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BIOACTIVE COMPOUNDS INTEGRATED WITH POLYMERIC NANOCAPSULES USED FOR CANCER TREATMENT

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ABSTRACT

Nanocapsules are nanostructures consisting either liquid or solid core with a polymeric shell. There is an emerging interest in the usage of nanocapsule for various drug delivery applications. In this review, various types of nanocapsules used in delivery systems as well as their use for cancer thernostics have been studied along with nanocapsule formulation, characterizations and applications. Incorporation of phytochemicals which possesses anticancer properties including vitamins, antioxidant phenolic, dietary fiber, flavonoids, and polyphenols becomes convenient due to encapsulation methods. Nanocapsules has been synthesized by using polymers as outer shell materials to protect internally filled bioactive compounds against external factors such as light, heat and oxygen which will increase the stability and improve the bioavailability of the nanoencapsulated compounds. Furthermore, the challenges faced due to conventional cancer therapy are reviewed and how nanocapsule can overcome them are studied. The progress in nanotechnology has favoured the development of various encapsulation methods which will regulate the pharmacological and biopharmaceutical properties of drugs and also provide favourable conditions to the encapsulated drug. The size, shape, charge and pattern of nanocapsule (nano therapeutic molecules) are parameters that need to be investigated in order to promote and optimize cell and tissue interaction. The nano encapsulation of antitumor active compounds is a promising approach to improve the efficacy of various tumour treatments. In this review different methods which are used to synthesize various nanocapsule are discussed and their applications for the treatment of several diseases are discussed by using examples from the literature.

KEYWORDS: Nanocapsule, encapsulation, bioactive compound, polyphenol, polymeric nanocapsule, cancer.

INTRODUCTION

Nanocapsules are type of nanoparticles which are made up of a protective matrix known as shell in which the therapeutic substance may be constricted and one or more active materials known as core. The nanocapsules became great interest because of their protective coating which is generally pyrophoric and easily oxidized. Nanocapsules are used in cancer therapy and diagnosis. Anticancer drugs are embedded in or conjugated with inert nanocarriers referred to as nanomedicine. More advantages of nanocapsules are seen therapeutically than free drugs and the inert carrier materials acts as the major component but possess low drug loading content and thus entail excessive use of parenteral excipients. Their main advantages are sustained release, drug selectivity and effectiveness, improvement of drug bioavailability, alleviation of drug toxicity. Nanocapsules reach the target and release the encapsulated drug when administered intravenously because of their nanosize. Polymeric nanoparticles considered as nanocapsules when a polymeric wall composed of non-ionic surfactants, macromolecules with an oil core (Tiwari and Rohiwal, 2019). The production of nanocapsules depends on their application and pharmaceutical, organic chemistry, electrical, optical or magnetic characteristics. The improved delivery of bioactive molecules through the targeted delivery by suggests that of a nanocapsule provides various challenges and opportunities for the analysis and future development of novel improved therapies.

Bioactive compounds carry out many functions in the body that may promote good health. Bioactive compounds includes polyphenols, carotenoids, vitamins, organic acids, nucleosides and phytosterols have attracted great interest due to their role in prevention of cancer, heart disease, and other diseases (Kamiloglu et al., 2021). They can be nanoencapsulated by different types of structures such as nanoemulsion, liposomes or nanocapsules. Encapsulation is able to provide an effective barrier between the bioactive molecules also called core materials or active ingredients or encapsulated agents, and the external environment. Encapsulation process is defined as the technique by which liquid droplets, solid particles, or gas compounds are enmeshed into thin films called coating materials or encapsulation matrices. The bioactive compounds can be used as the core material which are being coated or encapsulated, it may be liquid, solid, or gas in nature. Coating materials should form cohesive film with the core material. The properties such as strength, stability,

impermeability, thickness, and flexibility of the coating film should be well studied in order to ensure the successful encapsulation process of the bioactive compound (Mahfoudhi et al., 2016). Thus, nanoencapsulation can improve stability of bioactive compound also enhance the regulation of their release at physiologically active sites (Pateiro et al., 2021).

Methods for the preparation of nanocapsules

Various well-known techniques have been developed to manufacture nanocapsules using nanoprecipitation, double emulsification, emulsion-diffusion, emulsion-coacervation, layer-by-layer, and polymer coating as discussed in the following sections:

Interfacial deposition method

In Interfacial deposition method the presence of both solvent and non-solvent phases is mandatory. In short, the solvent phase essentially comprises a polymer solution (synthetic, semi synthetic, or natural polymer) and secondly the active ingredient, and an oil (with or without a hydrophobic surfactant) in a solvent or solvent mixture (acetone, ethanol, hexane, or methylene chloride). The non-solvent phase is composed of a nonsolvent or a mixture of non-solvents included with one or more hydrophilic surfactants. Generally, the non-solvent is called as aqueous and solvent phases are called as organic phases. Generally, the solvent is an organic medium where as the non-solvent is mainly water. With this nanoprecipitation technique, particle formation is spontaneous because of the polymer precipitation in the aqueous medium (Mora-Huertas et al., 2009). Nanocapsules with a hollow core could be constructed by using only organic solvents which can be removed by evaporation once the nanocapsules formed (Rață et al., 2019).

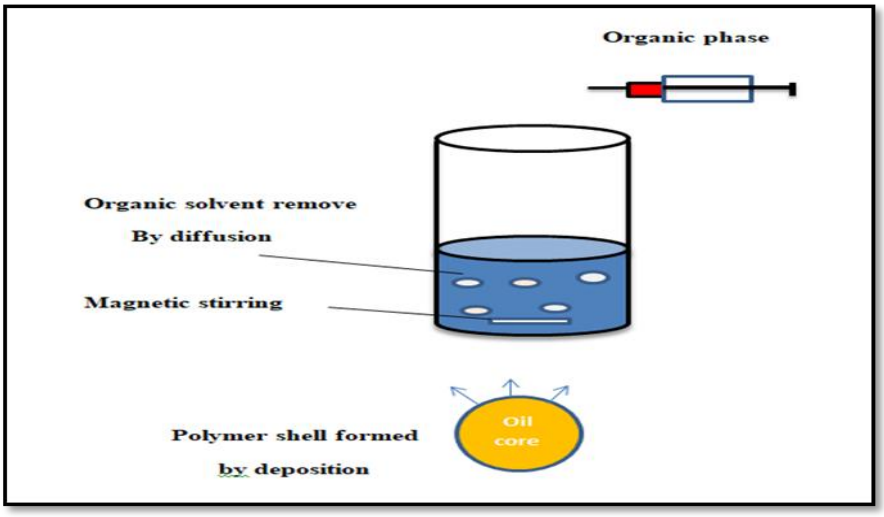

Fig 1: Interfacial deposition method.

