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# Nanocarriers based novel and effective drug delivery system

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## Highlights

- Nanosystems for drug delivery are promptly emerging science utilizing different nanoparticles as carrier.
- Nanocarriers propose numerous advantages to treat diseases via site-specific as well as targeted delivery of particular therapeutics.

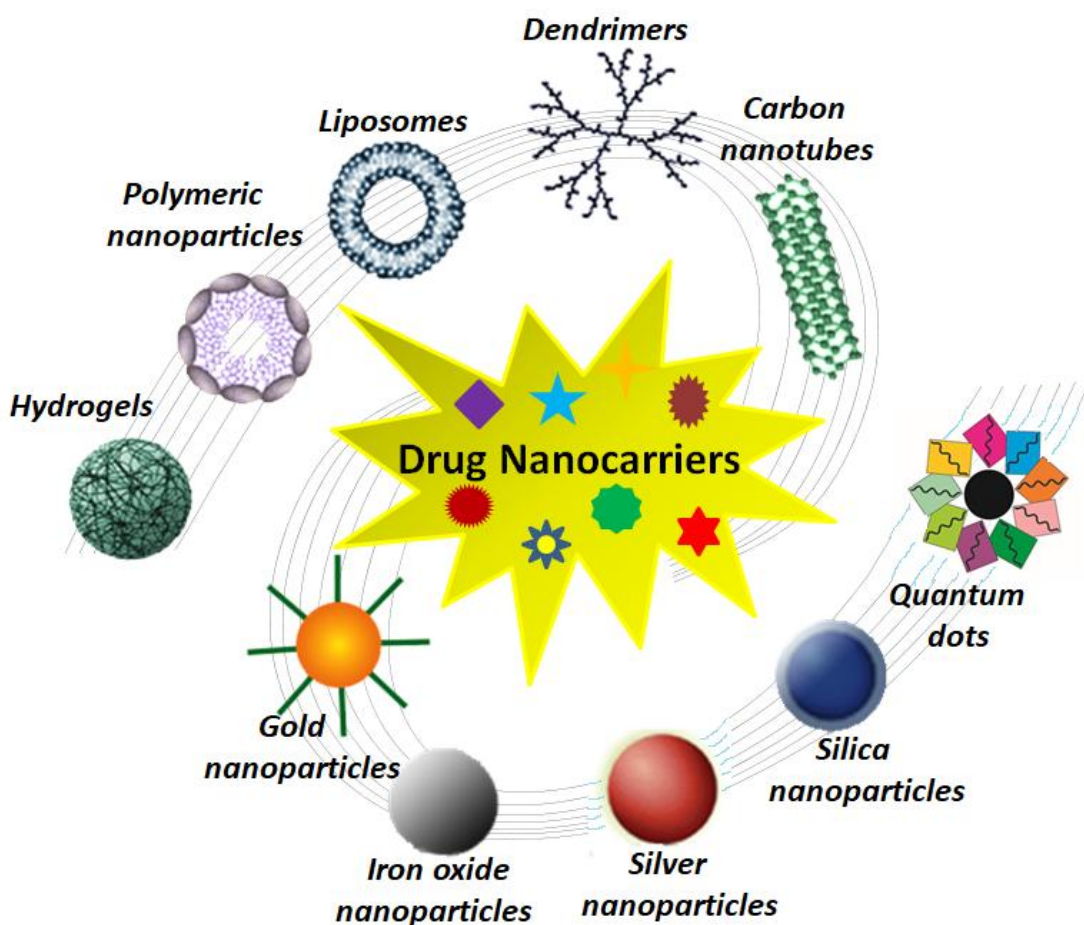
There are different types of nanocarriers (inorganic, organic, quantum dots, and carbon nanotubes) having remarkable potential for active drug delivery.

## ABSTRACT

Nanotechnology has ultimately come into the domain of drug delivery. Nanosystems for delivery of drugs are promptly emerging science utilizing different nanoparticles as carriers. Biocompatible and stable nanocarriers are novel diagnosis tools or therapy agents for explicitly targeting locates with controllable way. Nanocarriers propose numerous advantages to treat diseases via site-specific as well as targeted delivery of particular therapeutics. In recent times, there are number of outstanding nanocarriers use to deliver bio-, chemo-, or immuno- therapeutic agents to obtain effectual therapeutic reactions and to minimalize unwanted adverse-effects.

Nanoparticles possess remarkable potential for active drug delivery. Moreover, conjugation of drugs with nanocarriers protects drugs from metabolic or chemical modifications, through their way to targeted cells and hence increased their bioavailability. In this review, various systems integrated with different types of nanocarriers (inorganic, organic, quantum dots, and carbon nanotubes) having different compositions, physical and chemical properties have been discussed for drug delivery applications.

### Graphical abstract



### Keywords

Nanocarriers; Drug delivery; Inorganic; Organic; Quantum dots; Carbon nanotubes

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## **1. Introduction**

Nanotechnology is an interdisciplinary science, involving conception and consumption regarding constituents, devices, or methods on nano-scale. Currently this field is experiencing explosive growth on countless fronts leading to innovations and playing a pivotal role aimed at numerous bioapplications comprising drug delivery, molecular imaging, and biosensors. Precise drug therapies to the target sites and approaches intended for premature analysis regarding pathologies have been a significant investigation areas (Sahoo and Labhassetwar, 2003). Encapsulation or binding of drugs molecules to carrier has been an appropriate approach to handle restrictions as regards to orthodox dosage particularly inapt bioavailability, taste, constancy, also odor. These drug vehicles have been employed in pharmacological and agronomic exploration as spotless substitute in comparison to other formulations for drugs (Martinez Rivas et al., 2017).

Effectiveness, specificity, as well as ability of targeting regarding therapeutic agents have been increased via nanostructured drug vehicles. These functional platforms not only protect the payload from untimely decomposition in biological surroundings but also improve bioavailability along with persistent occurrence within blood as well as uptake by cells (Li et al., 2020b, Ayoub et al., 2011). Different techniques have been reported to develop delivery systems based on chemistry concerning to therapeutic agents in addition to the final application and retention time in body (Miladi et al., 2016). Nanocarriers of different dimensions and shape are developed by utilizing diverse matrices that control their uptake by cells and permeation through biological obstacles. Releasing mechanism of drugs through formulation is correspondingly significant because of suggested use in drug delivery. The mechanism for release could be modified subjected to nature and type of agent and nanomaterial used, respectively (Werner et

al., 2018).

Different therapeutic agents are consumed to treat diseases namely cancer, infectious diseases, and local anesthesia. Though operative doses, therapeutic impact, besides patient execution regarding these complexes are frequently restricted via their susceptibility of biodistribution in human body, resulting in side effects (Wang et al., 2019a). The profile for biodistribution and pharmacokinetics of drug molecules could be enhanced via enclosing or attaching them to the systems used for delivery that permit continuous release as well as persisting retention time. Even though, numerous systems for delivery are developed and revealed potential in biomedical applications, plus persistent release of drug molecules.

Nanoparticles, polymers, and carbon-based materials possess substantial prospective as both direct systems as well as delivery carriers for drug. Ideal carriers for drug delivery are required to be consistent, non-immunogenic, biodegradable, simple to fabricate, low-cost, and have ability to deliver payloads only to target sites (Ganesan et al., 2021). A characteristic system comprising organic (polymers, liposomes, dendrimers, etc.), inorganic (nanoparticles of magnetic, gold, silica), quantum dots, or carbon based materials (carbon nanotubes) are commonly deliberated to design systems for specific targeting of drugs (Patra et al., 2018b). The efficiency of these nano-drug carriers depends on dimensions, shapes, besides other intrinsic chemical/ biophysical features. Thus, nano-drug delivery systems propose manifold advantages to treat chronic diseases through targeted delivery regarding drug molecules.

In view of above-mentioned facts, this review reported various drug delivery systems focused on organic, inorganic, quantum dots, and carbon-based materials. The designs of different nanosystems for delivery regarding active drug molecules and evolving methodologies regarding different nanocarriers aimed at therapeutic applications were described here.

## **2. Drug design and drug delivery mechanism through nanocarriers**

With development of nanomedicine, in addition to drug design along with delivery systems for drugs, many therapeutic processes are suggested and customary clinical analytical methods are studied, for increasing diagnostic precision in addition to specificity related to drug. Innovative routes to administer drug are being explored, certifying their directed action within explicit regions, consequently decreasing their toxicity and enhancing their bioavailability inside organism (Jeevanandam et al., 2022). On this basis, designing of drug is hopeful that categorize novel drugs established upon understanding of biological targets. The innovations in investigational procedures along with computer sciences to categorize and purify biological targets are vital for growth of this area. Several studies on logical design of drug molecules and mechanisms of their release have been done (Wong and Choi, 2015).

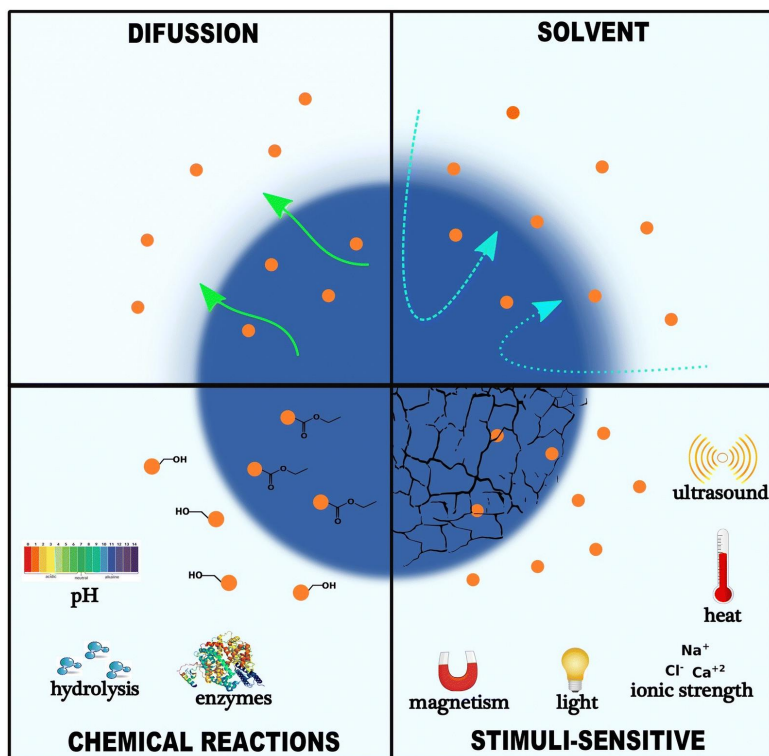
In last few years nanosystems for delivery of drugs have gained significant importance. These systems are able to stimulate release of therapeutic ingredients inside body using nanocarriers and developed newfangled opportunities as well as challenges for nanomedicine sector (Burkert et al., 2021). Remarkably, every nanosystems possess their own physical, chemical, and morphological features. They might have affinity towards diverse polarities of drugs via physical interfaces (for instance, van der Waals or electrostatic interactions) or chemical interfaces (for instance, hydrogen or covalent bonds) (Dikkumbura et al., 2022). Henceforth, all aspects effect of biological interaction with nanocarriers, in addition to kinetic regarding release of active molecules within organism (Kinnear et al., 2017). In addition to these interactions, additional parameters, for instance nanocarriers composition (for instance., inorganic, organic, CNTs, QDs, including hybrid nanomaterials) and configuration through which active molecules are linked to them forming matrix or core-shell system are likewise

essential to know about their profiles regarding drug release (Saini et al., 2020).

