NANOFORMULATION DEVELOPMENT

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Abstract:

The conventional drug delivery system has some limitations due to its less stability and more toxicity Therefore to overcome such problems the nanofomulations are developed. The Nano formulations are intended to improve the drug stability, drug solubility of drug in blood. The current article emphasizes on the Nanofomulations, its significance and types of nanoparticles, different types of drug delivery system. Liposomes, method of preparations of liposomes, Micelles, Types of micelles, Dendrimers, Cubosomes, Polymer nanoparticles, Solid lipid nanoparticles, small Nano carriers, Recently, many researcher did work on Nano formulation development like Nanosuspension of pyrazolone derivative, Nano formulation development to improve the bioavailability of fiestin flavonoid, Rifampicin loaded nanoparticles, Smart nanoparticles for treatment of cancer. Moreover, they have application in diagnosis of diseases, Medical field and treatment of Cancer therefore nanoformulation development are needed for the ease and rapid delivery of drug and it enhances the therapeutic potential in the disease conditions.

Keywords: Nano formulations, Types, Recent advancement, Applications

Introduction:

The Nanotechnology has attained more attention as it has applications in food, industries, Cosmetics, medicines. The nanotechnology has its origin from the material science. The Nano sensors, drones are being used in the manufacturing company for improving the quality of nanomaterial'. The recently the nanotechnology provides the way of delivery of drugs and how to improve its delivery in the food industry.[1]

Nano formulations are intended to improve the drug stability, improve the solubility of drug in the blood. The Nano formulations are target specific as the small size of the nanoparticles leading to the better penetration through the skin hence the nanoparticles produce the better therapeutic effect.

The Nanofomulations would be better than the conventional drug delivery system. The conventional drug delivery system may give toxic effect and have less stability, less efficacy. Whereas in case of the nanofomulations have less toxicity and more stability, increases the therapeutic efficacy of drugs. The

main challenge of Nano formulations is reproducibility and cost. The different Nano formulations may have different cost. Nanomaterial's sizes ranges from 1-20 micron the nanomaterial's are used to increase the stability of compound, The Nanomaterial's are categorized into two categories like metal-based nanoparticles, organic nanoparticles, inorganic nanoparticles Nanomaterial's have been used in the different fields like medicines, diagnosis of various diseases, and regenerative therapy.

Nanoparticles like doxil (Doxorubicin) have vital role in the treatment of cancer. The paclitaxel loaded drug used in the treatment cancer due to high solubility, good therapeutic effect than the free paclitaxel drug.