Emulsion-Diffusion Method

Emulsion–diffusion method includes three phases: aqueous, organic, and dilution. In preparation method, the organic phase is emulsified into the aqueous phase through vigorous shaking. This technique mainly depends upon on the formation of an oil/water emulsion including oil, a polymer and a drug in the organic solvent where as an aqueous solution of the stabilizing agent. The subsequent addition of water into the first emulsion causes the diffusion of the solvent into the external phase, leading to nanocapsule formation (Bamrungsap et al., 2012). The polymeric shell can be made by diffusion, evaporation, coacervation or combination of these methods. Mainly nanocapsules synthesized by double emulsion method can provide an excellent platform for encapsulation hydrophobic and hydrophilic substances simultaneously (Deng et al., 2020).

Double Emulsification Method

In this method the droplet of one dispersed liquid is further dispersed in another liquid that can be categorized into two major types: oil-water-oil (o/w/o) and water-oil-water (w/o/w) emulsions. In the primary w/o emulsion, the oil is replaced by an organic phase containing a solvent that is totally/partially miscible in water, a film-formed polymer, and a w/o surfactant. To obtain the w/o/w emulsion, water containing a stabilizing agent is added to the system. However in the given step particle hardening is obtained through solvent diffusion and polymer precipitation. For full solvent diffusion, water is added to the double emulsion. And then solvents are evaporated or extracted by vacuum leaving behind the hardened nanocapsules in an aqueous media (Garti, 1997).

Emulsion-Coacervation Method

Emulsion-Coacervation method is used to form nanocapsules using natural polymers like sodium alginate or gelatin. Polyelectrolyte materials or monomer/polymer possessing cross-linking function groups are primarily used for nanocapsules fabrication (Dubey et al., 2020). The o/w emulsion is formed by adding the organic phase (oil and active ingredient) to the aqueous phase which contains water, polymer and a stabilizer while stirring. A coagulation process is carried out by altering the temperature/pH or using sodium alginate-calcium chloride electrolytes. The nanocapsules obtained are purified by washing with water or by filtration. Cross linking agents such as calcium chloride, glutaraldehyde, or sodium borohydride are added so it can stabilize the nanocapsule (Mora-Huertas et al., 2009).

Layer-by-layer Method

In this method a colloidal template is needed onto which a polymer layer is adsorbed either by incubation in the polymer solution. Further, it is washed or by decreasing polymer solubility by addition of a miscible solvent. The commonly used polymers are chitosan, heparin, polylysine, protamine sulfate, gelatin, or dextran sulfate may possess polyanionic or polycationic properties (Jagadeesh et al., 2016). Diverse drug release behavior in different pH environment can be achieved by using different rearrangement of the layer order. This method allows accurate releasing of drug and target efficient properties to manifest by altering the composition and thickness of polymeric shells (Deng et al., 2020).

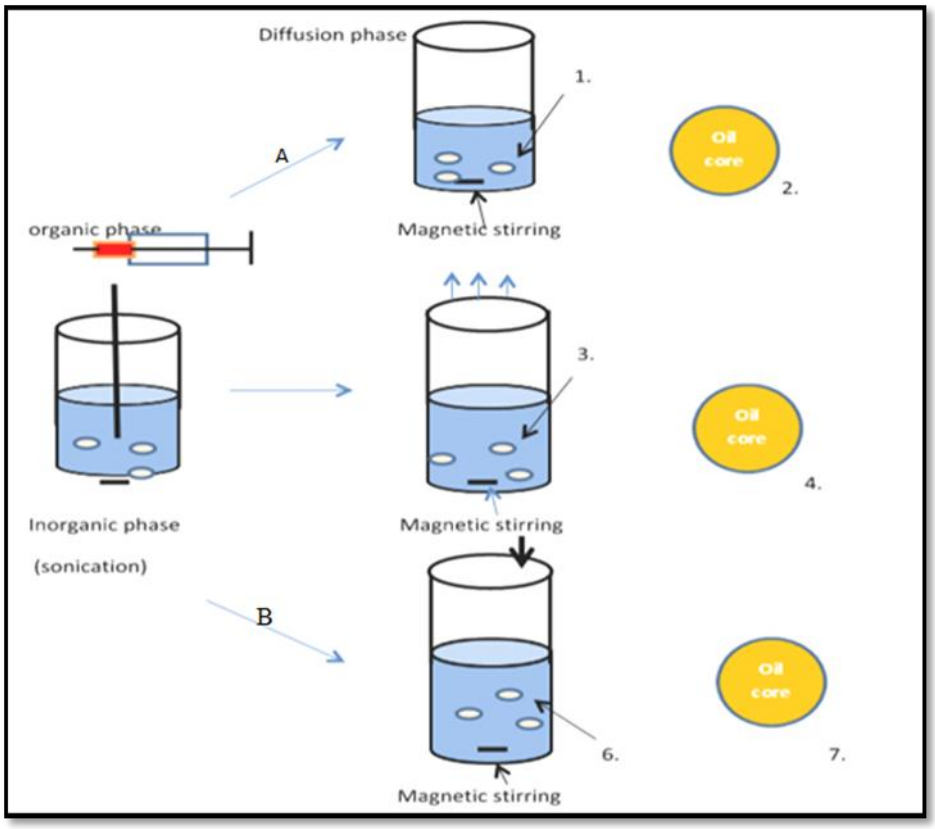

Fig 2: A: Emulsion– diffusion method, B: Emulsion–coacervation method, 1. Organic solvent removed by diffusion, 2. Polymer shell formed by deposition, 3. Organic solvent removed by Evaporation, 4. Polymer shell formed by deposition, 5. Organic solvent removed by Evaporation, 6. Polymer shell formed by physical or chemical cross linking.

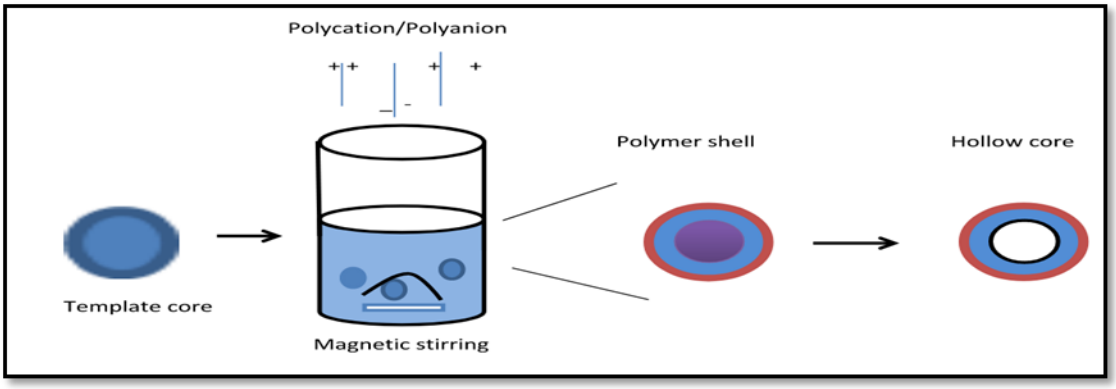

Fig 3: Layer-by-layer Method.

Properties of nanocapsule

Nanospheres are network systems in which the drug is dispersed throughout the structure or adsorbed onto the surface while nanocapsules are systems in which the drug is present within the core (aqueous or oily) covered by a polymeric shell (Cosco et al., 2015).