More than a few investigations have been done concerning mechanism of drug release consuming nanocarriers. Solvent, stimuli-controlled release, diffusion, as well as chemical reactions are some mechanisms representing drug release through nanocarriers (Fig. 1). Even though there are numerous nanocarriers having different profiles for drug release. Presently different approaches are being developed for improving precision of nanocarriers for targeting to exact site within organism, reducing immunogenicity with chemical modification or coating by different substances, for instance natural/synthetic polymers, biological molecules, and tunable surfactants, etc. (Hassan et al., 2021). In case of less affinity or binding of drugs with particular target or are not able to cross biological barriers like blood–brain barrier (BBB) or blood–cerebrospinal fluid barrier, these nanocarriers are modified with certain ligands that allow them to cross cell membrane and ensure planned delivery of drugs within specific environs (Jain and Jain, 2015). However, the design of nanosystems for drug delivery applications is laborious. Quite a few schemes for targeting have to be conducted formerly, considering physiological aspects like flow of blood, status of disease, tissue structural design, nanocarrier interaction with cell membranes, plus their mechanism of up taking by cells via non-phagocytic or phagocytic paths (Guliy et al., 2022). In the meantime some specific physicochemical features of nanocarriers are demanding to systematize action or interaction process of nanosystems inside cells. Alternatively, stimuli-responsive nanocarriers have capability to regulate profiles of releasing drugs triggered by external stimuli for example heat, ultrasound, magnetism, pH, light, as well as ionic strength (Fig.1). These factors improve targeting and permit better control over dosage. Consequently, now nanocarriers are among most favorable tools intended for targeted delivery because of their exclusive properties with improved performance for diagnostic



applications. Regardless of this, there is a lack of understanding about actual mechanisms regarding action as well as toxicity of these nanosystems aimed at delivery of therapeutic agents.



**Fig. 1.** Mechanisms intended for controllable drug release employing different nanocarriers. Reprinted from (Patra et al., 2018a) with permission from BMC.

### 3. Classification of drug delivery nanocarriers based on chemistry

In recent times, there is a huge advancement in area of systems designed for delivery for providing therapy agents to targeted location to treat various ailments. Numbers of systems to deliver drugs have been effectively engaged presently, though still some issues required to be coped with progressive technology intended for positive drug delivery to targeted sites (Obeid et al., 2017a). Conventional delivery systems have many issues regarding complex toxicity, and reduced specificity, in addition to drug opposed induction that lessens therapeutic proficiency of various drug systems. To fabricate an active system, combinatorial impact of shape, size, chemistry of the surface, patient-particular data, and additional parameters need to be considered

(Iqbal et al., 2015). Ideally, drugs molecules should be released to targeted sites in controllable way for improving their healing efficacy, in the meantime, lessen side effects. Receiving from precise release out of nano systems, loaded drugs can turn out to be “smart” (Moore et al., 2022).

Moreover, many drugs possess undesirable flavors (for instance astringency or bitterness) making them disagreeable for consumption. This can also be overcome by their encapsulation within capsules that provides not only shielding to them from hostile environment; but also they get released to the required desired site (Perry and McClements, 2020). Novel approaches to encapsulate or bind hydrophobic or hydrophilic, including natural compounds for their effective transport and delivery allows extensive range of application in the field of biotechnology (Aslan et al., 2013). Drugs possessing low solubility along with less ability of absorption can be either encapsulated within the nanoparticle or attached to the surface. They can be delivered to target with fewer doses in a controlled mode that lessen side effects coming from customary therapies (Mirza and Siddiqui, 2014). Particularly, encapsulation of drug molecules resolved core issues associated to conservative pharmacological therapies namely general distribution, quick clearance, unrestricted drug release, as well as little bioavailability (Yu et al., 2016). The general consequence is a reduction in toxicity as well as adversative reactions. Though, in spite of extraordinary advances in methodologies, many nanocarriers consumed for delivery of drugs possess undesirable side effects, which reduce their effective usage for nanomedicine. This indicated particular crucial concerns regarding strategy and fabrication of delivery systems, rising out of complex environs as well as multi-interactions developed in precise biological mediums (Liu et al., 2016).

The main objective of consuming nano vehicles for delivery of drugs is treatment of diseases effectually along with least side effects, thus targeting at profound innovation regarding

therapeutic effects using physiology and pathology of ailing microenvironment of a tissue. Novel smart nano systems are generally classified in organic, inorganic, quantum dots, and carbon based nanocarriers. Their physical and chemical characteristics are easily be altered by changing compositions, dimensions, shapes, and properties of surface. Many nanocarrier platforms are being accepted to treat several diseases (counting tumors), while rest are in various stages concerning clinical trials (Tran et al., 2017). In next sections, prominent features regarding different kinds of nanocarriers will be elaborated.

### *3.1. Inorganic nanocarriers for drug delivery*

Nanoparticles possess extremely innovative chemical features, and countless inorganic nanoparticles are being employed as carriers for drugs. Inorganic nanoparticles have exceptional physical and chemical properties for instance large surface area, unique optical and magnetic properties, and ability to get modified with different ligands that improves their attraction to target sites. They possess biocompatibility, hydrophilicity, non-toxicity, and stability compared with organic nanoparticles (Paul and Sharma, 2020). Drugs associated with inorganic nanoparticles showed release of drugs in a controlled manner and also protect its decomposition.

By incorporating drug with inorganic nanoparticles, the toxicity related to drug gets significantly reduced through a decrease in dosage and administration frequency. Inorganic nanocarriers increase the effectiveness and lessen adversarial effects. These nanocarriers commonly consist of a core region having inorganic constituent (namely silica, silver, gold, or iron oxide) surrounded with protective cover made up of organic polymers, which offers an appropriate substrate to conjugate biomacromolecules or guard core from undesirable physical as well as chemical interactions with exterior biologic microenvironment (Giner-Casares et al., 2016). Table 1 contains some of mostly employed inorganic nanocarriers, and few have been

explained below.

**Table 1**

Various inorganic nanocarriers utilized in systems aimed at delivery of drugs.

| Active drug molecules  | Inorganic nanocarrier | Size (nm) | Encapsulation efficiency | Advantages   | Disadvantages              | Ref   |
|--|-----------------------|-----------|--------------------------|--|----------------------------|---|
| Amoxicillin, pyrene 4-hydroxytamoxifen, capecitabine, tamoxifen and paclitaxel | Gold                  | 50-100 nm | 60-75 %                  | Facile synthesis, good drug loading capacity, biocompatibility and stability | Low degradability          | (Deng et al., 2020, Yahyaei and Pourali, 2019)  |
| Doxorubicin, topotecan, Quercetin  | Silica                | 500 nm    | 70-80 %                  | Biocompatibility, biodegradability, controllable porosity                    | Low stability, aggregation | (Aghapour et al., 2018, Deng et al., 2020)  |
| Rifampicin, cefotaxime, methotrexate   | Silver                | 15-25 nm  | 40-76 %                  | Biocompatible, stable, efficient loading,                                    | Cytotoxicity               | (Farooq et al., 2019, Halawani et al., 2020)  |
| Doxorubicin, curcumin, methotrexate, sorafenib                                 | Iron oxide            | 50-200 nm | 70-80 %                  | Excellent biodegradability, low toxicity, easy synthesis                     | Poor dispersion            | (Khizar et al., 2020, Ebadi et al., 2021, Nosrati et al., 2018, Yallapu et al., 2012) |
| Curcumin, doxorubicin  | Calcium carbonate     | 20-400 nm | 70 %                     | Affordability, low toxicity, biocompatibility,                               | -                          | (Deng et al., 2020, Zakaria   |

|                                       |                                |            |         |   |                       |   |
|---------------------------------------|--------------------------------|------------|---------|---|-----------------------|---|
|                                       |                                |            |         | cytocompatibility   |                       | et al., 2019, Popova et al., 2021)                        |
| Doxorubicin, paclitaxel               | Black phosphorus               | 200-300 nm | 70-90 % | Biocompatible, photothermal   | Unstable, degradation | (Chen et al., 2017, Zeng et al., 2018, Sang et al., 2021) |
| Curcumin, nedaplatin                  | Copper oxide                   | 60-90 nm   | -       | Antimicrobial action, biocompatible                                   | Toxicity              | (Aboeita et al., 2022, Targhi et al., 2021)               |
| 5-Flourouracil, doxorubicin, curcumin | Zinc oxide and magnesium oxide | 200-300 nm | 65-70 % | Stability, biocompatible, reactive, low toxicity and biodegradability | Cytotoxicity          | (Nigam et al., 2021, Batool et al., 2021)                 |

### 3.1.1. Gold nanocarriers

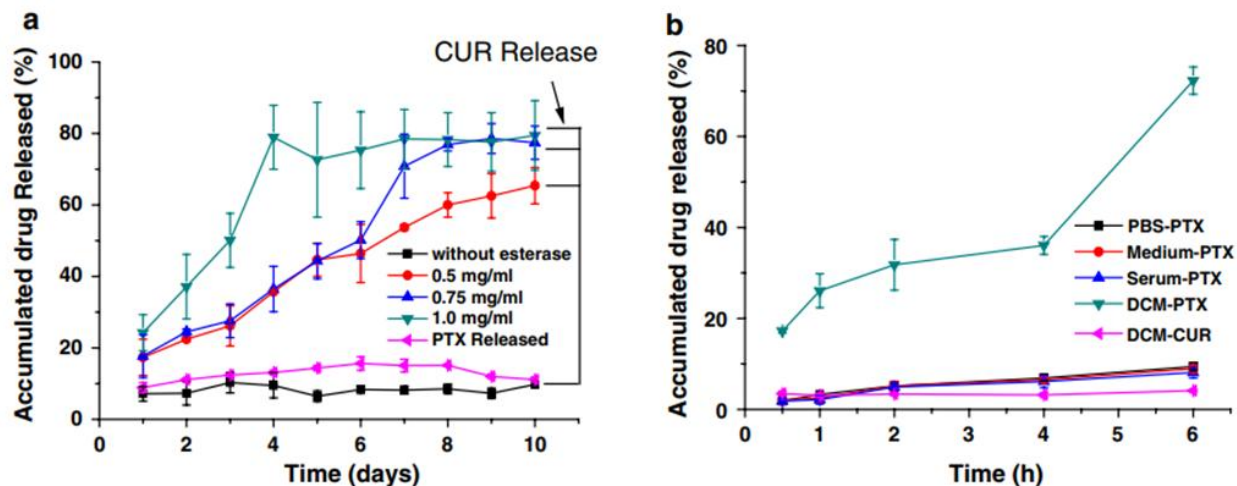
Modified nanoparticles of gold signify extremely fascinating and capable candidates intended for drug delivery application because of their exclusive sizes, tunable surface functionalities as well as controlled release of drug. Additionally, nanoparticles made from gold are biocompatible and simple to produce with accurate control on shape and size. Their exceptional optical properties enable them to scatter and absorb visible light. This section exemplifies some current advances in drug delivery consuming nanoparticles of gold as carriers aimed at therapy (Han et al., 2007, Siddique and Chow, 2020).

Hesperidin is a flavonoid glycoside used to treat different diseases. It is loaded on nanoparticles of gold (Hsp-AuNPs) to develop system for therapy. The cytotoxicity regarding Hsp-AuNPs was assessed on human cell line of breast (MDA-MB-231) cancer by crystal violet

as well as by MTT assays. A significant reduction was observed in growth inhibition and proliferation of treated cells as compared to normal epithelial cell line of breast (HBL-100). In vivo investigation was performed in mice for estimating toxicity concerning Hsp-AuNPs. Histological images of spleen, liver, kidney, and lung after their treatment by Hsp-AuNPs presented no superficial damages and abnormalities. They enriched macrophages functional activity against mice with tumor cells. Results clearly established that treatment with Hsp-AuNPs suggestively repressed IL-6, IL-1 $\beta$ , and TNF secretion (Sulaiman et al., 2020).

