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A Review on Current Scenario in Drug-Loaded Nanocapsules in Cancer Treatment

Randhir Patil[1], Manish Wani*[1], Dnyanesh Limaye[1], Poonam Patil[1], Ashwini Zade[1], Akshay Baheti[1], Mohamed Dehghan[2], Satish Polshettiwar[1], Amol Tagalpallewar[1]

1. Department of Pharmaceutics, School of Pharmacy, Dr. Vishwanath Karad, MIT World Peace University, Pune 411038, Maharashtra, India.
2. Department of Pharmaceutics, Y.B Chavan College of Pharmacy, Dr Rafiq Zakaria Campus, Aurangabad 431001 Maharashtra, India

Email: manish.wani@mitwpu.edu.in

ABSTRACT

Various types of carriers presently available in care of cancer for targeted medicine delivery, each with its own combination of advantages and disadvantages.Polymeric nanocarrier like, micelles, dendrimers, magnetic and gold nanoparticles,liposomes, quantum dots, silica nanoparticles, polyethylene glycol, and carbon nanotubes were given special consideration.To achieve controlled drug release and effective delivery of drug, nanocapsule of dispersed polymercan be used as a drug transporter that is nanoscale in size.The main determinants, stability of dispersion are the surfactant structure and the outer coating shape.The structure and configuration of capsule walls have a major impact on release and deterioration characteristics of the capsules.The nanocapsule size range is between 1 to 100 nm.There are major methods for producing nanocapsules arepolymerization, interfacial polymerization, arc discharge,emulsion polymerization andencapsulation of nanocapsule method.Measurement of capsule surface, Capsule radius distribution, thermal or chemical decomposition, capsule membrane thickness and permeability are the most significant capsule parameters.

Keywords: Nanocapsules; Cancer treatment;Drug-Loaded Nanocapsules; nanoencapsulation.

Introduction

Cancer is a word that refers to a group of diseases in which malignant cells develop abnormally and spread to other areas of the body[1,2]which results to cause death, hencecancer is one of the deadly illnesses on the planet.

Nanomedicine is the recent nanotechnology in medicinewhich is composed of Nanomaterials, whose sizes vary from around one nanometer to many hundred nanometers[3,4].

Various considerations can affect the use of Cancer-fighting nanomaterials detection and medicine distribution in cancer treatment.

- The nanomaterial's size.
- The nanosystem's biocompatibility.
- The nanosystem'scapacity to degrade.
- The drug's desired release profile.
- The encapsulated drug's toxicity and antigenicity.
- The entrapped medicine's properties in the nanomaterial
  Ex. medicationsolubility or stability in water and other solvents.

Nanocapsules are a type of nanoparticle that consists of a protective matrix known as shell and one or more active materials known as corein which the therapeutic substance can be enclosed. The protective coating on the nano-capsules,this is usually pyrophoric and rapidly oxidizes [5].

The use of nanoparticles as drug carriers has been widely studied, with majority of their applications in cancer care and detection. Chemotherapeutic agents that have beenconjugated with or incorporated into nanocarriers are known as nanomedicines.Sustained release, increased medication selectivity as well as potency, enhanced drug bioavailability and reduced toxicity of drugs are the significant features.When nanocapsules injected through the IV route, which are submicron in size, hit the target and release the encapsulated compound.

Nanocapsules are polymeric nanoparticles with a polymeric wall which is made up of macromolecule,surfactants that are non-ionicoil baseandphospholipids[6-9]. Interfacial nano-deposition and interfacial polymerization are the most popular methods for manufacturing of nanocapsules and they are used to deliver medicines in a controlled manner while also protecting proteins, enzymes and foreign cells.

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Because of their adverse side effects, some medications have a difficult time finding a marketplace. When drugs are inserted within the space of a nanocapsule, however, nanocapsuledeliver medication directly to the desired location in a reduced dose that is up to 10,000-fold and thereby significantly reduce or eliminate any side effects to a reasonable amount[10].

Nanocapsule development can be influenced by their intended use as well as biochemical, electrical, pharmaceutical, magnetic and opticalproperties. The improved distribution of bioactive molecules through selective delivery bynanocapsules creates various obstacles and prospects for future studyand development of better therapies.