Particle size

The bioavailability, targeting capability and toxicity of system of nanocapsule are all characterized by particle shape and size and size distribution in nanocapsule systems. It also impacts the drug loading capability, release of drug and nanoparticulate system stabilisation. The release of dose and the lag period of pharmacological activity are based on size of particles (Patil et al., 2021). The size of nanocapsule should be large enough with diameter approximately ~100 nm to prevent its rapid escape from blood capillaries and renal filtration but it should be small enough to avoid mononuclear phagocyte system clearance (Yang et al., 2016). For evaluation of the mean diameter and size distribution of nanoparticles many technique are used which include laser scattering (dynamic or static light scattering, laser diffraction), field flow fractionation, electron microscopy, analytical ultracentrifugation and centrifugal particle sedimentation, tunable resistive pulse sensing, and particle tracking analysis (Caputo et al., 2019). To confirm the location of nano-capsules containing an aqueous centre of oligonucleotides fluorescence intensity is used (Patil et al., 2021).

Surface area

Biodegradable copolymers which have hydrophilic segments such as polysorbate 80, polyoxamer, polyethylene oxide, poloxamine and polyethylene glycol are used to prepare nanocapsules. The charge present on a nanocapsule's surface described by using zeta potential which affects the biological behavior of polymeric nanocapsule (Couvreur et al.,

2002). Cationic or anionic particulates are more stable as they are able to avoid non-specific cellular uptake by phagocytes as compared to neutral ones of a same size (Wang et al., 2010). Cationic nanoparticles have better potential as drug delivery systems because of their strong interaction with negatively-charged genetic material and their cell surface binding activity. Thus it allows loading of genetic materials which cannot cross cell membranes and ensure effective cell uptake through endocytosis (Farshbaf et al., 2018).

Natural polymer used for nanocapsule synthesis

Polysaccharides are considered important natural polymeric material which used as drug carriers, profiting from biocompatibility, gelation conditions and mucoadhesive properties. In general, polysaccharides contains maximum amount of deprotonated amino groups or carboxylic acid groups, resulting in cationic or anionic charges which helps to form the polymeric shell by electrostatic attractive interactions (Deng et al., 2020). Natural polymers such as sodium alginate, chitosan, gelatin, albumin, etc., are used to prepare nanocapsules as they are non-toxic, biodegradable and less expensive. In addition to this alginate is also a pH-responsive polymer, which can provide effective protection for payloads at acidic pH conditions, while releasing drug at alkaline pH. So nanocapsules which are assembled by alginate have been developed as a favourable strategy for intestinal targeted drug delivery through oral administration (Mukhopadhyay et al., 2015). Nanocapsules formed by an alginate polymer have low stability which causes loss of the encapsulated materials. Cationic polymers such as chitosan have been employed with alginate for overcoming limitations associated with swift release of encapsulated material (Kumar et al., 2015). Biodegradable polymers include synthetic polymers such as poly (D, l-lactide) (PLA), poly (D, L-glycolide) (PLG), co-polymer poly (lactide-co-glycolide) (PLGA), polyalkylcyanoacrylates, poly-Ɛ-caprolactone are considered safe (Palma et al., 2018).

Protein-based polymers are other kind of macromolecules which can be used as polymeric shell for nanocapsules because they are biocompatible and adaptive. Proteins can be fabricated into a hollow caged nanostructure by defined number of subunits. Human serum albumin has served as shell for nanocapsules as it can control drug permeation rate also albumin corona can reduce the immunogenicity of nanoparticles. Albumin can also serve as targeting ligand for albondin receptors which are overly expressed on endothelial cells of tumour blood vessels thus providing an excellent drug targeting system. The synthesis of albumin-shell and oily-core nanocapsule which was used to load with combination of

hydrophobic drugs such as exemestane and hesperetin targeted towards breast cancer therapy. This protein-lipid hybrid nanocarrier was successfully formulated using a simple protein-coating method based on the electrostatic adsorption of negatively charged albumin shell onto the oily core containing cationic surfactant (Gaber et al., 2019). The oily core, vegetable oil or fatty acids (such as medium chain triglycerides) are absolute composition oleic phase for nanocapsules fabrication as it has capacity to dissolve lipophilic drugs and the safety of oil phase. Essential oils, turmeric oil and lemongrass oil can be used as oil core due to their antibacterial, antifungal, antioxidant, antimutagenic and anticarcinogenic properties (Natrajan et al., 2015).

Applications of nanocapsules

The nanocapsules are found to be suitable for various applications because of its size they have high reproducibility, which might be used significantly in life-science applications. They have potential application in various fields like agrochemicals, cosmetics products, gene-splicing techniques, wastewater treatments, cleaning products and adhesive agents. They also find applicability in encapsulating the enzymes, organic or inorganic catalysts, oils, adhesives, surface polymers, inorganic micro-particles and nano-particles, latex particles, or perhaps biological cells.

Nanocapsule as topical agents

The skin is an implicit physiological barrier for many active pharmaceutical agents because of its structure (the main barrier is which stratum corneum, is the outermost layer of the skin). Physicochemical properties of these agents determine the penetration in the skin. The less soluble hydrophobic molecules restrict their penetration in the viable layers of the skin as they have a major affinity towards the Stratum Corneum (SC). Nanocapsules have improved the biological conduct of encapsulated drugs by enhancing drug efficiency even as toxicity is avoided and they also promote drug interaction with intestinal mucosa, maintain residence time, and increase the permeability of the mucosal epithelium to enhance drug absorption which makes nanocapsule useful carriers that increase the oral bioavailability of drugs (Erdoğar et al., 2019). Nanoparticles provide improved absorption and therapeutic concentration of the drug in the target tissue, decreased administration frequency. Topical glucocorticosteroids have been frequently used to treat skin diseases. Their efficacy in the treatment of psoriasis and atopic dermatitis is due to vaso-constrictive, anti-inflammatory, immunosuppressive, and antiproliferative activities but the usage of topical corticosteroids

with topical and systemic administration is limited because of side effects like skin atrophy, steroid acne, hyper pigmentation, and allergic contact dermatitis.

Nanocapsule as a self healing material

Hydrogels and polymer acquired from acrylate, epoxy resins, etc. imitates the healing ability of organisms by exhibiting shape memory and tissue regenerative properties whereas the healing ability of some of the materials is due to external factors such as temperature, pH and light. Various chemical bonding such as ligand-metal, hydrogen bonding, π-π interaction etc. occurs at the molecular level to fill a damaged structure with high bond strength. The polymeric regenerative capabilities not only demonstrate the application of material science, engineering but also demonstrate a variety of applications in specific drug delivery, skin grafting, implants, dentistry and bone and tissue rehabilitation to improve damaged areas with better biocompatibility, better healing efficiency and high dynamic potential to serve as the next generation to increase use in the biomedical field (Pathan & Shende, 2021). The bioactive molecules l-arginine, l-phenylalanine and inositol which is a growth factor are used to synthesize a branched poly-ester amide to modulate nanocapsules for vitamin E delivery at wounded sites as they could protect cells from both extracellular and intracellular damage by scavenging reactive oxygen species. The inflammatory reaction could also be diminished benefiting from the introduction of l-arginine. When branched poly-ester amide is biodegraded the by products are natural metabolites of the body like amino acids and growth factors which guarantees the biocompatibility of the branched poly-ester amide nanocapsules (Yuan et al., 2021).