Gold possesses antiangiogenic and antioxidant features and has ability to obstruct angiogenic molecules. Nanoparticles of gold can be bonded to diverse types of biomolecules that improves their mobility across physiological barriers. Therefore, hyaluronan (HA) with low molecular weight was used with gold for ocular drug delivery systems to promote their circulation through ocular barriers and tissues to grasp retina. *Ex vivo*, *in vitro*, and *in vivo* analysis exposed protective impact of these nanocarriers to inhibit death of epithelial retina cells mediated by AGEs (advanced-glycation end-products) besides neovascularization. HA conjugation with gold nanoparticles increases the stability besides distribution because of interaction of specific receptor CD44. This suggested that they are capable candidates to treat ocular neovascularization in addition to associated disorders (Apaolaza et al., 2020). Doxorubicin is extensively used as operative chemotherapeutic drug. It has a disadvantage of causing cardiotoxicity. A system to deliver drug drug had been established on gold nanoparticles to solve this issue. Five analogs of thiolated doxorubicin were made to evaluate their biological activities. Two of them and ligands stabilized with PEG were bonded to gold nanoparticles and were evaluated. Results revealed that drug release might be attained through reducing agents for instance glutathione or else in acidic situations; however reductive release of drug provided

cleanest release. Nanoparticles of gold were synthesized with dissimilar doxorubicin (Au-Dox) and PEG loadings, and evaluated for toxicity and mammalian stability. Level of plasma of doxorubicin inside mice with Au-Dox was expressively low when compared to mice with same quantity of only doxorubicin. This indicates the stability of system in biological conditions. No histopathologically variances had been perceived between the mice after treatment with saline and Au-Dox. Although those having equivalent doxorubicin dose showed considerable histopathologically lesions (Du et al., 2018). Nanocarrier system was established utilizing gold nanorod, peptide modified cRGD modified, paclitaxel (PTX) along curcumin (CUR) to study combined anticancer outcome of PTX/CUR/Au NRs@cRGD. Precise cRGD bonding with integrin  $\alpha\beta3$ receptor onto surfaces of tumor enabled endocytosis concerning developed system, and improved release of drug release with chemotherapeutical efficacy. A slight NIR (near-infrared ray) presented pointedly increased *in vitro* apoptosis in addition to S phase detention in 3 cancerous cells. Additionally *in vivo*, better accumulation of drug at tumor sites inhibits growth of tumor. Thus dual drugs impact delivered a multipurpose approach towards cancer therapy. The release profiles of CUR and PTX from this system showed no effect on each other under different conditions (Fig. 2). Release of CUR release was investigated in esterase presence and PTX was anticipated to display no substantial release at same time. In various esterase concentrations, the releasing curves for CUR showed unlike efficiencies. More drug is released at high esterase concentration in tumor microenvironment. In comparison, no noticeable PTX was released in these conditions. PTX, as hydrophobic drug in our system delivers a prospect to get release in cells through drug detachment inside plasma lipophilic membrane. PTX was increasingly discharged from the system with lucid dual-phase profile (Zhu et al., 2019a).



**Fig. 2.** Drug releasing profile in various conditions. (a) PTX and CUR release from nanocarrier in esterase presence in diverse concentrations. (b) PTX and CUR release from nanocarrier. Reprinted from (Zhu et al., 2019a) with permission from PubMed Central.

### 3.1.2. Silica nanocarriers

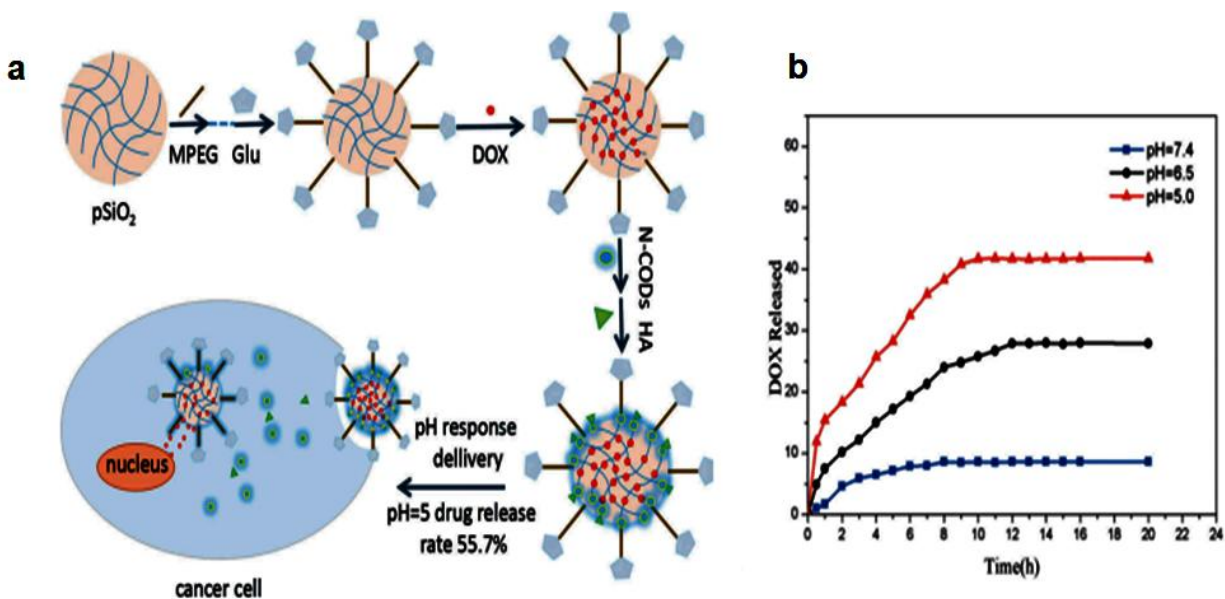
Inorganic mesoporous nanoparticles of silica (MSN) also contribute owing exclusive as well as outstanding properties particularly morphology, large surface area, controlled size of pores, as well as easiness of modification of surface. They release drug to the target site on requirement to treat cancer as well as intracellular infective disease. The drug is confined in pores till nanoparticles are triggered to discharge it (Chen et al., 2019). Stimuli-responsive system to deliver drug, having surface that is biologically active, is developed through end-crowning of MSNs by gold nanoparticles functionalized by peptide. First MSNs are modified with groups comprising acid-labile  $\alpha$ -amide- $\beta$ -carboxyl functionalities for having negative charges. After that they were covered by positive gold nanoparticles, modified by oligo-lysine possessing peptide. This hybrid system displays pH initiated lyso/endosomal release of drug. RGD peptide incorporation assists targeted delivery to  $\alpha$ v $\beta$ 3 integrin that overexpress cancerous cells. This system served as a versatile strategy to prepare multipurpose nanocarriers consuming



numerous efficient inorganic nanoparticles with bioactive peptides (Chen et al., 2016). A novel biocompatible drug delivery system (MSN-SS-PDA/DOX) was established consuming nanoparticles of silica loaded by doxorubicin, layered with polydopamine (PDA) through disulfide bonds. PDA acts as an agent for photothermal therapy (PTT) and as guard for controlling release of drug. This system showed outstanding monodispersity, release dependent on pH, redox, NIR, extraordinary photothermal conversion efficacy (40.21%), in addition to exceptional killing effectiveness of tumor cells. The pharmacodynamics and biodistribution of MSN-SS-PDA/DOX inside tumor 4T1 models specified that additional accumulation of drug in tumor as compared to free DOX with extended DOX circulation time in body. In the meantime, growth of tumor was inhibited more clearly than monotherapy. Therefore, new nano carriers grant hopeful future for combined therapy. MSN modified with biocompatible chitosan was prepared for obtaining release of drug dependent on pH. Modified MSN and chitosan takes benefit of large surface area with pore volume, along with particular chitosan features at various values of pH. The adaptation allows optimization regarding release of drug at lower pH. The release profile from these nanocarriers at various pH showed controllable curcumin release. At higher pH, release had been lower in contrast to release at lower pH (Santoso et al., 2019).

Doxorubicin loaded pH-responsive targeted system aimed at delivery of drug was designed by incorporating MSNs, MPEG (methoxy polyethylene glycol amine), N-CQDs (carbon quantum dots doped with nitrogen) Glu (L-glutamic acid), and HA (hyaluronic acid) (Fig. 3a). MPEG along with Glu grafted onto MSNs improved stability of system. While N-CQDs and HA constrain fast drug release. Rate of loading drug was equal to 8.9%. *In vitro* investigations proposed that developed silica delivery system was pH-dependent. The rate of release of drug is 55.7% at 5 pH, higher than release at 7.4 pH (Fig. 3b). MTT assay presented

that system could go into cancerous tissues or cells by endocytosis. DOX acts on nucleus of cell, revealing targeted treatment of cancerous cells (Bao et al., 2020).



**Fig. 3.** (a) Scheme for preparing system to deliver drug and illustration of pH-triggered process regarding delivery of drug. (b) Releasing profile of DOX from system at various pH within 20 hrs. Reprinted from (Bao et al., 2020) with permission from Taylor and Francis.

### 3.1.3. Magnetic nanocarriers

Currently, magnetic nanoparticles (MNPs) are promptly explored and gained global consideration because of their abundant prospective as heat mediators in hyperthermia and to deliver drugs at particular locations that limit systematic effects (El-Boubbou, 2018). Drug delivery by MNPs suggests different features for instance zero side-effects besides high effectiveness. The main purpose of using the nanocarriers in targeted delivery of drug is side-effects reduction regarding main treatment and therefore controlling the amount of drug delivered to exact tumor site (Gholami et al., 2020).

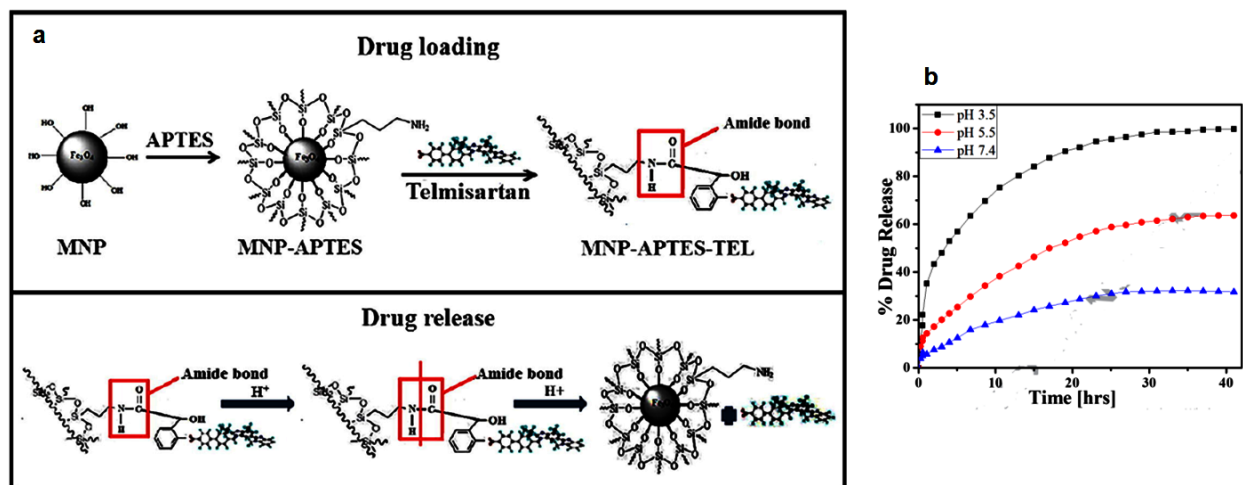
MNPs were modified with PEGylated curcumin to instantaneously take benefit of magnetic targeting feature regarding nanoparticles and drug conjugated with PEG. Incorporation

of curcumin was performed by EDC/NHS chemistry to hydroxyl PEG functionalities, and after that physical adsorption onto MNPs surface. These nanocarriers presented releasing of drug that depends on pH. At acidic value (5.4), there is more drug release in comparison to neutral pH of 7.4. The cell viability tests also exposed non-toxicity of nanocarriers at physiologic pH of 7.4 (Ayubi et al., 2019).

A nanocarrier involving magnetite core coated by mesoporous silica along with pH-sensitive shell of PEI (poly (ethyleneimine)), further bonded with folic acid was synthesized. Erlotinib was loaded as model anticancerous agent and release was assessed at 5.5 pH and 7.4 pH in four days. Release of Erlotinib increases upto 63% at low pH, whereas at 7.4, it was 33%. No noteworthy toxicity of nanocarriers without Erlotinib was perceived, although loaded nanocarriers repressed HeLa cell lines proliferation. Additionally, nanoparticles labeled with folic acid exhibited high cytotoxicity on cancer HeLa cells. Consequently, suggested system for drug release in controlled way reduces side effects concerning anti-cancerous drugs (Avedian et al., 2018).