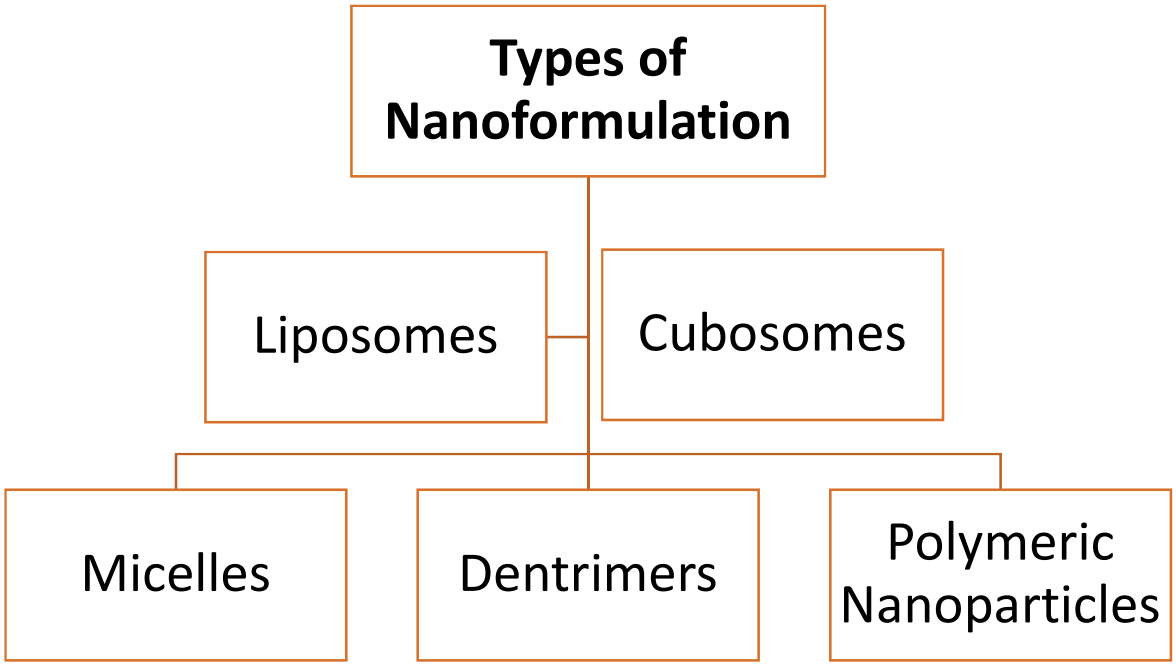
Types of nanoparticles

Organic Nanoparticles

- Solid Lipid Nanoparticles
- Liposomes

Inorganic Nanoparticles

- Chitosan based nanoparticle
- Metal nanoparticles
- Metal oxide nanoparticles
- Carbon based Nanoparticles



Liposomes are the Nano formulations consist of hydrophilic and lipophilic moieties for targeted drug delivery system.

The liposomes are categorized into different classes like unilamellar, multilamellar.

The liposomes were discovered in 1960 by Alec Bangham. The Liposomes are widely used in the cosmetic and Pharmaceutical industry. It is intended as a drug delivery system at the targeted site. The liposomes are vesicles which are made up of the lipids mimic the structure as like the cell membrane[2]

The liposomes are of different types like charged liposomes, conventional, stealth stable, actively targeted liposomes, stimuli responsive liposomes, bubble liposomes.

- **Charged liposomes[2]**

The oleic acid is most commonly used to prepare the anionic and cationic liposomes as it has more stability as compared to the conventional liposomes. The anionic and cationic surfactant are repel from each other hence the less chances of agglomeration. Cationic liposomes are specifically used in the gene therapy as it easily encapsulates the nucleic acid by the electrostatic attraction. Anionic liposomes are delivered through the transdermal delivery system as it easily penetrates to the stratum cornea of skin. And it is less stable that the cationic surfactant.

- **Conventional Liposomes**

Many researchers did work on the liposome synthesis with or without the cholesterol.

The Cholesterol provides the rigidity to the membrane, and increase the fluidity of the liposomes the cholesterol has vital role in order to provide the rigidity to the membrane and decreases in the fluidity of liposomal membrane but the depending upon the properties and nature of Phospholipid it affects the liposomal stability. Conventional liposomes have short blood circulation time due to its elimination through spleen.

Liposomes

The liposomes are vesicular drug delivery system. The liposomes are prepared by the different methods which are as follows

- Thin Film hydration techniques
- Solvent Injection Method
- Ether injection method

Thin film hydration method

The method in which the Phospholipid dissolved in the organic solvent like chloroform and dichloromethane allow to evaporate. If the small volume of solution, the nitrogen gas is used for the evaporation but if the large volume of solution, the rotary evaporator is used. Once the evaporation completed the hydration process with addition of distilled water, into aqueous buffer solution and thin film of lipid is attached to the vessel. The stirring is necessary for the detachment of lipid from the vessel.

Solvent Injection Method

The method in which the organic lipid phase injected into the aqueous phase like solvent ether or ethanol were added into the aqueous phase for the preparation of Nanofomulations.

Ethanol injection method

The method in which the lipid is dissolved in ethanol and mixed with the preheated tris Buffer or distilled water. The aqueous phase mixed with the lipid phase. The rapid aqueous solution favors the solubility of lipid. Finally the encapsulation of organic phase with aqueous phase. The formation of vesicles.

- ## Micelle

The micelle are amphipathic molecules composed of lipophilic and hydrophilic molecules which are soluble in water. It is spherical in shape, sometimes they are available in the cylindrical, ellipsoids in shape.

Structure of Micelle

Micelles are having different size ranges from 5-100 nm in diameter. The micelle is amphiphilic surfactant which are agglomerate in the water.

The critical micelle concentration is required for the formation of Micelles. The micelles are formed by dehydration of hydrophobic tails mechanism furthermore the micelles are formed by the Vander wall forces of attraction.

