano precipitation technique (23)

Drying technique for producing nanoparticals :

1) Spray drying:

Spray drying is a well-established technique with a long history of use in a variety of fields (e.g., foods and chemicals). The use of spray drying for the pharmaceutical industry dates to the early 20th century when it was used for the drying of blood(24). Since then, it has been employed for various pharmaceutical applications including formation of amorphous solid dispersions, encapsulation of drugs and essential oils in excipient matrices, and spray drying of biopharmaceuticals (e.g., proteins, vaccines, Deoxyribonucleic Acid (DNA), antibodies) (**25**).

Spray drying is widely applied to produce pharmaceutical powders with particle size ranging from the nanometre to the micrometre scale . It has been extensively used for the production of inhalation particles as it allows manipulation and control of properties such as particle size distribution, shape, density, flowability, moisture content, crystallinity and dispersibility of the powders (26).

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1218-1227 www.ijprajournal.com ISSN: 2249-7781

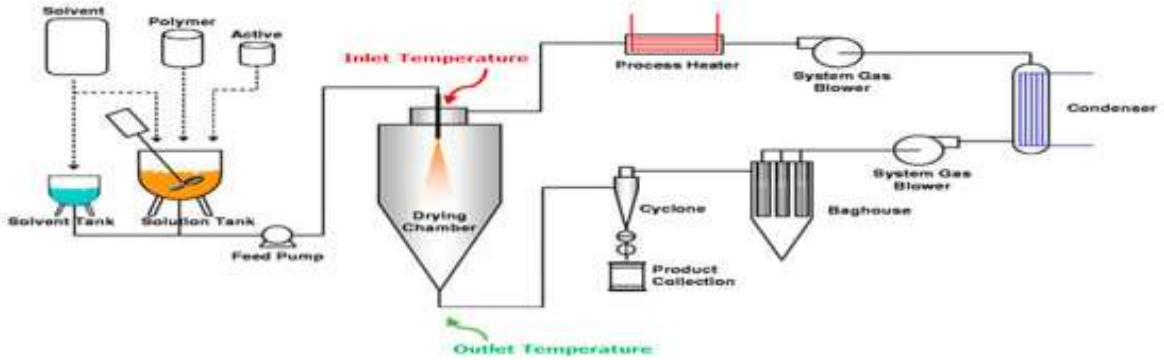

Fig. 6 Schematic representation of spray dryer instrumentation. Reproduced, with permission (27)

2)Freeze drying:

Freeze Drying is a process in which a completely frozen sample is placed under a vacuum in order to remove water or other solvents from the sample, allowing the ice to change directly from a solid to a vapor without passing through a liquid phase. This process, called sublimation, along with the minimal heat input that is required, is ideal because of the long-term preservation properties it provides to the integrity of the sample's biological and chemical structure. Lyophilization can be achieved in various volumes, from small at-home freeze dryers all the way up to large, production-scale equipment (28) .

Fig.7 Schematic representation of freeze dryer (29)

Carriers of nanoencapsulation :

1. Liposomes
2. Niosomes
3. Nanoparticles
4. Monoclonal Antibodies (30)

Liposomes :

Liposome was first discovered in the early 1965 by Alec D. Bangham which is derived from the Greek word, where lipo means "fatty" constitution and soma means "structure". Liposome are relatively small in size and it ranges from 50 nm to several micrometres in diameter. These are spherical vesicle in which aqueous core is entirely enclosed by one or more phospholipid bilayers. It having the unique ability to entrap both lipophilic and hydrophilic compounds. The hydrophobic or lipophilic molecules are inserted into the bilayer membrane, whereas hydrophilic molecules can be entrapped in the aqueous centre (31).

ADVANTAGES:

- Suitable for delivery of hydrophobic (e.g. amphotericin B) hydrophilic (e.g. cytrabine) and amphipathic agents.
- Liposome increases efficacy and therapeutic index of drug (actinomycin-D)
- Liposome increase stability via encapsulation
- Suitable for targeted drug delivery v. Suitable to give localized action in particular tissue
- Suitable to administer via various routes (32)

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1218-1227 www.ijprajournal.com ISSN: 2249-7781