MNPs possess high magnetization and are extremely appropriate for drug delivery applications. It aids drug accumulation at target site. Though, modification regarding MNPs aimed at binding of drug decreases magnetization that affects release of the drugs. MNPs functionalized by monolayer of (3-Aminopropyl) triethoxysilane (APTES) conserve magnetization (Fig. 4a). Anti-cancer drug TEL (telmisatran) had been loaded on monolayer of APTES deposited on MNPs. *In vitro* investigation regarding release of drug was carried out on human prostate PC-3 cancerous cell line. Loaded drug was released slowly, in addition at acidic values of pH; there was a considerable release than at physiological pH (Fig. 4b). Such strategy for functionalization might be applied to additional bioapplications in which we need high

magnetization (Dhavale et al., 2018).



**Fig. 4.** (a) Schematic illustration of development of drug loaded magnetic system. (b) Release of drug from system at different acidic and physiological pH. Reprinted from (Dhavale et al., 2018) with permission from Elsevier.

Ranibizumab is an effective monoclonal antibody which offsets active vascular endothelial growth factor A for neovascular macular deterioration treatment related to age. Magnetite was consumed to design as an effective nanocarrier to deliver ranibizumab to treat this. Ranibizumab was bonded to magnetic nanocarriers functionalized with PEG-PLGA (PEGylated poly lactide-co-glycolide). *In vitro* anti-angiogenic assessment regarding the developed system showed efficient inhibition of formation of tube inside Matrigel-based test employing endothelial cells of human umbilical vein. The established system with Ranibizumab showed no disturbance to proliferation of cells. Results do not display any substantial alterations in endothelial cells of human. These results revealed that these magnetic nanocarriers are extremely promising and different to treat neovascular age-related macular degeneration (Yan et al., 2018). MNPs are extensively used for the treatment of cancer after modification with biocompatible polymers. They have the ability to deliver anti cancerous drugs for instance 5FU.

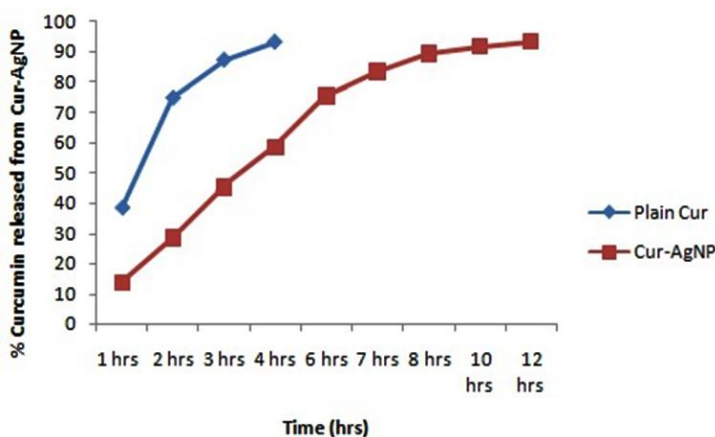
SPIONs (superparamagnetic iron oxide nanoparticles) functionalized by copolymers comprising polycaprolactone and polyethylene glycol (PCL-PEG-PCL) were used to encapsulate 5FU by double emulsion technique (water/oil/water). *In vitro* drug release profile concerning nanocarriers showed high as well as persistent release at 5.8 pH compared with 7.4 pH with 90% efficiency of encapsulation (Asadi et al., 2018).

#### 3.1.4. Silver nanocarriers

Silver nanoparticles (AgNPs) have countless applications in current era. Active AgNPs use requires surface modification with benevolent biologically moieties that improve their bio-acceptability along with additional functionalities for clinical utilization. The engineered AgNPs is one of the possible solutions for clinical difficulties, particularly enhanced drug delivery vehicles multidrug resistance, and pharmaceuticals designs with better bioavailability. Currently, AgNPs can be conjugated to antibodies, peptides, nucleic and amino acids in nanopharmaceutical model as potential drug carriers (Prasher et al., 2020).

A nanocomposite comprising cobalt ferrite, gaphene oxide, and AgNPs were produced and characterized. Its antibacterial activity was considerably improved after integration with drug ciprofloxacin. This presented robust synergistic influence in between drug and AgNPs inside composite. These composites act as strong antimicrobial agent having lower cytotoxicity as well as higher stability. Characterization results exposed the sticking of composite with cell wall of bacteria producing irreversible damage to cell. Multifunctional nanocomposite had also been explored as system to deliver ciprofloxacin in different pH solutions. Drug release is gradual and sensitive to pH in controlled way (Kooti et al., 2018). In another work, curcumin (Cur) was encapsulated in AgNPs (Fig. 5). Cur has low solubility and rate of absorption. Therefore conjugation with AgNPs increases absorption, solubility, in addition to effectivity

towards tumor. Result of hemolytic toxicity confirmed that Cur-AgNPs have less toxicity compared with plain Cur. 93.15% Cur get released from Cur-AgNPs in 12 hours from nanocarriers, whereas plain curcumin released up to 93.31% in 4 hours. *In vitro* cytotoxicity studies exposed cytotoxicity of system prompted by Cur to tumor depends on dose and effect significantly as compared to plain Cur. This displays that Cur encapsulated AgNPs illustrates probable activity against cancer (Garg, 2018).



**Fig. 5.** Releasing pattern of drug regarding plain curcumin and curcumin with silver nanoparticles. Reprinted from (Garg, 2018) with permission from An Official Publication of Society of Pharmaceutical Sciences and Research.

Anti-inflammatory and antimicrobial features regarding AgNPs combined with CHL (chlorhexidine) or MET (metronidazole) were explored for validating their applicability for treatment of Periodontal disease (PD). AgNPs-CHL is effective antimicrobial agent, though they exhibit more cytotoxicity compared with AgNPs-PEG-MET. On the other hand, both verified positive features if used within nonhazardous safe concentrations. The developed composites reduced proinflammatory cytokines namely IL-1 $\beta$ , IL-6, IL-8, and TNF $\alpha$  production. In addition they decreased metalloproteinases (MMP3 and MMP8) levels, indicating inhibition of degradation regarding tissues (Steckiewicz et al., 2022). Effect of AgNPs over HSA (human

serum albumin) configuration as well as role was measured by means of all-atom MDS (molecular dynamics simulations). Any alteration in HAS configuration, that is a transport protein, will hinder its role. Post MD studies displayed that conjugated system got stabilized due to interaction of AgNPs with HSA with time. AgNP intermingles with HSA with no effect on its secondary and tertiary configurations. Thus AgNPs are suggested for transporting integrated molecules of drug owing no adversarial impact on serum proteins. Subsequently HSA exist in circulation system, it might exposed numerous AgNPs usages in biomedical field (Hazarika and Jha, 2020). Amp-B (Amphotericin B), Nys (nystatin), and azole (fluconazole) got bonded to AgNPs. Unconjugated as well as conjugated drugs were examined for *Acanthamoeba castellanii* fitting towards T4 genotype utilizing host cell cytotoxicity in addition to amoebicidal assay. AgNPs combined with Amp-B and Nys showed substantial antiamoebic properties in comparison to drugs or AgNPs alone, revealed by viability tests. On the other hand, azole conjugation to AgNPs had imperfect result on antiamoebic features. Particularly, these drug nanocarriers subdued amoebae-facilitated cytotoxicity of host cell as evaluated by assessing release of lactate dehydrogenase. Generally, a new effective formulation was developed from AgNPs coated with drugs possessing potential aimed at future applications (Anwar et al., 2018).

### *3.2. Organic nanocarriers for drug delivery*

Organic nanocarriers to deliver drug grant modern advances in organic frameworks employed in pharmacological nanotechnology. They are an evolving class of nanocarriers by reason of their exceptional solubility in water, differences in elasticity regarding material production, simple accessibility concerning organic molecules, biodegradation, as well as photostability (Sharma et al., 2022).

These nanocarriers possess normally enhanced capacity to load drug in addition to higher

biocompatibility. They permit a useful regulation of chemical configuration and morphology. Their colloidal stability with comparatively big size permits incorporation besides loading a large number of hydrophilic and hydrophobic drugs (Souery and Bishop, 2018). Their application in systems used for drug deliver offers many benefits, particularly targeted drug release and its solubility plus stability (Fang et al., 2020). Numerous organic nanocarriers have been explored which are valuable in pharmaceutical industry. Table 2 gives summary of some organic nanoparticles and few have been explained in next section.

**Table 2**

Different inorganic nanocarriers utilized in systems aimed at delivery of drugs.

| Active drug molecules                              | Organic nanocarrier     | Size      | Encapsulation efficiency | Advantages   | Disadvantages    | Ref  |
|--|-------------------------|-----------|--------------------------|--|------------------|--|
| Rhodamine B, Paclitaxel, camptothecin, doxorubicin | Polymeric nanoparticles | 10-100 nm | 50-70 %                  | Biodegradable, easy surface modification, can load hydrophilic and hydrophobic drugs | Self-aggregation | (Sur et al., 2019, Begines et al., 2020a)  |
| Doxorubicin, paclitaxel                            | Liposomes               |           | 15-25 %                  | Can load hydrophilic and lipophilic drugs, easy to conjugate ligands                 | Cytotoxicity     | (Fan et al., 2021, Alavi and Hamidi, 2019) |



|  |               |           |         |   |   |   |
|--|---------------|-----------|---------|---|---|---|
| Doxorubicin, timolol, antisense oligonucleotides               | Dendrimers    | 50-100 nm | 70-80%  | Easy to synthesize with targeting ligands, water soluble, biocompatible | Rapid clearance, poor drug release profile, toxicity                  | (Begines et al., 2020b, Chauhan, 2018a)                       |
| Doxorubicin, amoxicillin, naproxen                             | Nanohydrogels | 10-200 nm | 75-95%  | Bio- and eco-compatible, enhanced drug dissolution, easy to fabricate   | Slow responsive, rapid drug release, possibility of drug inactivation | (Narayanaswamy and Torchilin, 2019a, Sun et al., 2020)        |
| Levofloxacin, Curcumin, dexamethasone, everolimus, bevacizumab | Micelles      | 20-400 nm | 80-90%  | Easily modified, comparatively small size, biocompatible                | Limited stability   | (Begines et al., 2020a, Majumder et al., 2020, Atanase, 2021) |
| Doxorubicin, curcumin,   | Exosomes      | 30-100 nm | 10-50 % | Organic-targeted effect, sufficient source                              | Poor uniformity and purity  | (Rajput et al., 2022, Thakur et al., 2020)                    |

### 3.2.1. Polymeric nanocarriers

Nowadays, polymeric nanoparticles are signified as most pioneering non-invasive tactics to be applied for drug delivery. They are key tools for improving bioavailability or precise delivery regarding drug at specific site. Polymers adaptability creates them hypothetically ideal

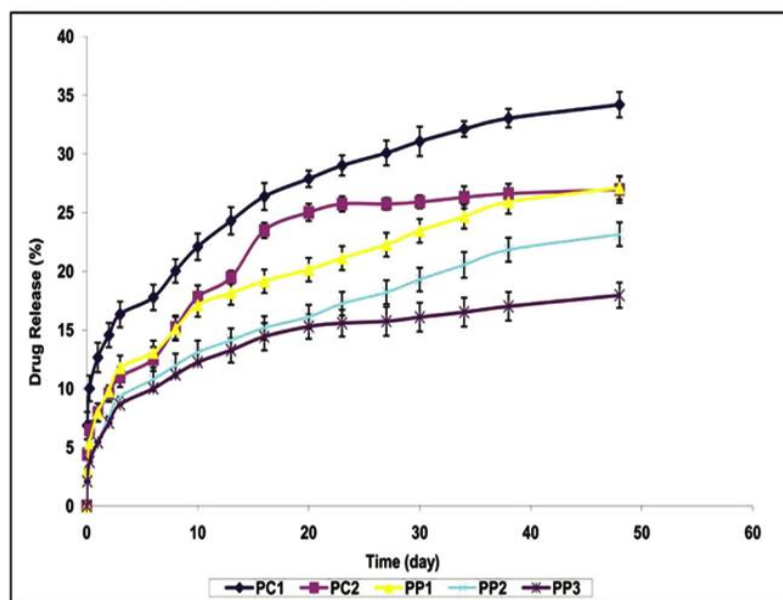
to fulfill all needs required for an accurate delivery system (Begines et al., 2020b). Major benefits comprise well control of size, slow clearance period, better therapeutic effectiveness and also less toxicity. They have the ability to deliver directly any therapeutic molecules like proteins, drugs, or nucleic acids to targeted tissues (Sur et al., 2019). Polymers are chains of monomers, mostly and naturally present inside body, consequently excreted easily without any toxicity. Numerous drugs can be internalized inside nanoparticles or dispersed physically therein. Polymeric nanocarriers can be functionalized for targeting particular cells or to cross membrane barriers (Calzoni et al., 2019).