Nanocapsule bandages against infection

The presence of pathogenic bacteria that cause infections will lead to the release of antibiotics from nanocapsules, which are directed to treatment before the infection spreads. Improved wound dressing will also change color when antibiotics are released. This will therefore lead to new advances in treating patients with burns, especially children, where infection can even lead to toxic shock. Ordinary dressings should be removed if the skin becomes infected, which will delay healing and could cause distress to individual. But this new method will speed up the treatment as it is automatically activated to release antibiotics only if the wound becomes infected so, dressing won't need to be removed thus increasing the chances of the wound healing without scarring. The change in color serves as an indicator of the disease that can be treated quickly also reduces the child's risk, and reduce the amount of time individual

has to spend in hospital. The skin usually contains natural microbes, which help to keep the skin healthy. This bandage will only work for germs that cause infections. The toxins produced by them will open capsules containing antibiotics that add color to the dressing. Thus it decreases the risk of developing antibiotic-resistant strains like MRSA (Methicillin-resistant *Staphylococcus aureus*).

Nanocapsule in nutraceutical

Nutraceuticals can be defined as components of a nutritional diet that provide medical or physical benefits beyond the basic nutritional requirements and cover a wide range of compounds. Due to limited bio access, poor absorption and / or chemical reactions within the intestinal tract they show very low bioavailability. This makes their health benefits very difficult to be obtained by consumers. A proper nutraceutical-delivery system should transport bioactive molecules to specific areas without releasing their cargo to previous locations. However, it is necessary to improve delivery systems as is done with conventional pharmaceutical products, due to the fact that some nutrients degrade within the body which affects their response compared to laboratory tests (Lidia et al., 2019). For better delivery of nutrients, bio-classification of proteins, rapid sampling of biological and nanoencapsulation of nutraceuticals intricated techniques are needed. Essential oils, flavors, antioxidants, coenzymes, minerals, vitamins and phytochemicals can be used as active carrier substance in nanocapsule which also increases their bioavailability. A new approach is being introduced here, to integrate casein micelles through nano-encapsulation thus strengthening of hydrophobic nutraceutical substances to develop non-fat or low-fat food products. Without altering their sensory properties such nano-capsules could be part of dairy products. This study introduces new opportunities for the integration and delivery of critical health-promoting products using natural GRAS ingredients which are considered safe (Semo et al., 2007).

Table 1: Application of various nanocapsule formulation.

Polymer	Active substance	Targeted diseases	Administ-ration route	Result	Reference
Lipid core nanocapsules (LNCs)	Antileishmania chalcone(CH8)	Cutaneous leishmaniasis	topical	LNC-CH8 controlled infection & delivered drug to infected dermal macrophages.	Escrivani et al. (2020)
Lipid core nanocapsules (LNCs)	Tretinoin	Acne & psoriasis	topical	Enhanced photostability & deduction in the skin	Ourique et al. (2011

				permeability	
Lipid core nanocapsules (LNCs)	Triamcinolone acetonide	Ocular diseases involving inflammation	topical	Higher anti-inflammatory activity & no affect on the viability of the human corneal epithelial (HCE) cells.	Formica et al. (2020)
Chitosan - poly (ε-caprolactone) core-shell nanocapsules	Tea tree oil (terpinen-4-ol, γ-terpinene, α-terpinene, ρ-cimene & α-terpineol)	acne treatment	topical	Significant decre- ase in *C. acnes* cell viability and well suited for topical application due to its slightly acidic	Da Silva et al. (2020)
Branched poly-ester amide nanocapsules	Vitamin E	Wound healing	topical	Accelerated wound healing and shows anti-inflammatory properties	(Yuan et al., 2021).
Poly(epsilon-caprolactone)	Triclosan	Bacterial infections	Topical	Improved anti-microbial activity, Highly resistant species to free triclosan (*P. aeruginosa*) became susceptible to small dose.	De Marchi et al. (2017)

Nanocapsule for cancer treatment

Healthy cells have a life cycle, producing and dying in a way that is determined by cell type. Old cells or broken cells as they die are replaced by newly produced cells. Cancer disrupts this process and ends up growing abnormally in cells caused by mutations. Cells will divide uncontrollably, inflicting growths referred as tumor. Tumor will cause widespread health issues, including where they grow inside the body. Cancer cells can migrate through blood or systema lymphaticum to various parts of the body which is called as process is called metastasis. Carcinoma is a cancer that starts in the skin or in the tissues connected to other organs. Cancer of the connective tissue such as bones, muscles, cartilage, and blood vessels is called sarcoma; leukemia is a bone marrow cancer; lymphoma and myeloma are cancers of the immune system.

Limitation of conventional methods of cancer therapy

Current cancer therapies include invasive procedures, systemic side effects from the nonspecific nature of chemotherapy drugs, and drug-resistant tumors. In addition to limited effectiveness the side effects of current treatments include anemia, bleeding or clotting, loss

of bone mass, bowel dysfunction, fatigue, hair loss, immune suppression, lung dysfunction, lymphedema, dementia, nausea, weight loss or gain, and urinary bladder problems (Parchur et al., 2019). The bulk of cancer treatment methods comprise radiation and chemotherapies in which off-target effects are primarily due to the nonspecific toxicity of these methods. Diminishing nonspecific toxicity will improve patient's quality of life, while not affecting tumour directed dose this provides the motivation to pursue tumour-targeted nanomedicine. Further, many current therapy methods do not adequately address the individual patient differences resulting from inter and intra-tumour heterogeneity (Seoane, 2017).

Proper disease treatment would noninvasively deliver therapy only to the targeted cells limiting side effects due to the nonspecific drug action. It also exposes the tumour to a sufficient amount of drug or other therapy such as heat or radiation. Multifaceted nanoparticles (NPs) assisting in the diagnosis (usually by acting as a different agent of traditional diagnostic methods) that may be directed at a specific molecular phenotype of tumour, and presenting therapies (nanotheranostics) provide unparalleled benefits with other therapies (Bardhan et al., 2011). Integration of drugs into nanoconstructs that can be noninvasively tracked for delivery to the tumour and activated at the disease site, offers a potential solution to both (Parchur et al., 2019).