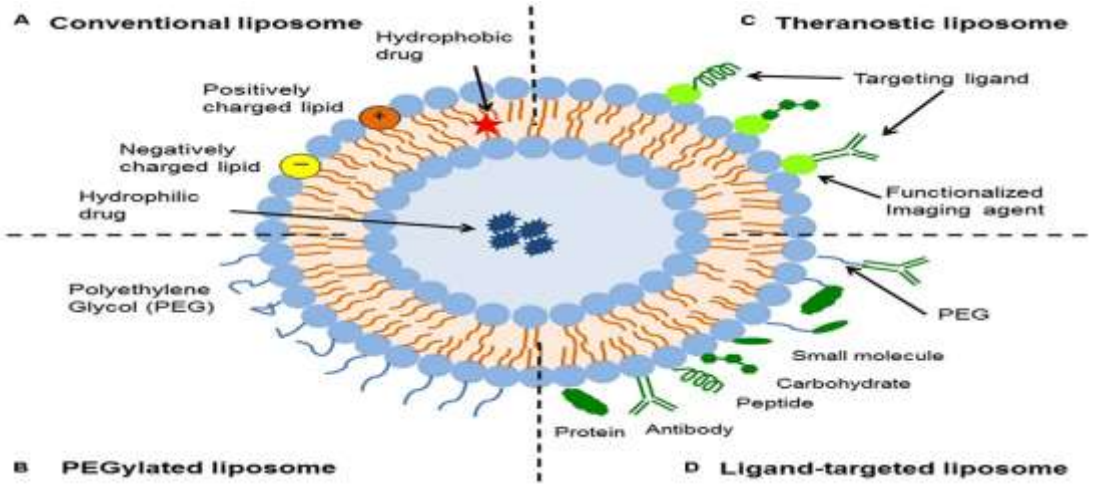

FIG. 8 Schematic representation of the different types of liposomal drug delivery system(33)

Niosomes:

Niosomes are one of the best among these carriers. The self-assembly of non-ionic surfactants into vesicles was first reported in the 70s by researchers in the cosmetic industry. Niosomes (non-ionic surfactant vesicles) obtained on hydration are microscopic lamellar structures formed upon combining non-ionic surfactant of the alkyl or dialkylpolyglycerol ether class with cholesterol.(34) The non-ionic surfactants form a closed bilayer vesicle in aqueous media based on its amphiphilic nature using some energy for instance heat, physical agitation to form this structure. The properties of the vesicles can be changed by varying the composition of the vesicles, size, lamellarity, tapped volume, surface charge and concentration. The stability of niosomes are affected by type of surfactant, nature of encapsulated drug, storage temperature, detergents, use of membrane spanning lipids, the interfacial polymerisation of surfactant monomers in situ, inclusion of charged molecule.(35)

Table 1 Effect of the nature of drug on the formation of niosomes(36)

Nature of the drug	Leakage from the vesicle	Stability	Other properties
Hydrophobic drug	Decreased	Increased	Improved trans-dermal delivery
Hydrophilic drug	Increased	Decreased	–
Amphiphilic drug	Decreased	–	Increased encapsulation, altered electrophoretic mobility
Macromolecule	Decreased	Increased	–

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1218-1227 www.ijprajournal.com ISSN: 2249-7781

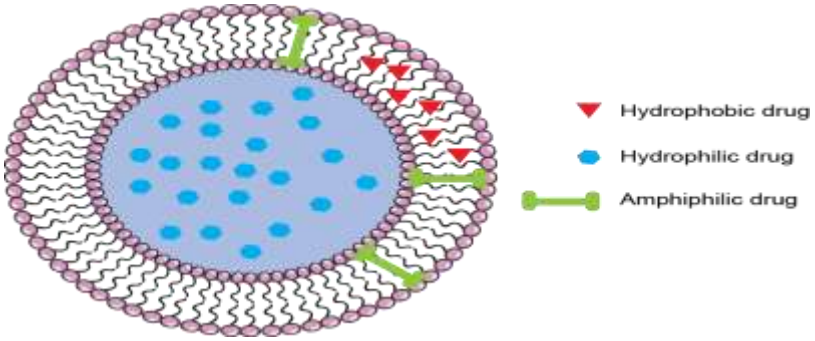

Fig. 9: Schematic representation of a Niosome(37)

Nanoparticle :

Nanoparticles (NPs) and nanostructured materials (NSMs) represent an active area of research and a techno-economic sector with full expansion in many application domains. NPs and NSMs have gained prominence in technological advancements due to their tunable physicochemical characteristics such as melting point, wettability, electrical and thermal conductivity, catalytic activity, light absorption and scattering resulting in enhanced performance over their bulk counterparts. A nanometer (nm) is an International System of Units (Système international d'unités, SI) unit that represents 10^{-9} meter in length. In principle, NMs are described as materials with length of 1–1000 nm in at least one dimension; however, they are commonly defined to be of diameter in the range of 1 to 100 nm. Today, there are several pieces of legislation in the European Union (EU) and USA with specific references to NMs. However, a single internationally accepted definition for NMs does not exist. Different organizations have a difference in opinion in defining NMs.(38) According to the Environmental Protection Agency (EPA), "NMs can exhibit unique properties dissimilar than the equivalent chemical compound in a larger dimension" .(39)