A different process of dopamine polymerization was developed for modifying surface of nanoparticles consisting of PLGA poly (lactic-co-glycolic acid) by albumin. These nanoparticles were compared for binding extent of albumin, surface attached to albumin conformation, as well as biological acts of albumin-coated nanocarriers. Dopamine polymerization conserves structure of albumin, making layer on surface facilitating nanocarriers passage and delivery of drug to tumor site through albumin interaction with attached proteins. While interfacial embedding of albumin (denatured) provides no specific advantage to interaction of nanocarriers with cancer cells, however stimulates uptake of mononuclear phagocytic system by indirect and direct interactions with scavenger A receptor. This work validates that albumin bounded to surface bring discrete effects compared with the mode they interact with nanoparticle surface and accordingly desired to be well-ordered to attain promising therapy outcomes (Hyun et al., 2018).

Photo-responsive conjugated polymer (poly (p-phenylene vinylene)) nanocarriers were used to encapsulate hydrophobic camptothecin (CPT) and hydrophilic Doxorubicin (Dox) aimed at well-ordered drug delivery. These nanocarriers releases drugs in cells on irradiations with visible-light having wavelength 550 nm. Additionally they also change their color, structure, as

well as polarity. Remarkably these nanoparticles loaded with drug displayed exceptional biocompatibility in dark, representing flawless control of release of drug on light activation. This approach permits distantly controlled delivery of drug on irradiation with visible light suitable to design delivery carriers directed for non-invasive therapy (Senthilkumar et al., 2018).

In one research, two biodegradable materials consisting poly (ethylene glycol)- diblock modified copolymer (PEGb-PLGA and PEG-b-PCL), approved by FDA, were consumed for generating polymer nanoparticles. Five formulations were formulated varying molecular weight of polymers (PC1, PC2, PC3, PC4, PC5). These nanoparticles acts as nanocarriers for delivering antiestrogen drug Fulvestrant (FLV). *In vitro* anti-proliferation impacts were evaluated for breast MCF-7 cancerous cells. To measure cellular uptake effectiveness regarding established polymeric nanocarriers, an unsolvable coumarin-6 (fluorescent dye) was enclosed as a substitute of FLV. FLV displayed dual phase releasing pattern, representing persistent or well-ordered release after preliminary burst (Fig. 6). Initial rapid release was due to FLV present on or just near to surface of nanoparticles. Thus this system has potential to treat hormone-sensitive breast cancer (Hascicek et al., 2017).

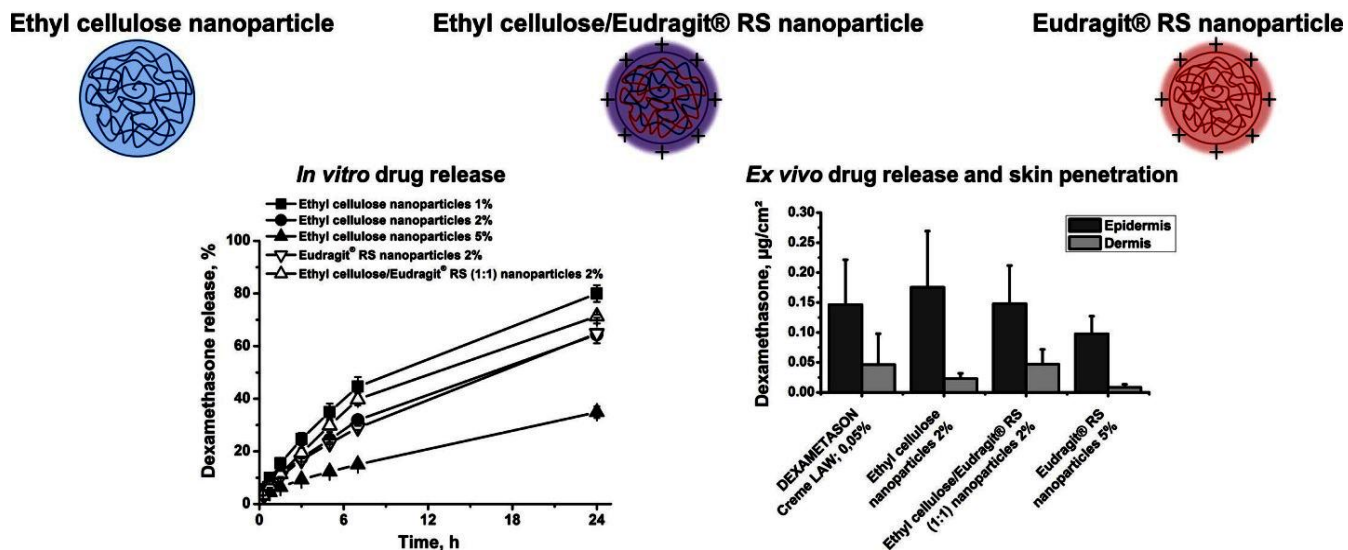


**Fig. 6.** *In vitro* suspension profiles regarding FLV from nanosystem, showing effect of composition of di-block copolymer in two different polymer matrixes on release of drug. Reprinted from (Hascicek et al., 2017) with permission from Elsevier.

Amphiphilic polymer (FTP) comprising accumulated-prompted emission fragments and polyethylene chains was effectively synthesized and engaged in loading anti-cancerous drug doxorubicin aimed at self-indicating therapy of cancer by double FRET procedure. FTP nano carriers loaded with DOX possess 21.77% drug content. They exhibited desirable hemolysis, colloidal stability, in addition to careful release of drug compared with *in vivo* anticancer impact towards DOX·HCl. The process of FRET in between acceptor (DOX) and FTP donor performed as indicator to monitor *in vivo* and *in vitro* release of drug. This nanocarrier represents favorable approach intended for realizing immediate checking regarding release and localization regarding drugs through delivery course (Wang et al., 2019b).

Corticosteroids delivery in controlled manner using polymeric nanoparticles to corneal and skin epithelium lessens side effects in addition to maximizing therapy effectiveness. Polymer nanoparticles of Ethyl cellulose, Eudragit® RS, as well as ethyl cellulose/Eudragit® RS loaded with Dexamethasone being synthesized were subjected to *in vitro* investigation utilizing Franz diffusion cells. Ex vivo diffusion of drug had also been evaluated consuming removed human skin. Nanoparticles of Eudragit® RS have low capacity to load (0.3–0.7%) compared with ethyl cellulose (1.4–2.2%). Loading capacity by mixing of two polymers reached to about 1.3%. Release of Dexamethasone and penetration expressively reduced through lessening ratio of polymer to drug and amplified when ethyl cellulose was mixed with Eudragit® RS (Fig. 7). Ex vivo penetration and release from these nanocarriers was slow compared with conservative cream. These nanocarriers have no toxicity excluding ethyl cellulose nanoparticles that have

potential of generating ROS at higher concentration. Lastly, these nanocarriers presented unlimited probability for regulating corticosteroids penetration and release on mucus membrane and skin (Balzus et al., 2017).



**Fig. 7.** Polymer nanoparticles of Ethyl cellulose, Eudragit® RS, as well as ethyl cellulose/Eudragit® RS loaded with Dexamethasone had been synthesized and investigated for *ex vivo* and *in vitro* drug release including skin penetration. Reprinted from (Balzus et al., 2017) with permission from Elsevier.

### 3.2.2. Dendrimers

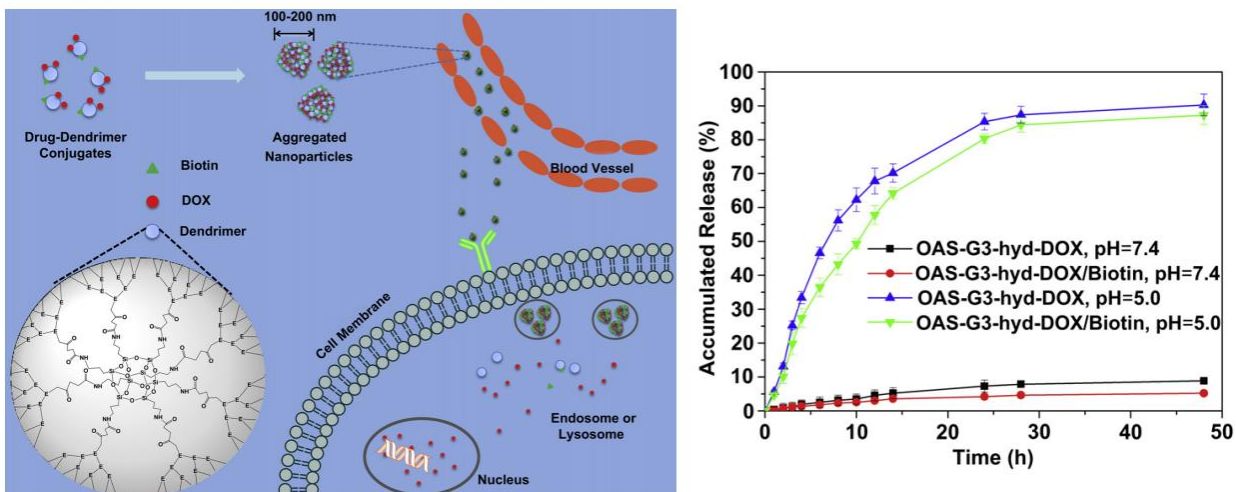
They are unique polymer nanocarriers having 3D-branched configuration with multifunctional moieties on surface that creates them multipurpose as well as biocompatible. The exclusive features of dendrimers for instance uniform nano-size, highly branched structure, multivalency, solubility in water, and vacant inner cavities. They are easy to synthesize that make them favorable carrier for delivery of therapeutic drugs and other pharmaceutical as well as for other biological applications. Incorporation of drug with them decreases toxicity related to drugs, improves their efficiencies, stability, in addition to oral drugs bioavailability (Sherje et al., 2018). They are used for drug delivery applications utilizing two methods. The first approach is

formulation in which drugs are enclosed physically inside dendrimers by means of non-covalent attachments. In second approach of nanoconstruct, drugs are covalently bonded onto dendrimers (Nikzamir et al., 2021). It is possible to regulate entrapment along with release of drug out of dendrimers via adapting their surfaces besides generations. These platforms could be designed to bond targeted ligands as well as molecules for imaging for fabricating nanodevice. Hence dendrimers, because of their multifunctional capability, have prospective of creating future generation nanodevices (Chauhan, 2018b).

A pH-sensitive CSTDs (core/shell tecto dendrimers) were established, encapsulating doxorubicin (anticancerous drug- DOX) through hydrophobic interfaces aimed at drug delivery uses. Shell is made up of G3.NHAc-BM dendrimers consisting BM (benzimidazole)-modified G3 (generation 3) poly(amidoamine) (PAMAM) and core is made of G5.NHAc-CD dendrimers consisting  $\beta$ -cyclodextrin (CD)-modified G5 (generation 5) PAMAM. The encapsulated drug is released in persistent way with fast release in slight acid condition (pH less than 6), that resembles acidic microenvironment of tumor. The improved intracellular DOX release and enhanced activity against cancer regarded presented effectual penetration of drug and inhibition of growth of 3-dimensional spheroids tumor because of quick DOX release within acid environs. Thus these pH-sensitive CSTDs possibly used as valued intelligent system aimed at delivery of different anticancerous drugs (Wang et al., 2019c). Polyacetal dendrimers modified by zwitterionic SB (sulfobetaine) loaded with DOX had been developed by thiol-ene click and aza-Michael addition reactions. These identical dendrimers have ability to form biodegradable and biocompatible micelles in water solutions, representing unique configurational stability, better resistivity towards absorption of proteins, as well as high efficiency of internalization for long interval. DOX-loaded nanocarriers displayed substantial pH-sensitive release of drug and

extraordinary anticancerous activity. Thus, polyacetal dendrimers usage concretes a good way to develop reliable as required anti-cancerous nanosystems along with noteworthy potential intended for medical translation (Wang et al., 2019d).