Advantages of nanocapsule[11,12]:

- At the molecular level, nanocapsules have the potential to penetrate and enter into specific tissue.
- Nanocapsules have huge surface area hence it provides high degree of absorption.
- Increased medication uptake and localization in cells.
- Drug distribution to cancerous cells is targeted and selective while avoiding conflicts with healthy cells.
- Because medications or small molecules are encapsulated, a lower dose is needed.
- Improved absorption of medications that are poorly soluble.
- Toxicity of medicines is reduced.
- Greater accuracy in drug deliver to the small body parts.
- Less drugs resistance is produced.
- Resistance occurring from physiological barriers in the body is minimized or suppressed.

Limitations:

- The excessive use detergent like poly vinyl alcohol can raises toxicity.
- Discontinuation of treatment is not possible.
- Inflammation of the alveoli and the lungs can occur.
- Nanoparticles interrupt autonomic function, which can affect cardiac and vascular function directly.

Materials, Composition and Method of Preparation

Materials:

In preparation of nanocapsule different types of polymers can be used-

1. Natural polymers:Ex. Gum Arabica
2. Synthetic polymers:Ex. Poly(L,D lactide),poly(E-caprolactone), poly(alkyl cyanoacrylate)
3. Semisynthetic polymers:Ex. Hydroxypropoxymethylcellulose Phthalate (HPMCP), Hydroxypropyl methylcellulose (HPMC), diacyl beta cyclodextrin[13,14].

Other than polymers, different oils including mineral oils or vegetable oils and pure compounds likebenzyl benzoate and ethyl oleate also used for the preparation of nanocapsules.

Composition of nanocapsules

An aqueous or oily core is coated with a thin polymer membrane to form nanocapsules. This nanocapsules were made using an inter-facial polymerization process for the monomer as well as anprocedure for interfacial nano-deposition of prepared polymers.Tumor cells targeting nano-scale vectors capable of carrying radioactive particles are being developed and it has benefited greatly from technological advancements in the pharmaceutical research field[15].

Methods

A. Polymerization method

To produce nanoparticles, the monomers are polymerized in awater solution.Through dissolving the active ingredient in a polymerization medium or adsorbing nanoparticle, the drug is placed.The ultracentrifugation system used tosterilise the suspension of nanoparticles,eliminates the different surfactants and stabilizers used in

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the polymerization process.The nanoparticles are then again suspended in a non-surfactantsolution that is isotonic. It's been proposed that it could be used to make polybutylcyanoacrylate or polyalkylcyanoacrylate nanoparticles.Physical, chemical stabilizersand surfactant concentrations all serve a major role in the creation of nanocarriersand their particle size.The nanoparticles are formulated using a phase-inversionmethod and have a 20-100 of mean diameter which depends on the amount of additives used[16,17].

B.Interfacial polymerization method

Condensation polymers are bulk polymerized,which will require higher temperatureis an alternative to interfacial polymerization.It is made up of two non-miscible solvents in which monomers in single solvent react immediately with monomers in another solvent and it is time dependent.The nanocapsules can be developed from an aqueous core containing isobutyl cyanoacrylate oligonucleotides in a water in oil emulsion then the nanocapsules are filtered using ultracentrifugation technique before being resuspended in aqueous solution to produce an aqueous core nanocapsule dispersion[18,19,20]

C. Arc-discharge method

Arc-discharge technology has been used to create accumulation of self-build nanocapsules.This system has also been changed into a modern way of synthesising aggregates using modified techniques, by adding $GdAl_2$ (gadoliniumaluminium alloy) ingot which is anode.By modifying the amounts of materials in the anode based on their vaporisation pressures which helps to create a different kind of magnetic nanocapsule with the inner metallic element that is the core is $GdAl_2$, while the shell is amorphous Al_2O_3 (aluminium oxide) has been created, potentially expanding the group of magnetic nanocapsules.Without the use of a catalyst or template, an arc-discharge technique was usedtobuildfrequentlyarranged 3D macroaggregates self-build by nanocapsules[21-24].

D. Emulsion polymerization method

Two parts of the pre-emulsion is blended together. Part I consist of styrene (40 gm), divinylbenzene (0.8 gm), 2,2′-azobisisobutyronitrile (0.82 gm) and Desmodur BL3175A (40 gm) and Part II consist of sodium dodecyl sulphate (1.71 gm), Igepal CO-887 (1.63 gm) and water(220 gm).In different containers Parts I and part II are magnetically combined for ten minutes.The contents of Part II were then passed to Part I and mechanically stirred at 1,800 rpm for 30 minutes.Then pre-emulsion was chilled at 5°C before being sonicated (until a particle size of 250 nm was achieved) with a Misonix sonicator 3000.The pre-emulsion was degassed for 30 minutes in a 3 neck circular bottom flask which consist of mechanical stirrer, nitrogen inlet and reflux condenser[25].The temperature was raised to 70°C and kept for 8 hours to complete the polymerization.Chemical vapour deposition, electron irradiation deposition,charge transferring, laser vaporization-condensation, organic reagent aided process,catalytic vapor-liquid-solid growth and solution-liquid-solid method are some of the other nano-capsule preparation processes[26-32].