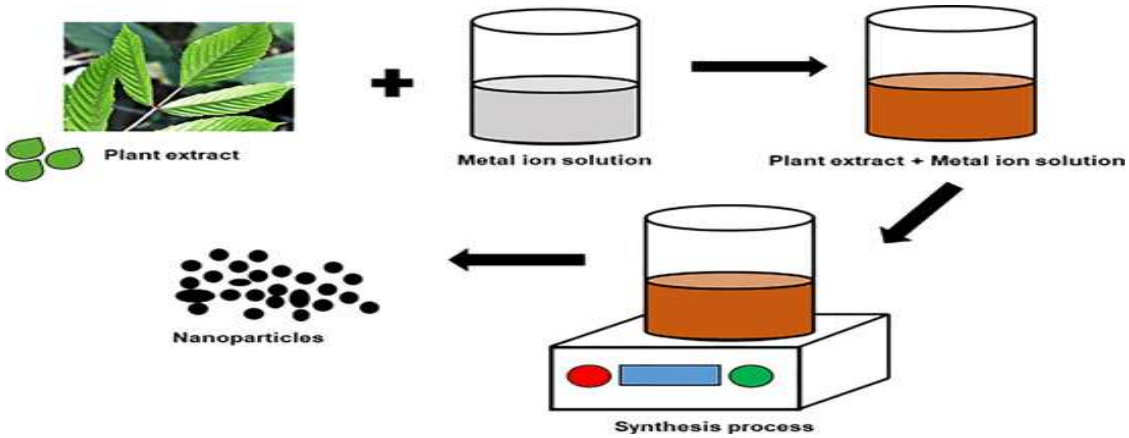

Fig. 10 Schematic diagram of green synthesis of nanoparticles. (40)

Monoclonal Antibodies :

The immune system functions by distinguishing self from non-self and has evolved a number of mechanisms related to removing non-self or foreign elements. Non-self is usually defined as invasive pathogenic organisms, such as bacteria, fungi, protozoa and viruses, but can also be considered as altered-self, such as virally-infected cells or the aberrant growth of cells, such as seen with cancer. The components of the immune system are many and varied with many pathways of stimulation, maintenance and function, but the system designed to detect and remove predominantlyn extracellular targets or antigens are the antibodies.Antibodies are a family of glycoproteins with exquisitelyunspecific binding properties that have evolved to become anmajor protective mechanism in neutralizing potentially harmful pathogens and molecules.(41)

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1218-1227 www.ijprajournal.com ISSN: 2249-7781

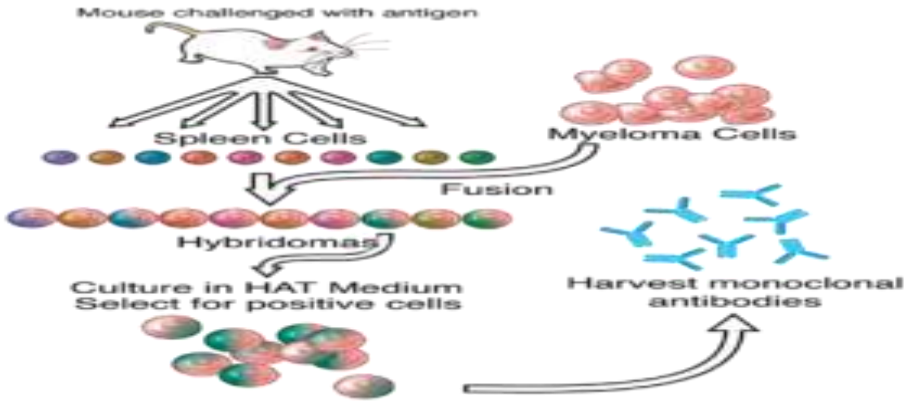

Fig. 11 Monoclonal antibodies(42)

III. CONCLUSION:

We verified that the review's principal method used in the nanoencapsulation of NA applied in food is emulsification. We believe that this fact is related.

- To the mainly hydrophobic characteristic of NA, especially the EO,
- To the different ways (high and low energy) for obtaining emulsions ,
- To the fact that they demonstrate a certain ease in penetrating the bacterial cell membrane.