Dendrimers of peptides symbolize capable drug nanocarriers because of possessing exclusive nanoarchitectures along with unique biocompatibility and degradability. Dendrimers of poly(L-glutamic acid) having cores of POSS (polyhedral oligomeric silsesquioxane) were produced. Biotin as tumor targeting moiety and DOX as therapeutic agent were restrained on to dendrimers by pH-responsive hydrazone links. Uptake by cells as well as *in vivo* and *in vitro* anti-tumor performance of conjugates revealed that conjugates were internalized in breast 4T1 cancerous cells of mice proficiently. The release profiles regarding drug without or with biotin (OAS-G3-hyd-DOX/Biotin and OAS-G3-hyd-DOX) were performed inside buffer having values of pH equal to 5.0 and 7.4 at 37 °C for analyzing possibility of consuming dendrimers of OAS-poly(L-glutamic acid) as pH-sensitive nanocarriers intended for delivery of drug (Fig. 8). Release profiles displayed rates regarding DOX release at value of pH of 5.0 were more rapid compared with at 7.4. 88% DOX had been released in forty-eight hrs at 5.0 pH, whereas it was less than 10% at 7.4. Result established DOX release was fast in acid condition and retarded in neutral situation. The *in vivo* experiments in mice designated that inhibition efficacy of conjugates was better free DOX (Pu et al., 2013).



**Fig. 8.** Illustration of OAS-G3-hyd-DOX/Biotin self-assembly in addition to targeting delivery of DOX to tumor. *In vitro* profiles regarding release of DOX out of nanoparticles OAS-G3-hydDOX/biotin and OAS-G3-hyd-DOX at pH value of 7.4 as well as at 5.0. Reprinted from (Pu et al., 2013) with permission from Elsevier.

Dendrimers surfaces made of G4-NH<sub>2</sub> (amine-terminated generation 4) PAMAM (poly (amidoamine)) were fabricated by poly (ethylene glycol)-cholesterol formed DPC self-assembled nanocarriers. Uptake of nanocarriers by cells escalates in cholesterol-form-reliant mode. DPC nanocarriers encapsulate photosensitizer Ce6 (chlorin e6) for obtaining DPCC nanocarriers aimed at PDT (photodynamic therapy). For improving PDT efficiency regarding nanocarriers for tumor hypoxic tissues, MnO<sub>2</sub> was created in nanocarriers for getting Ce6/MnO<sub>2</sub>@DPC nanocarriers (DPCCM). The designed nanocarriers improved PDT outcome on laser irradiation with wavelength of 670 nm. After intravenous employment, results confirmed adequate *in vivo* therapeutic consequences. This research work offers an innovative approach to enhance uptake of drugs by cells and suggests a scheme for making smart dendrimers based nanozymes (Xu et al., 2019).

### 3.2.3. Liposomes

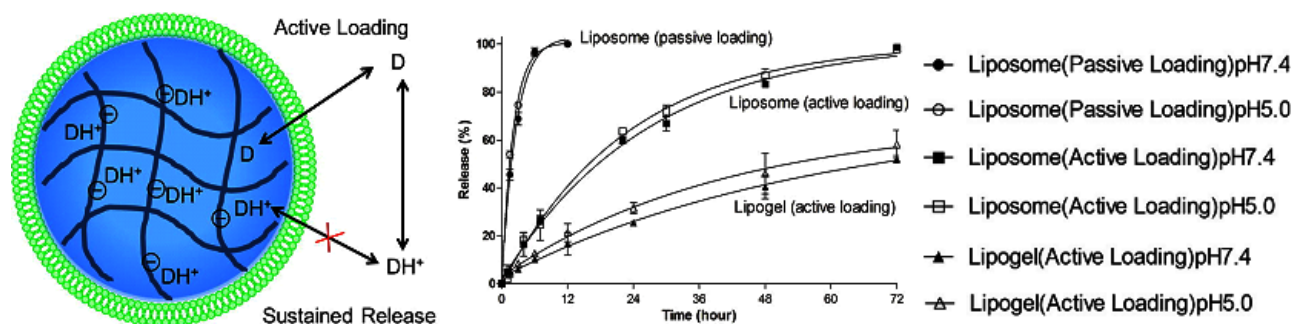
The applications of liposomes for delivering drugs in formulations have many advantages



including sustained preservation of large loads of drug at target site besides drug release in controlled manner, guaranteeing long therapeutic outcome; reduced possibility of toxicity and side-effects; in addition to improved drug protection from severe surroundings at target site (Antimisiaris et al., 2021). Liposomes are safe, nontoxic, inert and non-immunogenic, biocompatible, effective and biodegradable, signifying an influential system for delivering numerous drugs. They holds enriched therapeutic effectiveness via stabilizing complexes, controlling drug uptake by tissues and cells and enhancing its biodistribution to *in vivo* target spots, although reducing general toxicity (Guimaraes et al., 2021). Liposomes extensively used to treat numerous diseases, improving therapeutic ability by increasing absorption of drug though eluding fast drug degradation, extending its biological half-life. They have ability to label as well as solubilize both hydrophobic and hydrophilic materials. The easiness regarding their surface functionalization for adding targeting molecules create liposomes striking candidates aimed at delivery nanovehicles for drug. Many liposomal formulations are in different developmental phases of preclinical and clinical trials (Lamichhane et al., 2018).

Ammonium glycyrrhizinate-loaded ultra-deformed liposomes were evaluated for drug release and invasion through epidermis barrier and stratum corneum. *In vivo* anti-inflammatory influence regarding of loaded liposomes was verified on healthy volunteers. Results confirmed that prepared liposomes reduced inflammation of skin of human volunteers and increase topical deliverance of drugs in addition to allowing payloads distribution in blood stream. Thus these liposomes permits systemic release of various therapeutic agents in non-occlusive circumstances and possibly be employed as probable topical delivery system aimed at anti-inflammatory therapy (Barone et al., 2020). Lipogels were developed for the first time by incorporating hydrogel with liposomes as vehicles for delivering drug. It encapsulates 17-DMAPG,

anticancerous drug that is a geldanamycin (GA) derivative. This model drug holds enhanced water solubility in comparison to parent GA. Lipogels have core of hydrogels of polyacrylic acid, molded inside liposomes by DEAP stimulation and polymerization of acrylic acid and sodium ascorbate initiated by UV. Electrostatic attraction in between gel and drug are crucial intended for effective encapsulation as well as continual 17-DMAPG release with 88% loading efficacy. Dramatic sustained release of drug out of lipogels being free of pH of external solution and established that lipid double layer was integral in core (Fig. 9). *In vitro* cell culture investigations exposed that, lipogels exert no toxicity towards cells (Wang et al., 2013).



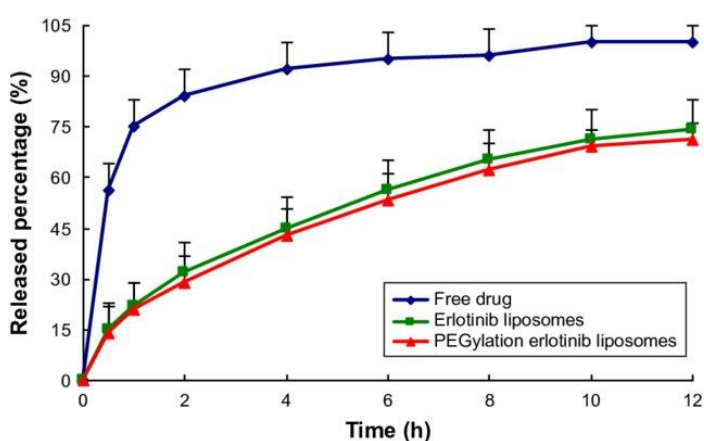
**Fig. 9.** *In vitro* kinetics regarding release at 37° C of lipogels and liposomes loaded with 17-DMAPG at pH of 7.4 and pH of 5.0. Reprinted from (Wang et al., 2013) with permission from Elsevier.

Liposomes hold capacity to incorporate hydrophilic as well as hydrophobic drugs to integrate chemotherapy for treating cancers. Folic acid (FA)-bonded liposomes incorporating irinotecan (Ir) and celastrol (Cs) were developed for breast cancerous therapy. Results exposed productive synthesis of drug loaded liposomes (Lipo/Cs/Ir-FA). This formulation displayed high releasing profiles of both drugs at pH of 5 in comparison to physiological pH of 7.4 that favors release to targeted cells. Moreover, *in vitro* investigation of cells presented higher uptake as well

as greater apoptosis within folate receiving-positive breast (MDA-MB-231 and MCF-7) cancerous cells. It was not observed in folate receiving-negative lung cancerous cells (A549). Furthermore, *in vivo* investigations for tumor model of mouse consuming MDA-MB-231 xenografts sustained operative delivery concerning liposomes bonded to folate via tumor targeting besides reducing contrary effects. Consequently, synthesized formulation gives an active therapy aimed at targeted treatment of cancer (Soe et al., 2018). A different mucoadhesive system for oral delivery was established by combining liposomes and alginates. Polymer delivers adhesives characteristics and prompts local drug release from carriers, whereas liposomes shield degradation of drug and increase its absorption by cells. 3 hybrid liposomes/alginate systems had been explored: hybrid paste having exceptional adhesive abilities, however rapid 90% release after 2 hours; hybrid hydrogel, representing well-regulated rate of release of 5%, 30% or 60% after 2 hours however reduced mucoadhesive features. This led to a cross-linked hybrid paste. This cross-linked hybrid paste offered release of 20% in controllable manner after 2 hours. Paste of alginate integrating liposomes loaded with doxorubicin presented same release and extremely active in stimulating death of cancerous cells. Consequently, such novel formulation, counting preferred mucoadhesion characteristics as well as constant release, is significant in advancement of oral cancer therapy (Shtenberg et al., 2018).

Erlotinib loaded PEGylated liposomes were assessed regarding their stability besides releasing characteristics. *In vitro* release of erlotinib out of liposomes in PBS follows Higuchi kinetic model. *In vitro* anticancerous activity displayed that blank liposomes possess low cellular toxicity. The cellular toxicity regarding erlotinib loaded liposomes amplified expressively in same incubation situation that contributes to enhance in intracellular concentration of drug by transporting liposomes. Two erlotinib loaded liposomes (without and with PEGylation) showed

same cellular toxicity without any considerably dissimilar concentrations. There is a fast release as regards free drug (Fig. 10). The other liposomes displayed comparable and persistent release with no initial burst release. Erlotinib loaded liposomes with PEGylation ominously alter pharmacokinetic performance related to drugs and advance bioavailability of drug by two times against liposomes without PEGylation. No damages for instance presence regarding epithelial necrosis or else epithelial cells sloughing had been noticed during histological investigations (Zhou et al., 2017).



**Fig. 10.** *In vitro* releasing profile from Erlotinib loaded PEGylated liposomes in PBS solution. Reprinted from (Zhou et al., 2017) with permission from PubMed Central.