- **Types of Micelles[4]**
- Polymeric micelle
- The polymeric micelles

It consists of surfactant with the low critical micellar concentration. The low CMC leading to the micelles reaches to the systemic circulation and at the site of action.

The block polymer is attached with two or more chain of polymer. The block polymer is divided into different classes like di block, tri block copolymer which are linked together.

The polymeric micelle contains the hydrophilic and hydrophobic moieties like polyvinyl and polyesters and polyether are used as core compound moreover the other core compounds have been used like propylene oxide and poloxamer.

- Lipid Micelle
- Hybrid polymeric lipid micelle
- Hybrid micelle with metal nanoparticle
- Drug loaded micelles
- The drug loaded micelles have taken more attention in the chemotherapy. As the doxorubicin and paclitaxel are recently invented and approved for the cancer treatment so the doxorubicin and paclitaxel loaded drugs have been widely used for the chemotherapy of cancer.

The various methods used for the preparation of drug loaded micelles like oil in water, water in oil in water emulsion, Co-solvency, Lyophilization, co-solvent evaporation method.

The Co-solvency, Lyophilization, co-solvent evaporation method is most often used for the encapsulation of lipophilic drugs whereas the water in oil water emulsion method mostly preferred for the synthesis of the encapsulation of hydrophilic compounds.

The micelles which have been approved for the cancer of different organs like NK105 contains the Paclitaxel having the 85nm size which is commonly used for breast and gastric cancer, the NK012 contains the SN-38 having 20 nm size used in treatment of triple negative breast cancer furthermore, NK911 drug having the 40 nm size which have potential role in the cancer of solid tumors, NK6004

drug having the 20 nm size, which is used a carrier for the treatment of pancreas cancer. The Micelles characterized by using the Nuclear magnetic resonance, Infrared spectroscopy, Mass spectroscopy.

Dendrimers[5]

The dendrimers are spherical nanoparticle which consist of inner and outer layer with the small branches like tree. The Dendrimers are prepared in such way that different compounds have been synthesized with different properties. There are different methods for the preparation of dendrimers like convergent and divergent. In divergent method the dendrimers are prepared from the inner layer to the outer layer after the actual formation of layer whereas in case of convergent method, the dendrimers are prepared from outer layer until the dendrimers linked together.

Many active Pharmaceutical ingredients have been rejected from the pharmaceutical industry due to its poor solubility. The anticancer drugs like doxorubicin, daunorubicin have poor solubility so the dendrimers are mixed with such insoluble compounds which improved the solubility of compound without hampering the efficacy of drugs.

The delivery of drug to the central nervous system is very difficult even though in the presence of blood brain barrier hence the blood brain barrier linked to the polyamidoamino dentrimers which provides the ease delivery of drug to the central nervous system as it definitely produces expected therapeutic effect.

ISAsomes

The internal self –assembled some or particles. It includes the hexosomes, cubosomes and solid nanoparticles, the compounds which are Nano carriers intended for the drug delivery.

Cubosomes

Cubosomes are bilayer compound with the liquid crystal. It is made up of the glcerylmonooleate. The glyceryl monooleate having the melting point 60-70C with the hydrophilic and lipophilic balance value 3. The GMO consist of oleic acid monohydrate The GMO is amphiphilic compound which has ability to forms a liquid crystal. The GMO is compound possesses the hydrophilic and hydrophobic moieties due to the hydroxyl group present on the head region and the hydrogen bond in the tail region. This is suitable for the cubosomes formation. The phytantriol is an optional to the GMO but it has more stability as compared to the others and due to its more skin penetration power therefore it has attained more attention in the medical field. This is more specifically used for the hydrophilic drugs. The cubosome are thermodynamically stable compound it has good compatibility. The drug release mechanism is associated with drug diffusion process. The Fick's drug diffusion equation to be followed while studying the drug release of the cubosomes.

The cubosomes are used as a drug delivery system through the oral, intravenous drug delivery, subcutaneous drug delivery. The oral drug delivery is provided for the evaluation of bioavailability of specific drugs like the Cinnarizine, doxorubicin. The doxorubicin loaded cubosomes was administered to rat to evaluate its bioavailability or its antitumor activity then such activity is to be compared with the standard compound like Adriamycin which was administered through the intravenous route. The doxorubicin loaded cubosomes increases the oral bioavailability and having more efficacy than the others.in few cases the MO cubosomes (antifungal) administered through the oral route in rat whereas the Fungizone marketed preparation is to be administered through the intravenous route of administration. It was observed that not only cubosomes, hexosomes have

effective delivery through the oral route of administration but also all the nanoparticles have effective delivery and therapeutic effective if it is administered through the oral route.