Potential use of nanocapsule in cancer treatment

Nanocapsules are potential nanocarriers for several strategies in oncology. Nanocapsule is a vesicular system that shows a typical core-shell structure in which active molecules are enclosed in a reservoir or cavity that is surrounded by a polymer membrane or coating. It can enhance drug accumulation at a specific tumour site, thereby reducing the side effects associated with most chemotherapeutic drug. Different kind of nanocapsule are synthesized such as lipid nanocapsule, starch based nanocapsule. Lipid nanocapsules are lipid-based nanocarriers which can be prepared with GRAS excipients without use of toxic solvents which are easy to scale up as well as it encapsulate hydrophobic molecules (Tsakiris et al., 2019). Lipid nanocapsule where incorporated with paclitaxel (PTX) and acriflavine (ACF) which are identified as the most promising molecules to inhibit cancer-associated fibroblast development. LNC-ACF inhibited cancer-associated fibroblast and whole tumour inhibition by LNC-PTX was observed altogether a new strategy was applied to reduce cancer-associated fibroblast populations in the colorectal microenvironment (Fourniols et al., 2020). Gemcitabine is a nucleoside analogue which acts against different human solid tumors, was

modified with lauroyl and administrated in low dose of PEGylated lipid nanocapsules (LNCs). They showed monocyte-targeting proprieties that can be useful to deplete myeloid-derived suppressor cells and attenuate tumour-associated immunosuppression (Sasso et al., 2016).

Incorporation of phytochemicals which possesses anticancer properties including vitamins, antioxidant phenolic, dietary fiber, flavonoids, and polyphenols becomes convenient due to encapsulation methods. Less stable garlic oil compounds. i.e. diallyl disulfide (DADS) and diallyl trisulfide (DATS) which possesses anticancer properties can be encapsulated in the oil core nanocapsule based on a derivative of hyaluronic acid will prevent oxidation and unrequired interaction of garlic oil compounds with digestive components preserving the anticancer property of DATS & DADS (Janik-Hazuka et al., 2021).

Curcumin derived from the roots of *Curcuma longa* is efficient therapeutic drug for cancer treatment, it affects the of cancer cells. A sustained curcumin release system should be synthesized, so it can play an important role in drug delivery and tumour cell theranostic. Curcumin and Au nanocapsule showed combined effect on inhibition of tumour cell growth and induction of cell apoptosis (Fu et al., 2017). The pectin extract mediated synthesis was found to be effective in the formation of the curcumin loaded PLA particles in nanoscale regime. The present study was successful in developing a system (PLA-10Cur NPs) with efficient encapsulation technique with controlled drug delivery and improved uptake and retention in cancer cells. The optimized PLA-10Cur nanoparticles has shown repression towards the growth and spreading of cervical cancer (HeLa) cells and provided a comfortable base for the adhesion and proliferation of normal (L929) cells. According to the earlier reports the curcumin loaded PLA nanoparticles for the evaluation of therapeutic effect had drawbacks such as higher particle size and lower penetration into the cancer cells which hindered their effectiveness in cancer treatment, which has been overcome in the given work (Alippilakkotte & Sreejith, 2018).

Calcitriol (1, 25-dihydroxyvitamin D3) can act as an anticancer agent but it requires supraphysiological doses also it is associated with hypercalcemia. Nanoprecipitation method was used to prepare calcitriol-loaded polymeric nanoparticles with different polymer to oil ratios. Human breast adeno carcinoma cells (MCF-7) were used in vitro to evaluate antiproliferative and cytotoxic activities of prepared calcitriol which showed that calcitriol-induced cell growth inhibition was closely related to its release kinetics (Nicolas et al., 2018).

Resveratrol is a naturally occurring polyphenol which could effectively starts the apoptosis pathway to inhibit cancerous cell proliferation as well as it increase the sensitivity of drug-resistant cancer cell. This property resveratrol of allows it to conjugate with either other anticancer drug or as a single drug itself which might reduce the side effects in chemotherapeutic treatment (Subramanian et al., 2010). Resveratrol can be encapsulated in a lipid-core-nanocapsule because of its excellent in vitro and in vivo stability and controlled release of resveratrol throughout the study. Cellular uptake capacity of resveratrol lipid nanaocapsule was studied in HT29 colon cancer cells. Resveratrol lipid-core-nanocapsule induced a remarkable ~36% of cell apoptosis indicating its superior anticancer effect in the case of HT29 colon cancer cells. Resveratrol kills tumour cells in part through the generation of the high amount of reactive oxygen species intracellularly. High reactive oxygen species levels induce DNA damage and activates p53 related apoptotic cascade. Resveratrol interacts with the hydrogen peroxidise - oxidase system and generates reactive oxygen species in HT 29 cancer cells and leads to cancer cell apoptosis (Feng et al., 2017).

Many fruits and vegetables contain lycopene which is a carotenoid without provitamin- A activity. Lycopene has many beneficial properties such as modulation of intercellular gap junction communication, hormonal and immune system and metabolic pathways may also be involved. Lycopene-rich extract from red guava were used to produce poly-ε-caprolactone lipid-core nanocapsules which were evaluated for cytotoxic effects on human breast cancer cells. Interfacial deposition method was used to prepare lipid-core nanocapsules which contained the extract. Viability of the MCF-7 cells was significantly reduced by lycopene rich nanocapsule particles after 24 hr & 72 hr of exposure at the lowest concentration tested (Vasconcelos et al., 2020).

Hypericin is a naturally occurring photosensitizer which is extracted from *Hypericum perforatum* plants it displays strong fluorescence which is important for imaging does not induce toxicity without irradiation. Hypericin; hydrophobic and insoluble molecule can be integrated in nanocapsule so that it gets favourable physiological conditions which can be assessed for photo diagnostic and photodynamic therapy. Its incorporation into lipid nanocapsule reduced aggregation of hypericin in aqueous media and increased its solubility. The photodynamic activity of hypericin -loaded lipid nanocapsule on human cervical carcinoma and human embryonic kidney cells showed a decrease of the cell viability to 50-60% at 0.5 µM and 10-20% at 1 µM. This study provides an in vitro proof of concept for

using hypericin -loaded lipid nanocapsules for photodynamic therapy and hold potential application of this system for in vivo photodynamic therapy for cancer treatment due to a prolonged circulation time and accumulation in tumour-bearing mice (Barras et al., 2013).

Thymoquinone is a phytochemical compound found in *Carum carvil* seeds (*C. carvil*) which has a lot of applications especially in cancer therapy. As thymoquinone is hydrophobic in nature because of which its solubility, permeability and bioavailability in biological any medium is poor. Nanoprecipitation technique was used to prepare thymoquinone -loaded polymeric nanocapsules which exhibited a delayed release pattern from the nanocapsules in vitro where as anisamide-targeted thymoquinone nanocapsules showed higher cytotoxicity against HT-29 cells over expressing sigma receptors compared to their non-targeted counterparts and free thymoquinone after incubation (Ramzy et al., 2020). Thymoquinone and near-infrared plasmonic gold nanorods (AuNRs) were loaded in folate-targeted pegylated poly (d, l-lactide-co-glycolide) (PLGA-PEG-FA) nanocapsules. Polymeric structure of both thymoquinone and AuNRs showed exhibited *in vitro* sustained release kinetics. Tumour regression and histopathological examinations showed enhanced anticancer efficacy. Thus it is proved that the proposed regime has the ability to achieve strong synergistic anticancer effects and selective tumour targeting via dual-modal targeted system (El-Sherbiny et al., 2021).