E. Encapsulation of nanocapsules method

Many encapsulation strategies use isocyanates in either a form of solvent or a bulk form to create shellor matrix substance for encapsulating usable materials and releasable fill materials[33, 34].Encapsulation postpones drug release from nanocapsules, such as Aerosil 200 and Xerogelsare used as encapsulated products.The Aerosil 200 has the significant disadvantage of bursting nanocapsules.Several methods for reducing the outburst release of medicines from xerogel mesopores have also been suggested.It has been recommended that polymeric nano-capsules can be intended as a coating material for the accumulationof drug containing xerogel to prevent a severe burst release. They could delay the microparticles' interaction with water, preventing a burst and delaying drug release[35, 36.]

Physical Characterization of Nanocapsule

Particlesize:

The bioavailability,in-vivo distribution, targeting capability and toxicityof system of nanoparticlesare all determined by particle shape and size and size distribution in nanocapsule systems. It also has an important impact on drug loading capability,release of drug and nanoparticulate system stabilisation. The impact of dose release and thelag period of pharmacological activity are based on size of particles. Since tiny particles have more surface area and many therapeutic drugs interactwithsurface particle which cause immediate release of drug, while big particles with large surface of core disperse out over time[37].

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Surface area:

(a)Surface coating of nanocapsules with hydrophilic surfactants and hydrophilic polymers[38],
(b)Biodegradable copolymers having hydrophilic segments, such as polysorbate 80, polyoxamer, polyethylene oxide, poloxamine and polyethylene glycol, are prepared as nanocapsules. The charge present on a nanocapsule's surface described by using zeta potential[39].

Fluorescence intensity:

Fluorescence intensity is primarily used to confirm the location of nano-capsules containing an aqueous centre of oligonucleotides[40-42].

General EvaluationMethods of Nanocapsule

X-Ray Diffraction studies

Powder X-ray diffraction with graphite monochromatized using a Rigaku D/max-2000 diffractometerCuK atcurrent of 250 mA and a voltage of 50 kVis used to determine the phase of the materials. The phase composition ofprepared products can be seen in the XRD pattern[43].

Scanning Electron Microscopy

The structure of clustered aggregates with branches made up of nanocapsules may beflocculent, with tiny clusters, large clusters, and huge branches appearing at various sizes, confirming the structures self-similar properties. It can be distinguished by using PhilipsXL-30 scanning electron microscope that displays the transparentmorphology of small clusters at high magnification. Clusters are created by tinyparticles adhering together to create a flocculent arrangement. A low-magnification SEM picture of coral-like structure having branched features along with the axial and directions in lengthwise can be shown[44,45].

Differential Scanning Calorimetry

Both open (without a lid) and closed (with a lid) samples are subjected to DSCexamination (small hole in the pan capped centre). According to theobservations, both approaches have similar thermal activity[46].

Transmission Electron Microscopy

Transmission electron microscopy can be used to investigate the transportationofnanocapsules, especially insulin-loaded nanocapsules, through the epithelium after theyhave been given orally to experimental rats and studiedin-vivo and in-vitro. Theingestion of biodegradable nanocapsules in the intestine leads to insulin transferthrough the epithelium mucosa, according to TEM findings[47, 48].

High-Resolution Transmission Electron Microscopy

Core or shell configuration of the nanocapsules is distinctly seen in the complexmorphology of the related nano-capsules studied using high-resolution transmissionelectron microscopy. Low-magnification TEM photographs are used to examine thecomposition of nanocapsules that make up the aggregates[49,50].

X-Ray Photoelectron Spectroscopy

The surface aluminium atoms valency existing on the nanocapsules at a range of 1.6 nm was determined by X-ray photoelectron spectroscopy quantification on an ESCALAB-250 with monochromatic x-ray sources.Due to the limited spectrum of photoelectrons excited, the XPS technique isparticularly unique to the solid surface. A concentric hemispherical analyser (CHA) isused to calculate thephotoelectrons excited energy which is emitted from the sample, whichdisplays a spectrum of different photoelectron peaks.Depending on the element, the binding energies of the peaks change. The peak areas are used to demonstrate thestructure of the surface materials (with similar susceptibility factors). The emitting atom of chemical state will alter the form of each peak and the bindingenergy moderately. Chemical bonding information is also provided by the XPSmethod[51].