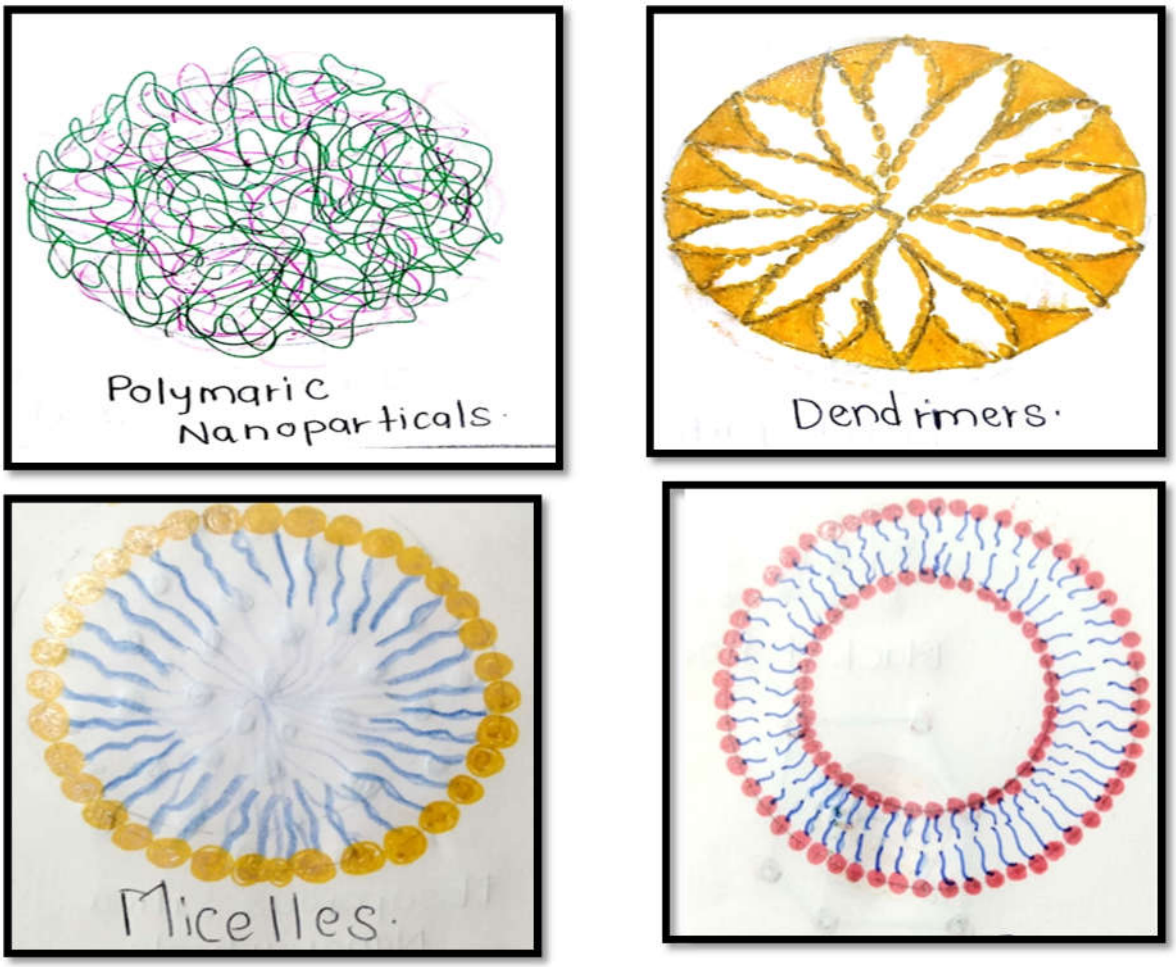
Intravenous drug delivery system

The cubosomes and hexosomes were administered though the intravenous route in mice. From the observation it was revealed that the hexosomes accumulation in spleen and liver is greater than the cubosomes but sometime its accumulation depends upon the content of lipid present. The difference in the addition F27 stabilizer. Similarly, the Nanoparticles administered through intravenous route of administration in mice in this case might be there is chances of its accumulation in liver.