CONCLUSION

Nowadays study of polymeric nanocapsules is emerging as an alternative method for most of the medical application. Advances in polymeric nanocapsules as a drug delivery system in the medical field has been studied in the review. Nanostructure of a specific core-shell has been synthesized using various materials with the help of interfacial deposition method, nano-emulsion method, emulsion-coacervation method, layer-by layer method. The selection of polymers and construction methods mainly depends on the chemical composition and the purpose of use. Polymeric nanocapsules as drug delivery systems can improve the bioavailability of compounds and achieve sustained release of drug with target specific delivery which will overcome the limitations of conventional methods used in tumour theranostics. Different materials can be used to nanoencapsulate bioactive compounds in which polymeric nanocapsules are the most stable ones during storage and have high efficiency in controlled release of the encapsulated compound because of which it has been in focus for various studies in future use. Polymeric nanocapsules protects drug inside from

failure or damage caused by biologic environment. The study on development and characterization of bioactive compound loaded polymeric nanocapsules has been done. However, although many efforts have been made to develop targeted nanocarriers, only a few are approved for clinical use by the FDA (Barenholz, 2012). As there are still research and studies going on use of nanocapsules so this situation is because of the lack of knowledge on the distribution and accumulation of targeted nanocapsule after administration through particular method. The application of nanocapsule for the combined therapy of tumour which is simultaneous delivery of multiple anticancer drugs or the combination of commonly used chemotherapeutics with other treatment system also delivery of anticancer drugs in combination with photosensitizing agents, polyphenols, and antiangiogenic compounds may all better use of the flexibility of the proposed systems and their ability to enhance the anticancer effect.

REFERENCES

1. Abdelwahed, W., Degobert, G., & Fessi, H. (2006). A pilot study of freeze drying of poly(epsilon-caprolactone) nanocapsules stabilized by poly(vinyl alcohol): Formulation and process optimization. *International Journal of Pharmaceutics*, *309*(1–2): 178–188. https://doi.org/10.1016/j.ijpharm.2005.10.003
2. Agarwal, A., Lvov, Y., Sawant, R., & Torchilin, V. (2008). Stable nanocolloids of poorly soluble drugs with high drug content prepared using the combination of sonication and layer-by-layer technology. *Journal of Controlled Release*, *128*(3): 255–260. https://doi.org/10.1016/j.jconrel.2008.03.017
3. Alippilakkotte, S., & Sreejith, L. (2018). Pectin mediated synthesis of curcumin loaded poly(lactic acid) nanocapsules for cancer treatment. *Journal of Drug Delivery Science and Technology*, *48*: 66–74. https://doi.org/10.1016/j.jddst.2018.09.001
4. Bamrungsap, S., Zhao, Z., Chen, T., Wang, L., Li, C., Fu, T., & Tan, W. (2012). Nanotechnology in therapeutics: a focus on nanoparticles as a drug delivery system. *Nanomedicine*, *7*(8): 1253–1271. https://doi.org/10.2217/nnm.12.87
5. Barras, A., Boussekey, L., Courtade, E., & Boukherroub, R. (2013). Hypericin-loaded lipid nanocapsules for photodynamic cancer therapy in vitro. *Nanoscale*, *5*(21): 10562. https://doi.org/10.1039/c3nr02724d
6. Barenholz, Y. C. (2012). Doxil®—the first FDA-approved nano-drug: lessons learned. *Journal of controlled release*, *160*(2): 117-134.

7. Bardhan, R., Lal, S., Joshi, A., & Halas, N. J. (2011). Theranostic Nanoshells: From Probe Design to Imaging and Treatment of Cancer. *Accounts of Chemical Research*, *44*(10): 936–946. https://doi.org/10.1021/ar200023x
8. Blanco, E., Shen, H., & Ferrari, M. (2015). Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology*, *33*(9): 941–951. https://doi.org/10.1038/nbt.3330
9. Caputo, F., Clogston, J., Calzolai, L., Rösslein, M., and Prina-Mello, A. (2019). Measuring particle size distribution of nanoparticle enabled medicinal products, the joint view of EUNCL and NCI-NCL. A step by step approach combining orthogonal measurements with increasing complexity. *J. Contr. Release*, 299: 31–43. doi:10.1016/j.jconrel.2019.02.030
10. Cosco, D., Paolino, D., De Angelis, F., Cilurzo, F., Celia, C., Di Marzio, L., et al. (2015). Aqueous-core PEG-coated PLA nanocapsules for an efficient entrapment of water soluble anticancer drugs and a smart therapeutic response. *Eur. J. Pharm. Biopharm*, 89: 30–39. doi:10.1016/j.ejpb.2014.11.012
11. Couvreur, P., Barratt, G., Fattal, E., & Vauthier, C. (2002). Nanocapsule Technology: A Review. *Critical Reviews in Therapeutic Drug Carrier Systems*, *19*(2): 99–134. https://doi.org/10.1615/critrevtherdrugcarriersyst.v19.i2.10
12. da Silva, N. P., Carmo Rapozo Lavinas Pereira, E. D., Duarte, L. M., de Oliveira Freitas, J. C., de Almeida, C. G., da Silva, T. P., Melo, R. C., Morais Apolônio, A. C., de Oliveira, M. A. L., de Mello Brandão, H., Pittella, F., Fabri, R. L., Tavares, G. D., & de Faria Pinto, P. (2020). Improved anti-Cutibacterium acnes activity of tea tree oil-loaded chitosan-poly(ε-caprolactone) core-shell nanocapsules. *Colloids and Surfaces B: Biointerfaces*, *196*: 111371. https://doi.org/10.1016/j.colsurfb.2020.111371
13. De Marchi, J., Jornada, D. S., Silva, F. K., Freitas, A. L., Fuentefria, A. M., Pohlmann, A. R., & Guterres, S. S. (2017). Triclosan resistance reversion by encapsulation in chitosan-coated-nanocapsule containing α-bisabolol as core: development of wound dressing. *International journal of nanomedicine*, *12*: 7855–7868. https://doi.org/10.2147/IJN.S143324
14. Deng, S., Gigliobianco, M. R., Censi, R., & di Martino, P. (2020). Polymeric Nanocapsules as Nanotechnological Alternative for Drug Delivery System: Current Status, Challenges and Opportunities. *Nanomaterials*, *10*(5): 847. https://doi.org/10.3390/nano10050847