At the end of the nanoencapsulation process, factors such as EE, particle size and homogeneous distribution, stability, and resulting charge are essential for the nanoencapsulated NA's antimicrobial activity. They are often not analyzed in the studies. Lipids, proteins, polysaccharides, and carbohydrates are provided to be the most common food-grade materials used as wall material in an NA nanoencapsulation system. These materials are inexpensive, non-toxic, and compatible with food formulations. However, there is still no consensus as to which wall material is best, as it will depend on the nanoencapsulation process, the core material, and the food to be inserted. In large part, the NA does not act with a single mechanism but a set of mechanisms inhibiting and even destroying the microbial cell. Although the action of free NA can be faster, immediate, it is precisely the slow and controlled release of NA from nanostructures that makes it able to act throughout the food shelf life.

REFERENCE:

[1]. "Encapsulation technologies: A general overview" – Capsulae
[2]. https://link.springer.com/referenceworkentry/10.1007/978-94-007-6178-0_50-2/figures/1.
[3]. Leong, T. S. H., Wooster, T. J., Kentish, S. E., &Ashokkumar, M. (2009). Minimising oil droplet size using ultrasonic emulsification. UltrasonicsSonochemis
[4]. Silva, H. D., Cerqueira, M. A., & Vicente, A. A. (2012). Nanoemulsions for food applications: development and characterization. Food Biopro
[5]. www.azonano.com/article.aspx?ArticleID=1875
[6]. "Encapsulation technologies: A general overview" – Capsulae
[7]. Anuradha, V. (2017). Microencapsulation and Nanoencapsulation: A Review. International Journal of Pharmaceutical and Clinical Research 9(3); 233-239. DOI: 10.25258/ijpcr.v9i3.8324.7. Suganya, V., &
[8]. Guterres, S. S. (2009). Spray drying technique to prepare innovative nanoparticlulated formulations for drug administration: a brief overview. Brazilian Journal of Physics, 39, 205–209.
[9]. Soh, S. H., Lee, L. Y. (2019). Microencapsulation and Nanoencapsulation Using Supercritical Fluid (SCF) Techniques. Pharmaceutics 11(21). DOI: 10.3390/pharmaceutics11010021.
[10]. Jafari, S. M. (2017). An overview of nanoencapsulation techniques and their classification. Nanoencapsulation Technologies for the Food and