Solid lipid particles

Smart Nano carriers

Types of Nanocariers



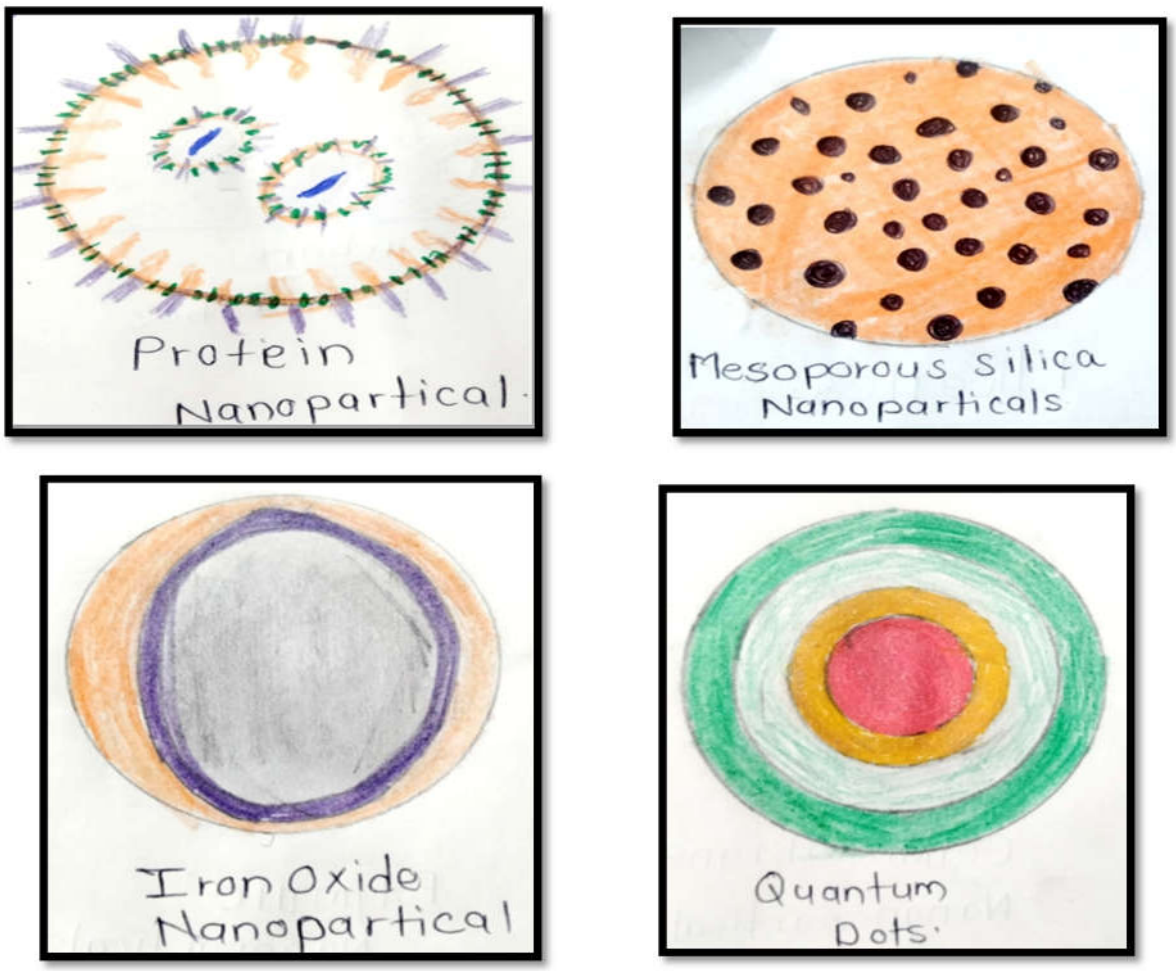


Fig No 1 Types of Nano carriers

Recent advancement in Nanoformulation development

- **Liu, W.-Y., Lin, C.-C., Hsieh, Y.-S., & Wu, Y.-T[9].**
  The fiestin is the naturally occurring compound like flavonoid, the fruits like strawberry is the richest source of fiestin, similarly, the cucumber, apple are richest source of the flavonoid (flavanol). The fiestin loaded nanoparticles have been prepared by using the Nano precipitation method. The method in which the fiestin is mixed with the PLGA as an organic phase and dissolved in the acetone. The PVA aqueous phase mixed with an organic phase at the flow rat of 600rps hence, fiestin-PLGA the suspension is formed. The acetone was evaporated in the rotary evaporator. The suspension is subjected for the centrifugation and the supernatant liquid removed and settled nanoparticles collected. The prepared nanoparticles employed for the drug design by the central composite design. The nanoparticles were optimized and characterized by the different methods like Zeta potential, Particle size determination, polydisperible index, drug release study, differential scanning Calometry, Permeability study, X-Ray diffraction. The study emphasis on the fiestin loaded nanoparticle which is to be used as an oral carrier.

The rifampicin drug is widely used in treatment of the Tuberculosis but due to its poor bioavailability, its short half-life and its side effect such as hepatotoxicity it was decided to improve the bioavailability of rifampicin by the nanomicro emulsion method .The current study emphasis on two methods first is dispersion of SLN and low aqueous volume. The first method adopts the preparation of SLN nanomicroemulsion and second method constructed a ternary phase diagram. The low aqueous volume method became successful by addition of sufficient amount of cold water.

In this method the ternary phase diagram was constructed followed by the mixing the Rifampicin with tween and sorbitol compounds which are acts as surfactant later mix the Compritol and water properly in order to get the optimum concentration of mixture. The prepared mixture was employed for heating above its melting point until the formation of single phase. Add the sufficient amount of water until the precipitation was visible in the clear solution. The prepared emulsion is known as the w/w emulsion.

The specific rotation of mixture was recorded. The care must be taken while handling the emulsion as it should be covered properly because the more chances of evaporation of water. The ternary phase graph was plotted using the Chemix software which highlighted the regions of clear micro emulsion. The prepared micro emulsion was characterized by zeta potential, Particle size analysis, Invitro release, entrapment efficiency and its total drug content was determined, in-vitro drug release was analyzed by the dialysis bag method, drug stability were studied. From the result and discussion, it was revealed that the Nano particulate drug delivery system like rifampicin loaded drug should be high as compared to its lipid content and it could improve the bioavailability of drug.