15. Dubey, V., Mohan, P., Dangi, J. S., & Kesavan, K. (2020). Brinzolamide loaded chitosan-pectin mucoadhesive nanocapsules for management of glaucoma: Formulation, characterization and pharmacodynamic study. *International Journal of Biological Macromolecules*, *152*: 1224–1232. https://doi.org/10.1016/j.ijbiomac.2019.10.219
16. El-Sherbiny, R. H., Hassan, M. M., El-Hossary, W. H., Shata, M. S., & Darwish, W. M. (2021). Folate-targeted polymeric nanoparticles for efficient dual (chemo-photothermal) therapy of oral squamous carcinoma. *International Journal of Polymeric Materials and Polymeric Biomaterials*, *70*(6): 414-424.
17. Escrivani, D. O., Lopes, M. V., Poletto, F., Ferrarini, S. R., Sousa-Batista, A. J., Steel, P. G., ... & Rossi-Bergmann, B. (2020). Encapsulation in lipid-core nanocapsules improves topical treatment with the potent antileishmanial compound CH8. *Nanomedicine: Nanotechnology, Biology and Medicine*, *24*: 102121.
18. Erdoğar, N., Akkın, S., & Bilensoy, E. (2019). Nanocapsules for Drug Delivery: An Updated Review of the Last Decade. *Recent Patents on Drug Delivery & Formulation*, *12*(4): 252–266. https://doi.org/10.2174/1872211313666190123153711
19. Farshbaf, M., Davaran, S., Zarebkohan, A., Annabi, N., Akbarzadeh, A., and Salehi, R. (2018). Significant role of cationic polymers in drug delivery systems. *Artif. Cells, Nanomedicine, Biotechnol*, 46: 1872–1891. doi:10.1080/21691401.2017.1395344
20. Formica, M. L., Gamboa, G. U., Tártara, L. I., Luna, J. D., Benoit, J. P., & Palma, S. D. (2020). Triamcinolone acetonide-loaded lipid nanocapsules for ophthalmic applications. *International journal of pharmaceutics*, *573*: 118795.
21. Fourniols, T., Bastien, E., Canevat, A., Feron, O., & Préat, V. (2020). Inhibition of colorectal cancer-associated fibroblasts by lipid nanocapsules loaded with acriflavine or paclitaxel. *International journal of pharmaceutics*, *584:* 119337.
22. Fu, C., Ding, C., Sun, X., & Fu, A. (2018). Curcumin nanocapsules stabilized by bovine serum albumin-capped gold nanoclusters (BSA-AuNCs) for drug delivery and theranosis. *Materials Science and Engineering: C*, *87*: 149–154. https://doi.org/10.1016/j.msec.2017.12.028
23. Gaber, M., Hany, M., Mokhtar, S., Helmy, M. W., Elkodairy, K. A., & Elzoghby, A. O. (2019). Boronic-targeted albumin-shell oily-core nanocapsules for synergistic aromatase inhibitor/herbal breast cancer therapy. *Materials science & engineering. C, Materials for biological applications*, *105*: 110099. https://doi.org/10.1016/j.msec.2019.110099

24. Gagliardi, A., Giuliano, E., Venkateswararao, E., Fresta, M., Bulotta, S., Awasthi, V., & Cosco, D. (2021). Biodegradable Polymeric Nanoparticles for Drug Delivery to Solid Tumors. *Frontiers in Pharmacology*, *12*. https://doi.org/10.3389/fphar.2021.601626
25. Garti, N. (1997). Double emulsions — scope, limitations and new achievements. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, *123–124*: 233–246. https://doi.org/10.1016/s0927-7757(96)03809-5
26. Graf, A., Rades, T., & Hook, S. M. (2009). Oral insulin delivery using nanoparticles based on microemulsions with different structure-types: Optimisation and in vivo evaluation. *European Journal of Pharmaceutical Sciences*, *37*(1): 53–61. https://doi.org/10.1016/j.ejps.2008.12.017
27. Jang, J., Bae, J., & Park, E. (2006). Selective Fabrication of Poly(3,4-ethylenedioxythiophene) Nanocapsules and Mesocellular Foams Using Surfactant-Mediated Interfacial Polymerization. *Advanced Materials*, *18*(3): 354–358. https://doi.org/10.1002/adma.200502060
28. Jagadeesh P, Dasthagiri S, Nethravani G. Review of nanocapsules. World J Pharm Pharmaceut Sci., 2016; 5(2): 1365-80.
29. Janik-Hazuka, M., Kamiński, K., Kaczor-Kamińska, M., Szafraniec-Szczęsny, J., Kmak, A., Kassassir, H., Watała, C., Wróbel, M., & Zapotoczny, S. (2021). Hyaluronic Acid-Based Nanocapsules as Efficient Delivery Systems of Garlic Oil Active Components with Anticancer Activity. *Nanomaterials*, *11*(5): 1354. https://doi.org/10.3390/nano11051354
30. Kamiloglu, S., Tomas, M., Ozdal, T., Yolci-Omeroglu, P., & Capanoglu, E. (2021). Bioactive component analysis. *Innovative Food Analysis*, 41–65. https://doi.org/10.1016/b978-0-12-819493-5.00002-9
31. Kumar, S., Chauhan, N., Gopal, M., Kumar, R., & Dilbaghi, N. (2015). Development and evaluation of alginate–chitosan nanocapsules for controlled release of acetamiprid. *International Journal of Biological Macromolecules*, *81*: 631–637. https://doi.org/10.1016/j.ijbiomac.2015.08.062
32. Lidia, A. V., Carlos, Z. M., Alicia, R. M., Amalia, V., & Jose, V. B. (2019). Nutraceuticals: definition, applied nanoengineering in their production and applications. *International Journal of Biosensors & Bioelectronics*, *5*(3). https://doi.org/10.15406/ijbsbe.2019.05.00154
33. Mahfoudhi, N., Ksouri, R., & Hamdi, S. (2016). Nanoemulsions as potential delivery systems for bioactive compounds in food systems: preparation, characterization, and

applications in food industry. *Emulsions*, 365–403. https://doi.org/10.1016/b978-0-12-804306-6.00011-8

34. Moinard-Checot, D., Chevalier, Y., Briançon, S., Fessi, H., & Guinebretière, S. (2006). Nanoparticles for Drug Delivery: Review of the Formulation and Process Difficulties Illustrated by the Emulsion-Diffusion Process. *Journal of Nanoscience and Nanotechnology*, *6*(9): 2664–2681. https://doi.org/10.1166/jnn.2006.479
35. Mora-Huertas, C., Fessi, H., & Elaissari, A. (2010). Polymer-based nanocapsules for drug delivery. *International Journal of Pharmaceutics*, *385*(1–2): 113–142. https://doi.org/10.1016/j.ijpharm.2009.10.018
36. Mukhopadhyay, P., Chakraborty, S., Bhattacharya, S., Mishra, R., & Kundu, P. (2015). pH- sensitive chitosan/alginate core-shell nanoparticles for efficient and safe oral insulin delivery. *International Journal of Biological Macromolecules*, *72*: 640–648. https://doi.org/10.1016/j.ijbiomac.2014.08.040
37. Natrajan, D., Srinivasan, S., Sundar, K., & Ravindran, A. (2015). Formulation of essential oil-loaded chitosan–alginate nanocapsules. *Journal of Food and Drug Analysis*, *23*(3): 560–568. https://doi.org/10.1016/j.jfda.2015.01.001
38. Nicolas, S., Bolzinger, M. A., Jordheim, L. P., Chevalier, Y., Fessi, H., & Almouazen, E. (2018). Polymeric nanocapsules as drug carriers for sustained anticancer activity of calcitriol in breast cancer cells. *International Journal of Pharmaceutics*, *550*(1–2): 170–179. https://doi.org/10.1016/j.ijpharm.2018.08.022
39. Ourique, A. F., Melero, A., Silva, C. D. B. D., Schaefer, U. F., Pohlmann, A. R., Guterres, S. S., Lehr, C. M., Kostka, K. H., & Beck, R. C. R. (2011). Improved photostability and reduced skin permeation of tretinoin: Development of a semisolid nanomedicine. *European Journal of Pharmaceutics and Biopharmaceutics*, *79*(1): 95–101. https://doi.org/10.1016/j.ejpb.2011.03.008
40. Palma, E., Pasqua, A., Gagliardi, A., Britti, D., Fresta, M., & Cosco, D. (2018). Antileishmanial Activity of Amphotericin B-loaded-PLGA Nanoparticles: An Overview. *Materials*, *11*(7): 1167. https://doi.org/10.3390/ma11071167
41. Parchur, A. K., Jagtap, J. M., Sharma, G., Gogineni, V., Hansen, C. P., White, S. B., & Joshi, A. (2019). Nanostructures for Externally Triggered Chemo/Thermal Therapies. *Hybrid Nanostructures for Cancer Theranostics*, 105–124. https://doi.org/10.1016/b978-0-12-813906-6.00006-8
42. Pateiro, M., Gómez, B., Munekata, P., Barba, F. J., Putnik, P., Kovačević, D. B., & Lorenzo, J. M. (2021). Nanoencapsulation of Promising Bioactive Compounds to