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Superconducting Quantum Interference Device

Quantum DesignMPMS-5s and MPMS-7sof SQUIDsare used to test the magnetic properties of nanocapsules.SQUID detectors are the most sensitive for detecting minute variations in magnetic flux, which accountsfor the vast range of applications that SQUID instruments can be used[52].

Multi Angle Laser Light Scattering

The shape of a vault is similar to a capsule shape with a very tiny shell (less than twonano meters)encasing a huge internal space. A nanocapsule's vault particle has enormous potentialfor compound encapsulation, safety, and distribution.Using multiangle laser light scattered to investigate vault conformation in solution, the interconversion of opened and closed conformers is stimulated. The regulation of entrapment and release ofencapsulated materials is possible thanks to these tests. Vaults containing radioactivemetal binding sites are crucial for environmental and medical detoxification[53-56].

FT-IR analysis

FTIR analysis is used to establish the existence of distinctive peaks. The peaksrepresent the compound's characteristic functional units[57,58].

Use of Nanocapsules

Nanocapsules have the potential to be employed as smart medicationsthat only bind to certain cells and have specific chemical receptors.This receptor is what gives the drug its "smart" properties, that allows it to target cancer cells.

The following are some of the benefits of nano-encapsulation technologyapplications for pharmaceuticals:

- Smaller dosage volumes with higher dosage loading.
- Increased dosage retention at certain sites.
- Increased absorption of active medication components.
- The drug's bioavailability has improved.
- Greater effectiveness and safety.
- Increased patient compliance[59].

Applications of Nanocapsules

1. Nanocapsules as novel Systems

The surfactant composition and the design of theoutside layer are the key determinants of dispersion stability and primary physiological action.The composition and arrangement of the capsule walls have a big impact on their escape and degradation property.The significant capsule properties include surface of capsule, capsule radius distribution of capsule, membrane thickness of capsule and permeability of capsule and thermal and chemical decomposition.

2. Nanocapsules as Drug Delivery System

Australian scientists have created nanocapsules that can be intendedfor targeting anti-cancer agents on tumours while avoiding side effects on healthy tissue.The capsules, which are about 1 micron in diameter toa thousandof a millimetres can be covered with an antibody that aretransferred from the bloodstream to the tumour.When it enters into the tumor, a rapid rupture without causing damage to the skin-penetrating lasers that produces near-infrared radiation, allows the capsules to break and release the contents.

3. Hormone-dependent breast cancer treatment

The research reveals that oestrogen receptor alpha (ER) can be targeted using complex siRNAs encapsulated in nanocapsules. After injecting these nanocapsules through IV into estradiol-stimulated MCF-7 cell xenografts, tumour formation and ER expression in tumour cells were significantly reduced.It implies that a new technique depend upon ERsiRNA delivery for the treatment of hormone-dependent breast tumours might be developed[60].

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4. The use of radioactive materials in nuclear nanocapsules for cancer treatment:

Astatine, like radium and uranium is radioactive compound, emits higher velocity alpha particles from radioactive decay of radioactive agents, that are approximately around 4,000 times quicker than the decay of beta released electrons, and it is frequently intended radioactive compound in treatment of the tumor.The alpha particle is special in that has a low penetration capacity and a large particle size, making it ideal for single-cell tumour targeting[61].

5. Nanocapsules against melanomas

Melanoma's cancer are extremely aggressive tumours with a poor prognosis, particularly when it has spread. In contravention of major attempts in improving adjuvant treatments, that gives better response than the regular approved drug dacarbazine by the FDA which is less than 16%. The following steps should be taken to target specific cancer cell[62]:

i) Passive improved permeability retention because of the nanocapsules' size, structure and shape properties;
ii) Antibody coupling allows for active targeting.

The physicochemical characteristics, half-life, aggregation at tumour site and therapeutic advantages of various nanocapsule forms have all been examined. The magnetic nanoparticles and selenium-based anti-cancer agent loaded polylactic-co-glycolic nanocapsules provide an unique and strategically magnetic drug delivery mechanism suitable for the treatment of cancer via active drug and magneto hyperthermia[63].