Karimi etal, were studied, the Cr doped aluminum oxide was prepared by the sol gel technique, the technique in which the chromium nitrate mixed with the aluminium nitrate followed by addition of deionized water. Mix the solution properly and kept on magnetic stirrer at 60 C temperature to make the homogenous solution. Meanwhile the aluminium and chromium ion dissolved in water to make the precursor (aluminium hydroxide and chromium hydroxide) subsequently the surfactant like oleic acid added into the mixture of aluminium and chromium hydroxide. Furthermore, the solution was subjected for the homogenization at 3000 rpm for 4 hr, make sure that the homogenous mixture was synthesized. Once the homogenous mixture is formed the supernatant liquid was removed by evaporation of mixture by heating at 250C for 6hrs the formation of black gel. The prepared gel was allowed to different reactions like decarboxylation, dehydration reaction. The reaction was carried out in order to convert the amorphous gel into the crystalline Chromium doped aluminum oxide nanoparticles with addition of chromium and aluminium oxide compound.

Igbokwe etal[11], were studied the Nano formulation of Pyrrazolone derivatives and Evaluation of their antibacterial, Antioxidant activities. The Pyrazolone derivatives are widely used in different diseases, but the bioavailability and solubility problem of compounds it was suggested that to formulate the Nano formulation of Pyrazolone derivatives. The Nano formulations were prepared by Nano precipitation method. The method in which the organic phase like poloxamer, Phosphate buffer saline solution dissolved in the acetone and the Poly co glycolic acid dissolve in the previous mixture until the homogenous mixture was formed so it would be better to use the Magnetic stirrer for the preparation of homogenous mixture, it is called as he nanosuspension. The blank solution made without addition of sample. The triplicate form of solution was prepared and the suspension labelled as PBC-PLGA 301,302 for compound I and Compound II. The pyrazolone derivatives already quantified by using the High-

performance liquid chromatography. The prepared Nano suspensions were characterized by using the high-performance liquid chromatography, entrapment efficiency, zeta potential. The Nano formulation of pyrazolone prepared by addition of PBC-PLGA suspension so the encapsulation of pyrazolone derivatives which were characterized and evaluated by different methods. The Nano formulations were employed for the antibacterial, antioxidant activities.