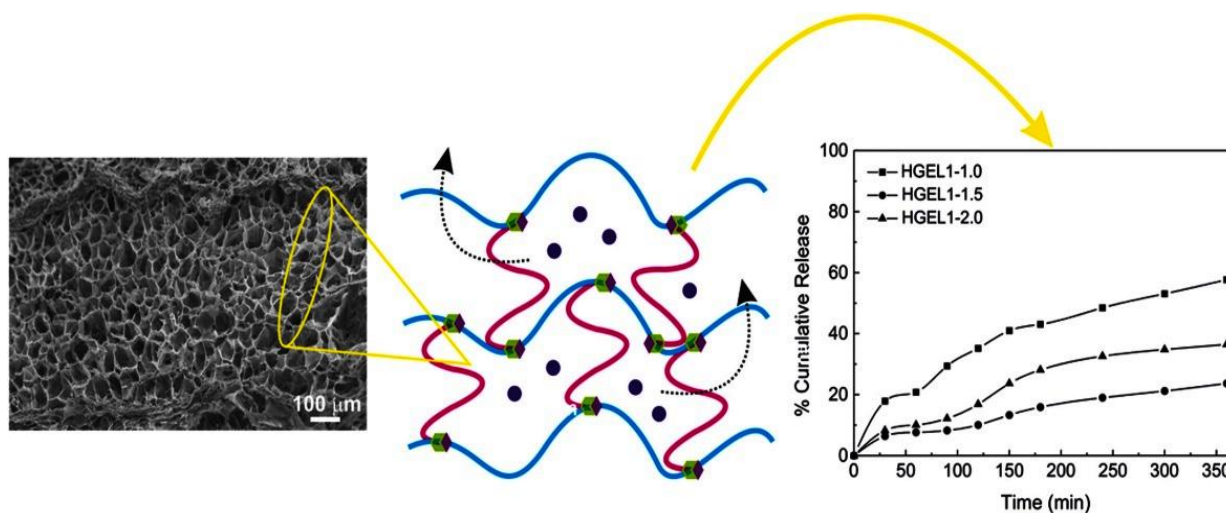
### 3.2.4. Nanohydrogels

Nanohydrogels proposes appropriate, promising, and efficient nanocarriers for delivery of therapeutics drugs used to treat numerous diseases, counting diabetes and cancer. Tunability in their physical features allows pronounced release of drug in controlled way and protects drug degradation (Vigata et al., 2020). The flexibility and variety regarding hydrogels range their usages afar from targeted delivery of drugs in addition to contact lenses, wound dressings, and tissue engineering. They hold water to about 90% as well as extremely porous for accommodating drugs that facilitate delivery and orderly release (Narayanaswamy and Torchilin,

2019b). Hydrogel nanocarriers have fewer side effects compared with general chemotherapy. Hydrogels are commonly used to deliver hydrophilic drugs. Though, different methods to integrate hydrophobic drugs in hydrogels have been developed as many drugs in market are hydrophobic in nature (Larraneta et al., 2018). Furthermore, hydrogels possess outstanding biodegradability, biocompatibility, and low toxicity against simple nanocarriers. Smart systems based on hydrogels respond to various environmental stimuli (namely; ultrasound, pH, heat, and light), allowing controlled release of drug that significantly increases suitability and efficacy of delivery systems for drugs (Sun et al., 2020).

A different method was developed to release lipophilic drugs founded on double pH-sensitive hydrogel actuator. Precisely, drug (carotenoid) is enclosed and released by pH-controlled hydrogels capsule switch. These capsules have two types of pH-sensitive hydrogels, covalently bonded with each other by silane coupling mediators. They have ability to bend mutually in acidic and basic situation for achieving “switch on” motion of capsule. By incorporation of comparable elastomer strips onto one bilayer side of hydrogel, numerous movements such as actuator bending, twisting, and rolling were attained. *In vitro* release of lipophilic drug was examined and opens possibilities to develop various delivery systems for drugs (Han et al., 2020). A multipurpose injectable mucoadhesive and pH-sensitive hydrogels sequences were made utilizing chitosan-grafted-dihydrocaffeic acid (CS-DA) and OP (oxidized pullulan) by Schiff based reaction. Such sequences showed better ability to being injected, appropriate gelling interval, *in vitro* ratios of enlargement depending on pH, morphologies, as well as rheological features. The *in vitro* doxorubicin release, loaded in hydrogels had been observed at various values of pH. These hydrogels displayed better drug release, efficiently killing colon cancerous cells (HCT116 cells), in addition to better antibacterial features for E.

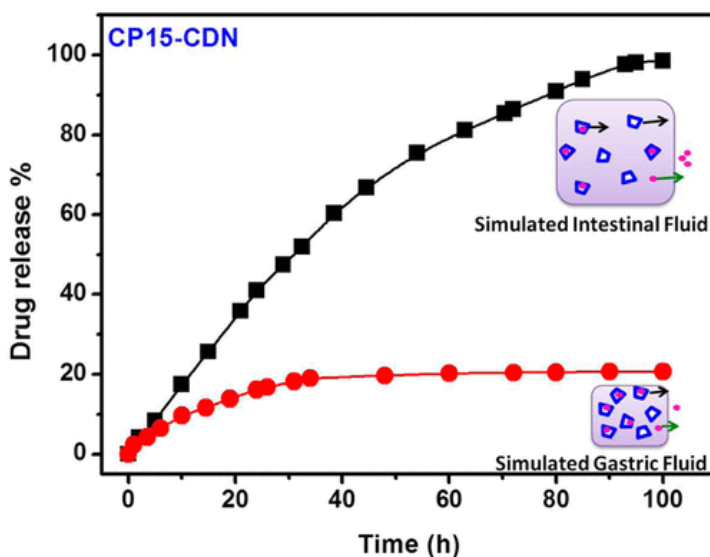
coli and *S. aureus* when amoxicillin (antibacterial drug) being enclosed within hydrogels. They exhibit sustained drug release of both drugs. They also revealed better mucous adhesion, representative their possible usage in mucosal-local systems aimed at drug delivery. These are ideal candidates to develop nanocarriers for treating colon cancer (Liang et al., 2019). Hydrogels based on porcine gelatin were synthesized consuming various cross linkers amount in water medium (Fig. 11). Hydrogels morphology was studied in various environs, to enlighten influence of permeable network configuration regarding drug delivery characteristics. Releasing outcomes presented that network was critical towards uptake and delivery of drugs. Profiles for release are almost same for every composition and found to be sustained release in precise manner. This release process was linked to network porosity in addition to cross-linker hydrophilicity (García-Astrain et al., 2016).



**Fig. 11.** Morphology (SEM image) and releasing profile from Porcine gelatin-based hydrogels having different concentration of cross linkers in PBS at 37 °C. Reprinted from (García-Astrain et al., 2016) with permission from Elsevier.

Smart pluronic (F127) hydrogels had been utilized as injectable controlled drug nanocarriers because of their fascinating properties. These hydrogels enhance patient passivity, reduces side effects, dose besides frequency related to drugs. Pharmacologically, such systems

are captivating due to safety, biocompatibility, and injectability in form of solutions before transformation to gel at body temperature. Configurational changes regarding F127 systems in exact temperature after flow, was observed during actual physical injection. Prompted structural transformation can be used to tune drug releasing profile (Shriky et al., 2020). pH-sensitive inter-polymeric hydrogels consuming glutaraldehyde cross-linked with polyvinyl alcohol and chitosan were developed. Preformed additional naproxen composite along  $\beta$ -cyclodextrin (1:1) had been loaded in hydrogel directly. They showed extreme growth at neutral pH and presented insignificant release within replicated gastric besides continued release within intestinal fluid. Initial kinetic examination exposed that rate for relaxation concerning chains of polymers was effected by cyclodextrin, resulting in slow release (Fig. 12). Harmful impact regarding naproxen on gastro-intestinal tract epithelium was reduced via utilizing cyclodextrin comprising hydrogel systems to deliver drugs since they deliver measured release leading to less concentration concerning free drug. Additionally, pH-dependent release out of such hydrogels possibly is employed aimed at targeted delivery of drug for treating cancer of colon (Das and Subuddhi, 2013).



**Fig. 12.** Drug release of drug out of developed inter-polymeric hydrogels depending on pH.

Reprinted from (Das and Subuddhi, 2013) with permission from American Chemical Society.

### 3.3. *Quantum dots nanocarriers for drug delivery*

Quantum dots (QDs) are semiconductors having nano dimensions representing an efficient tool for drug delivery applications. They have exclusive electronic and photoluminescence properties comprising wide-ranging and uninterrupted absorption spectrum, constricted emission spectrum within visible to near-infrared region of wavelengths, high illumination creates them as appropriate probe materials in drug assays (Badıllı et al., 2020). QDs have been deliberated as an effective fluorescence labels employed in system aimed at drug delivery to monitor drug metabolism inside body owing to extraordinary physico-chemical characteristics. They have been exploited in various bio-applications, particularly detection of disease in addition to fluorescence analyses aimed at drug inventions. QDs labeling approaches have assisted drug delivery investigations on various living cells and small animals. They perform as major nanocarrier for are portion of complex configuration as per fluorescent labels (Matea et al., 2017).

QDs facilitate the drug targeting and increase its bioavailability in biological areas. QDs drug nanocarriers possess potential regarding timely recognition, monitoring, as well as confined therapy of particular sites of disease. Furthermore, QDs nanocarrier drug systems enhance drug stability; prolong time for *in vivo* circulation, increases target absorption, besides advancing drug distribution along with metabolism procedure in body. Subsequently, QD drug nanocarriers come to be flash point in investigations related to nano-drugs (Zhao and Zhu, 2016). Ideal QDs drug nanocarrier have no reaction with drugs, high efficiency of encapsulation and capacity to load drug, suitable synthesis and refining technique, better biocompatibility, lower toxicity, positive mechanical power and constancy, in addition to proper particle shape and size, long *in*

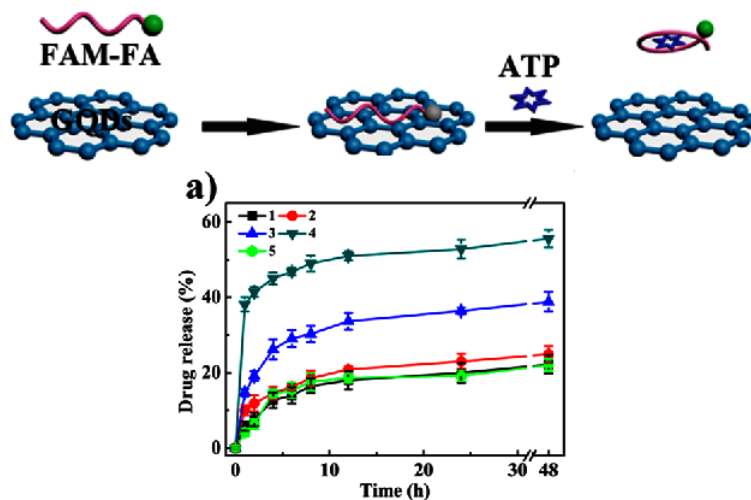


*vivo* residence duration (Mansur and Mansur, 2015).

A new drug delivery targeted system consuming QDs of Ag (silver)–In (indium)–Zn (zinc)–S (sulphur) was established. QDs were fabricated by 11- MUA (mercaptoundecanoic acid), L-cysteine, and lipoic acid modified by FA (folic acid) being employed as innovative system for delivery aimed at targeting drug (doxorubicin) to FARs (folate receptors) onto adenocarcinomic human alveolar basal (A549) epithelial cells. Biologic screening exposed that nanoconjugates comprising QD–FA–DOX possess high toxication compared with other prepared QDs, signifying cytotoxicity of DOX released out of QDs. In contrast to nanoconjugates comprising QD–MUA–FA–DOX appeared to be more toxic towards A549 cells among others. *In vitro* analysis showed substantial migration inhibition regarding A549 cell after treating them by QD–MUA–FA–DOX. Investigations demonstrated all nanoconjugates at IC50 influenced more breakage in DNA than witnessed in non-treated cells. Thus, QD–MUA–FA–DOX nanocarriers indicated highest genotoxicity and cytotoxicity, considerably inhibiting drifting potential concerning A549 cells (Ruzycka-Ayoush et al., 2021). An easy and effectual process to develop sulphur and nitrogen doped photoluminescent carbon QDs has been established aimed at targeting cancerous cells. Development of innovative imaging agents intended for cancerous cells is important as well as extremely reliable approach designed for treating cancer. The fluorescence carbon QDs made of folic acid and  $\kappa$ -carrageenan served as a proficient carrier for labeling cancerous cell stating folate receptor onto their surface. These QDs revealed good solubility in water, exceptional photostability, as well as biocompatibility. They act as nanocarriers for anticancerous drug capecitabine in various pH environs. Moreover, they can be valuable as unseen indicator in addition to finger pattern recovery uses. Folate receptor in QDs results in remarkable targeting of cancerous cells and holds a pronounced potential for

biomedical research (Das et al., 2019).