Nutraceutical Industries. DOI: 10.1016/B978-0-12-809436-5.00001-X.
[11]. "Nanoencapsulation Techniques" – Microfluidics
[12]. Mukerjee, A., &Vishwanatha, J. K. (2009). Formulation, characterization and evaluation of curcumin loaded PLGA nanosphere for cancer therapy. Journal of Anticancer Research, 29(10), 3867– 3875.
[13]. Sekhon, B. S. (2010). Food nanotechnology—an overview.Nanotechnology, Science and Applications, 3(10).
[14]. https://www.sciencedirect.com/topics/food-science/emulsification
[15]. Royal Society. (2004). Nanoscience and nanotechnologies: opportunities and uncertainties. July 2004. Available at: http://www.nanotec.org.uk/ finalReport.htm
[16]. Silva, H. D., Cerqueira, M. A., & Vicente, A. A. (2012). Nanoemulsions for food applications: development and characterization. Food
[17]. Zuidam, N. J., &Shimoni, E. (2010). Overview of microencapsulation use in food products or processes and methods to make them. In N. J. Zuidam& V. A. Nedovic (Eds.), Encapsulation technique for active food ingredients and food processing (pp. 3–29). New York: Springer
[18]. https://www.researchgate.net/figure/Preparation-of-NPs-by-emulsion-evaporation-method_fig4_292671903
[19]. Xing, F., Cheng, G., Yi, K., & Ma, L. (2004). Nanoencapsulation of capsaicin by complex coacervationgelatin, acacia, and tannins. Journal of Applied Polymer Science, 96(6), 2225–2229.
[20]. De Paz, E., Martin, A., Estrella, A., Rodriguez-Rojo, S., Matias, A. A., Duarte, C. M. M., &Cocero, M. J. (2012). Formulation of βcarotene by precipitation from pressurized ethyl acetate-on water emulsions for application as natural colorant. Food Hydrocolloid, 26(1), 17–27
[21]. Zimet, P., &Livney, Y. D. (2009). Beta-lactoglobulin and its nanocomplexes with pectin as vehicles for ω-3 polyunsaturated fatty acids. Food Hydrocolloid, 23(4), 1120–1126.
[22]. https://www.sciencedirect.com/topics/chemistry/coacervation
[23]. Copyright © 2022 Elsevier B.V. or its licensors or contributors. ScienceDirect® is a registered trademark of Elsevier B.V.
[24]. Vehring, R.; Snyder, H.; Lechuga-Ballesteros, D. Spray drying. In Drying Technologies for Biotechnology and Pharmaceutical Applications, 1st ed.; Ohtake, S., Izutsu, K., Lechuga-Ballesteros, D., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2020; pp. 179–216. [**Google Scholar**]
[25]. Partheniadis, I.; Karakasidou, P.; Vergkizi, S.; Nikolakakis, I. Spectroscopic examination and release of microencapsulated oregano essential oil. AdmetDmpk **2017**, 5, 224–233. [**Google Scholar**] [**CrossRef**][**Green Version**]
[26]. Vehring, R. Pharmaceutical particle engineering via spray drying. Pharm. Res. **2008**, 25, 999–1022. [**Google Scholar**] [**CrossRef**][**Green Version**]
[27]. Dobry, D.E.; Settell, D.M.; Baumann, J.M.; Ray, R.J.; Graham, L.J.; Beyerinck, R.A. A model-based methodology for spray-drying process development. J. Pharm. Innov. **2009**, 4, 133–142. [**Google Scholar**] [**CrossRef**] [**PubMed**][**Green Version**]
[28]. https://www.labconco.com/articles/introduction-to-freeze-drying
[29]. https://www.google.com/search?q=freeze+drying+in+nanoencapsulation+techniques&sxsrf=ALiCzsav8spi6K76uMIZyCoyQpOSKe2jxw:1671007416958&source=lnms&tbm=isch&sa=X&ved=2ahUKEwj_zITc2_j7AhU_sVYBHQd1AwcQ_AUoAXoECAIQAw&biw=1034&bih=620&dpr=1#imgrc=f9aGxXNJkg0ZVM&imgdii=HJQF1Zv7MT6yhM
[30]. SP Vyas Roop K KharSonal Vyas CBS Publisher & Distributors Pvt Ltd
[31]. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. In RoopKhar, Vyas SP, Farhan A, Jain Gaurav, editors. Novel Drug Delivery Systems, 3 rd, Varghese Publishing House; 2014. p. 872-906
[32]. Lasi DD, Applications of Liposomes. In Lipowsky R, Sackmann E, editors.Volume 1, 2014.p. 493-94.
[33]. Sercombe, L., Veerati, T., Moheimani, F., Wu, S. Y., Sood, A. K., and Hua, S. (2015). Advances and challenges of

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1218-1227 www.ijprajournal.com ISSN: 2249-7781

liposome assisted drug delivery. Front. Pharmacol. 6:286. doi: 10.3389/fphar.2015.00286

[34]. Malhotra M, Jain NK. Niosomes as drug carriers. Indian Drugs. 1994;31:81–6. [Google Scholar]

[35]. Udupa N. Niosomes as drug carriers. In: Jain NK, editor. Controlled and novel drug delivery. 1st edition. New Delhi: CBS Publishers and Distributors; 2002. [Google Scholar]

[36]. Yoshioka T, Stermberg B, Florence AT. Preparation and properties of vesicles (niosomes) of sobitan monoesters (Span 20, 40, 60, and 80) and a sorbitantriester (Span 85) Int J Pharm. 1994;105:1–6. [Google Scholar]

[37]. Giddi HS, Arunagirinathan MA, Bellare JR. Self-assembled surfactant nano-structures are important in drug delivery: a review. Indian J ExpBiol 2007;45:133-59.

[38]. Boverhof, D. R.; Bramante, C. M.; Butala, J. H.; Clancy, S. F.; Lafranconi, M.; West, J.; Gordon, S. C. Regul. Toxicol. Pharmacol. **2015,** 73, 137–150. doi:10.1016/j.yrtph.2015.06.001 Return to citation in text:

[39]. United Nations. Questions About Nanotechnology. 2012; https://www.epa.gov/chemical-research/research-nanomaterials (accessed Aug 21, 2014). Return to citation in text:

[40]. https://www.researchgate.net/figure/Schematic-diagram-of-green-synthesis-of-nanoparticles-For-interpretation-of-the_fig3_350780814

[41]. Janeway CA, Travers P, Walport M, Shlomchik M. Immunobiology: The immune system in health and disease (5th ed). Garland Science: New York 2001.

[42]. Cytochrome P450 Mediated Drug and Carcinogen Metabolism using Monoclonal Antibodies". home.ccr.cancer.gov. Retrieved 2 April 2018.