- **Applications**

Cancer treatment

Sun etal[7] were studied the polymer micelle has taken more attention as an anticancer agent. The polymer micelles have more advantages like it control release of drug and it prevent the degradation of drug. The paclitaxel micelles have potential effect in cancer treatment. The micelles are affected by the temperature and pH difference. The pH difference between the cancerous cell and normal cells it affects the sustain release of drug. The micellar solubilization of drugs improve the solubility of insoluble drugs. The folate and doxorubicin loaded micelles mixture may effectively reduce the systemic toxicity and it does not affect to the normal tissues of heart and brain but it specifically targets to the tumor region hence it produces the anticancer effect.

Siddiqui etal were studied the Resveratrol Nano formulation drug delivery system used in the treatment of the cancers. The resveratrol is non-flavonoid found in the grapes, peanuts and red wine as is used as food in supplementary diet.

Many researchers did work on resveratrol non flavonoid in the human being for cancer treatment. The resveratrol works by suppressing the cell cycle of cancer cells. This polyphenoilic compound have provocative role in the carcinogenesis of tumor present in the mammary gland of mice.

Method[8]

The Nano formulation prepared by using the following methods

Synthesis of Nanoparticles: The resveratrol mixed with the polymer in a container later it is employed for sonication followed by the dialysis. The nanoparticles encapsulating the resveratrol leading to the development of Resveratrol Nano formulation. The synthesized Nano formulation to be injected into the tumor containing rats. Once the Nanoformulation enters into the blood circulation, it moves freely until and unless it reaches to the site of action, that is tumor.

Niloufar Rashidi etal[14], the different drugs have been approved as an anticancer drug like L-asparagine loaded polymer protein conjugate marketed as Oncaspar which is usually used in the treatment of blood cancer. The doxorubicin loaded liposomes marketed as Myocet used in the treatment of breast cancer. Furthermore, daunorubicin loaded liposomes marketed as daunoxome used in the treatment of Kaposi's sarcoma associated with HIV.

Diagnosis of diseases[12]

The artificial intelligence is the branch of the computer science. There are different types of artificial intelligence like deep learning, artificial neural network, Machine learning. The artificial intelligence provides a computer-based machines, works faster and efficiently than the human being. The Computer based machine having the databases, Nano sensor. The Nano sensors are used for the identification of patient tumor and the Nano sensors are used for the delivery of nanoparticles to the

site of action. The machinery having navigators which deliver the drug to the targeted site. The system finds the position of patient and relieve the patient's symptoms

The artificial intelligence has designed the algorithms which optimized the efficacy of nanoparticles and improve the efficacy of anticancer drugs. Furthermore, the algorithm can perform the optimization of nanoparticles size, shape, drug encapsulation, interactions of nanoparticle with biological membranes leading to the improved the therapeutic effect of drug.

Oral drug delivery system[13]

In this case the doxorubicin loaded with phytrinol cubosomes improved the bioavailability of drug in rats. Furthermore the nanoparticles lower the cardio toxicity of drug as compared to the Adriamycin, which was administered through the intravenous route of administration.

Yang etal, reported that, the improved in the amphotericin loaded MO cubosomes with the standard drug like fungi zone which was administered through the intravenous route of administration. From the result it was revealed that the prominent effect of amphotericin loaded MO cubosomes.

Ocular drug delivery system

It was Reported that the nanosuspension which were prepared from the ibuprofen salt and sodium salt-coated chloro trimethyl-ammonium methyl methacrylate, delivered to the rabbit eye by the topical route of administration. From the observation it was revealed that the drug reaches to the aqueous humor and increase in the drug level in the aqueous humor and improved the penetration to the anterior chamber hence the improved the drug delivery at the site of action.

Conclusion

The Nano formulation development needed for the targeted drug delivery system and for reduction of dose and improved the bioavailability of free drugs. As they are better than the conventional drug delivery system. The Nano formulation approach have taken more attention in the ease of drug delivery and diagnosis of diseases. The Nano formulation development make the delivery of drugs more easily and it could give the therapeutic effect rapidly.

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