Anticancer Drugs Formulated into Nanocpasule

Anticancer agents efficacy can be affected byhigh excretion, low water solubility and low permeability through the cells. The drug delivery technologies are intended to increase therapeutic agent's security and effectiveness while also increasing patient acceptance.Many medications containing the most commonly camptothecin, cisplatin, docetaxel,doxorubicin, paclitaxel and curcuminare being studied these days.

1. Paclitaxel

It's used to treat cancers of the ovary,lung, breast, neck, head and undisclosed origin.For more than two decades, this drug's less aqueous solubility has been a major barrier to its widespread use.Nanotechnologies is the type of polymer-based controlled release method have been proposed as one distribution strategy. OncoGel is a device that incorporates paclitaxel inside ReGel has been developed for local administration of paclitaxel to solid tumour cells for selective cytotoxicity. Several forms of cancer have been successfully treated using this delivery system.Paclitaxel can releasefrom the ReGel at the tumour site and its surroundings area for six weeks[64-67].

2. Docetaxel

Chemotherapeutic agents that are most commonly used in theof solid tumour treatment. Its effectiveness has been shown against various tumours, including prostate and breast cancer.Zhang and co-workers made micelles that contains docetaxel to increase intracellular drug delivery and therapeutic effectiveness in cancerous cells.Both micelles had a less diameter (< 80 nm), a spherical in shape and a large encapsulation quality. Themolecules containing DXT were evenly distributed inside micelles and did not interact chemically with the polymers.

3. Camptothecin

Camptothecin is a natural alkaloid, derived from the Camptotheca accuminata plant that inhibits DNA topoisomerase I action.It is difficult to the administer to cancer cells due to its toxicity to human cells, unstable structure and non-polar properties.PEG-based nanoparticles, paramagnetic Fe_3O_4 nanoparticlesand lipid nanoparticles have all been used in CPT-mediated drug delivery studies[68-71].Biodegradable, biocompatibleand targeted sterically stabilised micelles are the nanocarriers used for camptothecin to overcome its insolubility, instability, and toxicity.

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4. Doxorubicin

They are widely used in various types of malignant tumourstreatment, involving acute leukaemia, Hodgkin's as well as non-Hodgkin'slymphoma and a variety of solid tumours like neuroblastoma[72-75].The therapeutic use of this drug is limited by the side effects of combined dosage dependent cardiotoxicity, myelosuppression and the high delivery amount and short life span in physiological conditions[76,77].Using different nanoparticle forms as drug carriers such as micelles, polymer-based nanoparticles, magnetic particles and liposomes, these toxic effects have been effectively decreased[78-80].

5. Daunorubicin

Daunorubicin is an anthracycline-based chemotherapeutic drug that is used to treat some cases of leukaemia (acute myeloid leukaemia and acute lymphocytic leukemia).

6. Cisplatin

Rosenberg identified the biological action of the very first platinum-based cytostatic compound that is cisplatin, which has now become one of the most commonly used cytotoxic agents, in 1965 while studying the influence of an electric current on bacterial development[81,82].

7. Curcumin

Curcumin is a natural polyphenol isolated from turmeric that has anti-carcinogenic properties and low inherent toxicity.Curcumin was shown to be pharmacologically stable in many human trials and animal studies, including at extremely high doses.It has a very low polarity and deteriorates rapidly in acidic as well as alkaline environments with a short half-life (<10) minutes, resulting in very less bioavailability following vascular and orally administration.Curcumin distribution through nanocarriers has recently been investigated as a way of avoiding these limitations[83].

Conclusion

To summarise, various nonencapsulated technologies include novel research pathways that are sufficient recent strategies for development in cancer diagnosis and diagnostic techniques, as well as drug administration in cancer therapy. In pharmaceutical industry,nonencapsulated structuresin particular, play significant role in the administration of anticancer medicines.Nanoencapsulation has been used in medicineare greatly helped in the resolution of a number ofIssuesincluding toxicity, drug absorption and improved solubility, tumour site targeting,drug resistance, and so onAmong the benefits are a reduction in theneeded dose and regulated drug release. Asaresult, the nanomedicine use has transformed our capacity to detect tumour and treat it.Nanocapsules are a reference to the methodological advancement of multiple formulationprocesses, primarily interfacial polymerization and interfacial nano-deposition.Nanocapsules are also useful in a variety of areas, including agrochemicals, sewagetreatment, gene therapy, makeup, hygiene materials, and adhesive materials.Eventually, they may be used to transport active pharmaceutical ingredients (APIs). Inthefuture, they will have new and efficient drug delivery technologies.

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