Improve Their Absorption, Stability, Functionality and the Appearance of the Final Food Products. *Molecules (Basel, Switzerland)*, *26*(6): 1547. https://doi.org/10.3390/molecules26061547

43. Pathan, N., & Shende, P. (2021). Strategic conceptualization and potential of self-healing polymers in biomedical field. *Materials Science and Engineering: C*, *125*: 112099. https://doi.org/10.1016/j.msec.2021.112099
44. Patil, R., Wani, M., Limaye, D., Patil, P., Zade, A., Baheti, A., Dehghan, M., Polshettiwar, S., & Tagalpallewar, A. (2021). A Review on Current Scenario in Drug-Loaded Nanocapsules in Cancer Treatment. *Annals of the Romanian Society for Cell Biology*, *25*(6): 6823-6833.
45. Pohlmann, A. R., Cruz, L., Mezzalira, G., Soares, L. U., Silveira, N. P. D., & Guterres, S. S. (2007). Structural model of polymeric nanospheres containing indomethacin ethyl ester and in vivo antiedematogenic activity. *International Journal of Nanotechnology*, *4*(5): 454. https://doi.org/10.1504/ijnt.2007.014744
46. Ramzy, L., Metwally, A. A., Nasr, M., & Awad, G. A. (2020). Novel thymoquinone lipidic core nanocapsules with anisamide-polymethacrylate shell for colon cancer cells overexpressing sigma receptors. *Scientific reports*, *10*(1): 1-15.
47. Rață, D. M., Cadinoiu, A. N., Atanase, L. I., Bacaita, S. E., Mihalache, C., Daraba, O. M., Gherghel, D., & Popa, M. (2019). "In vitro" behaviour of aptamer-functionalized polymeric nanocapsules loaded with 5-fluorouracil for targeted therapy. *Materials science & engineering. C, Materials for biological applications*, *103:* 109828. https://doi.org/10.1016/j.msec.2019.109828
48. Sasso, M. S., Lollo, G., Pitorre, M., Solito, S., Pinton, L., Valpione, S., ... & Benoit, J. P. (2016). Low dose gemcitabine-loaded lipid nanocapsules target monocytic myeloid-derived suppressor cells and potentiate cancer immunotherapy. *Biomaterials*, *96:* 47-62.
49. Semo, E., Kesselman, E., Danino, D., & Livney, Y. (2007). Casein micelle as a natural nano-capsular vehicle for nutraceuticals. *Food Hydrocolloids*, *21*(5–6): 936–942. https://doi.org/10.1016/j.foodhyd.2006.09.006
50. Seoane, J. (2017). Division hierarchy leads to cell heterogeneity. *Nature*, *549*(7671): 164–166. https://doi.org/10.1038/nature23546
51. Souza, L. R. R., da Rocha Neto, A. C., da Silva, C. R., Franchi, L. P., & de Souza, T. A. J. (2019). Green Synthesis Approaches of Nanoagroparticles. *Nanobiotechnology in Bioformulations*, 353–380. https://doi.org/10.1007/978-3-030-17061-5_15

52. Subramanian, L., Youssef, S., Bhattacharya, S., Kenealey, J., Polans, A. S., & van Ginkel, P. R. (2010). Resveratrol: Challenges in Translation to the Clinic — A Critical Discussion. *Clinical Cancer Research*, *16*(24): 5942–5948. https://doi.org/10.1158/1078-0432.ccr-10-1486
53. Tiwari, A., & Rohiwal, S. (2019). Synthesis and Bioconjugation of Hybrid Nanostructures for Biomedical Applications. *Hybrid Nanostructures for Cancer Theranostics*, 17–41. https://doi.org/10.1016/b978-0-12-813906-6.00002-0
54. Topcul, M., & Cetin, I. (2014). Endpoint of Cancer Treatment: Targeted Therapies. *Asian Pacific Journal of Cancer Prevention*, *15*(11): 4395–4403. https://doi.org/10.7314/apjcp.2014.15.11.4395
55. Tsakiris, N., Papavasileiou, M., Bozzato, E., Lopes, A., Vigneron, A. M., & Préat, V. (2019). Combinational drug-loaded lipid nanocapsules for the treatment of cancer. *International journal of pharmaceutics*, *569*: 118588.
56. Vasconcelos, A. G., Valim, M. O., Amorim, A. G., do Amaral, C. P., de Almeida, M. P., Borges, T. K., Socodato, R., Portugal, C. C., Brand, G. D., Mattos, J. S. C., Relvas, J., Plácido, A., Eaton, P., Ramos, D. A., Kückelhaus, S. A., & Leite, J. R. S. (2020). Cytotoxic activity of poly-ε-caprolactone lipid-core nanocapsules loaded with lycopene-rich extract from red guava (Psidium guajava L.) on breast cancer cells. *Food Research International*, *136*: 109548. https://doi.org/10.1016/j.foodres.2020.109548
57. Wang, J., Sui, M., and Fan, W. (2010). Nanoparticles for tumour targeted therapies and their pharmacokinetics. *Curr. Drug Metabol*, 11: 129–141. doi:10.2174/138920010791110827
58. Weber, J., Funk, N. L., Motta, M. H., Guedes, A. M., Visintainer, A. P. C., Tedesco, S. B., & Da Silva, C. D. B. (2016). Association of borage oil and betamethasone dipropionate in lipid-core nanocapsules: characterization, photostability and in vitro irritation test. *Journal of nanoscience and nanotechnology*, *16*(2): 1354-1362.
59. Yang, Q., & Lai, S. K. (2015). Anti-PEG immunity: emergence, characteristics, and unaddressed questions. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, *7*(5): 655-677.
60. Yuan, Q., Huang, J., Xian, C., & Wu, J. (2021). Amino Acid-and Growth Factor-Based Multifunctional Nanocapsules for the Modulation of the Local Microenvironment in Tissue Engineering. *ACS Applied Materials & Interfaces*, *13*(2): 2165-2178.