A smart nanocarrier for drug utilizing FRET (fluorescence resonance energy transfer) had been invented through coating graphene QDs (GQDs, as acceptor) on fluorescent MSNS (as donor) by ATP aptamer for immediate control of ATP-stimulated release of drug (Fig. 12). In extracellular situations, fluorescence regarding MSNs is in "off" position at low level of ATP that is incapable to stimulate drug release. When precisely accepted and internalized in target cells via AS1411 aptamer, in cytoplasm rich in ATP, configuration switch of ATP aptamer results in detaching of GQDs from nanocarriers, releasing drugs and therefore leading to severe toxicity. Concurrently, MSNs fluorescence switched "on" resulting in decomposition of GQDs. It permits immediate regulation of drug release out of pores. This system represents high particularity of bi-target revealing with AS1411 along with ATP aptamer in addition to extreme sensitiveness of FRET-dependent controlling strategy. Release of drug was performed at various ATP levels (Fig. 13). There is an increase in DOX release with time in presence of various ATP amounts. Therefore, projected multipurpose ATP activated FRET-nanosystem would find prospective usage aimed at adaptable drug-release observation, effectual drug vehicle, as well as targeted therapeutics for cancer (Zheng et al., 2015).

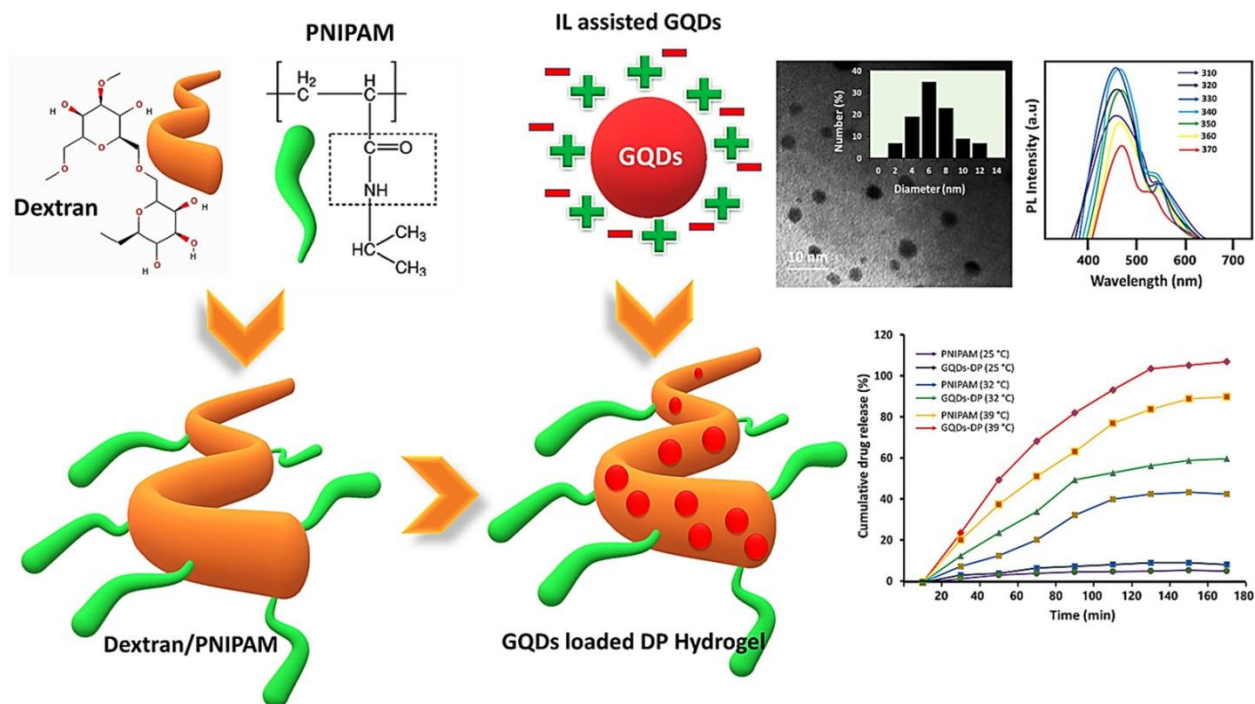


**Fig. 13.** Diagram showing ATP aptamer interaction with QDs. 1-4. Releasing profiles from FRET-nanocarriers having various different ATP concentrations in 10 mM phosphate buffered saline with pH 5.0. ATP amounts added were 0 mM, 1 mM, 5 mM, and 10 mM, correspondingly. 5. Releasing profiles regarding G-FMSNs-Dox-PEG on adding ATP (10 mM) in PBS (phosphate buffered saline). Reprinted from (Zheng et al., 2015) with permission from American Chemical Society.

Hybrid SiO<sub>2</sub>-coated QDs (HQDs) bonded to graphene were designed aimed at cancer imaging and tracking along with controlling delivery of drug along cancer treatment. Shell of hybrid SiO<sub>2</sub> onto surface of QDs lessen their toxicity and guard fluorescence from quenching via graphene. A targeted imaging system was developed by modifying HQDs-bonded graphene surface by Trf (transferrin). It was able of different uptake and imaging cancerous cells, expressing Trf receptor. Extensively used drug, doxorubicin was adsorbed on graphene surface. This system displays dissimilar fluorescent color in between DOX and graphene-HQDs in water core on irradiation with same wavelength used for tracking and observing drug delivery. The developed simple multipurpose nanocarrier could deliver DOX to targeted sites and allow localization of graphene-HQDs besides regulating intracellular release of DOX (Chen et al., 2013). QDs are used as an ideal hard nanocarrier for intracellular activated actuation for achieving spatiotemporal manipulation of release of drug as well as modulation related to drug effectiveness. Two peptides were bonded to QDs, one peptide for cell-penetration that helps uptaking of QDs in endocytic path and second one is display peptide bonded to drug doxorubicin by means of three bonds i.e. disulfide, ester, and hydrazine, which are sensitive to enzymatic partition, decreasing conditions, and lower pH, correspondingly. QD-peptide-DOX-CPP composite regulate peptide ratio of both species bonded to QDs and ultimate dose of drug carried

to cells. Delivery of composite led to cytotoxicity regarding ester bond analogous to free drug (DOX). DOX bonding through hydrazone link eased intermediate cytotoxicity, whereas amide and disulfide bonds presented minimum toxicity. Results validate usage of composites as multipurpose scaffolds to control simultaneously cellular uptake and toxicity concerned to drug. Thanks to chemical bonding that affixes drug to QDs based nanocarrier (Sangtani et al., 2018).

An innovative nanocarriers comprising thermo-sensitive graphene QDs (GQDs) loaded with copolymeric matrix of dextran/poly (N-isopropylacrylamide) (Dex/PNIPAM) were prepared and examined for persistent system for drug delivery, tissue viability at implantation site (Fig. 14). Functionalization of copolymeric complex with GQDs was done for obtaining thermal receptive delivery of drug without any harmful effect at implantation site. These nanocarriers are irregular having porous and uniform structure that is considerably positive for cellular uptake as well as act as an active nanocarrier of drug to cells along with better flow of fluid. PNIPAM composite displayed continual and improved percentages regarding release of drug with increase of temperature at 39 °C which is above LCST (low critical solution temperature). It is analogous to cumulative release below LCST at 32 °C. This confirmed thermo-sensitive polymer played an important role in delivery systems. GQDs-Dex/PNIPAM had no inflammatory reaction and displays remarkable stromal infiltration concerning cells (Yue et al., 2019).



**Fig. 14.** Scheme of DP hydrogel development loaded with GQDs. *In vitro* buprenorphine releasing profile depending on temperature from hydrogel matrix, below (25 and 32 °C) and above LCST (39 °C). Reprinted from (Yue et al., 2019) with permission from Elsevier.

A simplistic method was established for synthesizing carbon QDs modified with hyaluronic acid (HA) loaded with doxorubicin as delivery platform. HA-functionalized CQDs were prepared to target CD44 with branch-PEI and citric acid as core source for carbon. HA acts as hydrophilic moiety as well as targeting ligand besides QD component for such system. The release of drug is pH dependent. Prepared nanocarriers showed good *in vitro* hemocompatibility and serum constancy, whereas displayed higher toxicity towards 4T1 cells. The higher *in vivo* nanocarrier accumulation inside tumor had been affirmed by live imaging. Blood hematology as well as biochemistry confirmed that prepared nanocarriers had no evident cytotoxicity that established their biocompatibility. Hence this formulation delivers a substitute approach aimed at targeted therapy of breast cancer (Li et al., 2020a).

Graphene QDs (GQDs) as well as doped GQDs are potential nanocarriers for delivering

drug Iso (isoniazid). To synthesize these QDs, hexa-peri-hexabenzocoronene (GQD model) along with its BN-, BP-, AlN-, and AlP- doped ( $C_{36}X_3Y_3H_{18}$  where  $X = B, Al$  and  $Y = N, P$ ) types had been designated. Consequences specified adsorption energies concerning Iso onto doped GQDs had been considerably adverse compared with pristine GQDs. Furthermore, calculations of adsorption regarding Iso on AlP- and AlN-doped GQDs were thermally promising. The AlP-Iso and AlN-Iso composites possess little energy gaps, and lower chemical capacities, in addition to lower overall hardnesses that were suitable to attach to targeted sites. Results established that AlP- and AlN-doped GQDs are promising nanocarriers to be applied for drug delivery (Vatanparast and Shariatnia, 2018).

Hydrophobic core-shell fluorescence QDs of ZnSe:Mn/ZnS and paclitaxel had been co-encapsulated within folate bonded hybrid nanocapsules of silica through F127 micelles. These composites display higher photoluminescence constancy in temperature range of 19 to 49 °C. Additionally, PTX solubility in water was proficiently increased to 630 times. Sustained release of drug was perceived in 12 hours. Tunable fluorescence, improved loading efficacy with constant release marked these hybrid nanocarriers as hopeful theragnostic platform intended for joined imaging and therapy in future (Zhao et al., 2017). A parenteral multipurpose system for drug delivery comprising nanostructured lipid carriers (NLC) co-loaded by paclitaxel and QDs (CdTe/CdS/ZnS). These NLC were spheroid in shape with comparatively smooth morphology. 80 % encapsulation efficiency with 4.68% capacity to load drug were noted. The co-loaded NLC showed a dual phase release of drug. The rate of inhibition for growth of tumor was found out to be 77.85%. *Ex vivo* and *in vivo* imaging consequences showed ability of NLC for precisely targeting and detecting tumour H22. Tissues exhibited no noteworthy cytoarchitectural variances. Therefore formulation of NLC is promising parenteral system to deliver drug aimed at

cancer theranostics (Olerile et al., 2017).

The drug 5-FU (5-Fluorouracil) was loaded in Mn-ZnS QDs enclosed within chitosan (CS), combined with folic acid (FA). *In vitro* 5-FU release from loaded nanocarriers confirmed regulated release in comparison with release of free drug. The synthesized nanocarriers persuaded high *in vitro* apoptosis in cancerous breast cells against cells with free drug. Moreover, *in vivo* toxicity of these nanocarriers in comparison to control had no increase in kidney and liver activities. They were especially collected inside tumor, contributed to less occurrence of metastasis when compared with cells treated with free drug. Results confirmed selected *in vivo* and *in vitro* anti-cancer effectiveness for breast 4T1 and MDA-MB231 cancerous cells, respectively. It provides a design to improve drug efficiency and cancer targeting selectivity with restricted systematic toxicity (Bwatanglang et al., 2016).

Black phosphorus quantum dots (BPQDs) are combined with bilayers of liposomes for fabricating system of drug delivery having exceptional NIR (near infrared) photo-thermal features and light regulated releasing of drugs. Doxorubicin is encapsulated in these nanocarriers and its NIR-controlled release was investigated (Fig. 14). Encapsulation efficacy was found to be 89.6%. There is a rapid release of DOX out of liposomes on irradiation with light. Releasing profile displays rapid release in first five minutes in addition to continued release later. After five minutes, at power densities equal to 1.5, 1.0, and 0.5 W cm<sup>2</sup>, release percentages regarding drug were 20.0%, 42.6%, and 48.1%, correspondingly. It indicates that rate of release can be attuned by adjusting power of laser. *In vitro* investigations validate their better biocompatibility and NIR-induced photothermal-chemo antitumor efficacy (Geng et al., 2018).

#### 3.4. Carbon nanotubes nanocarriers for drug delivery

Carbon nanotubes (CNTs) display exceptional inherent chemical and physical

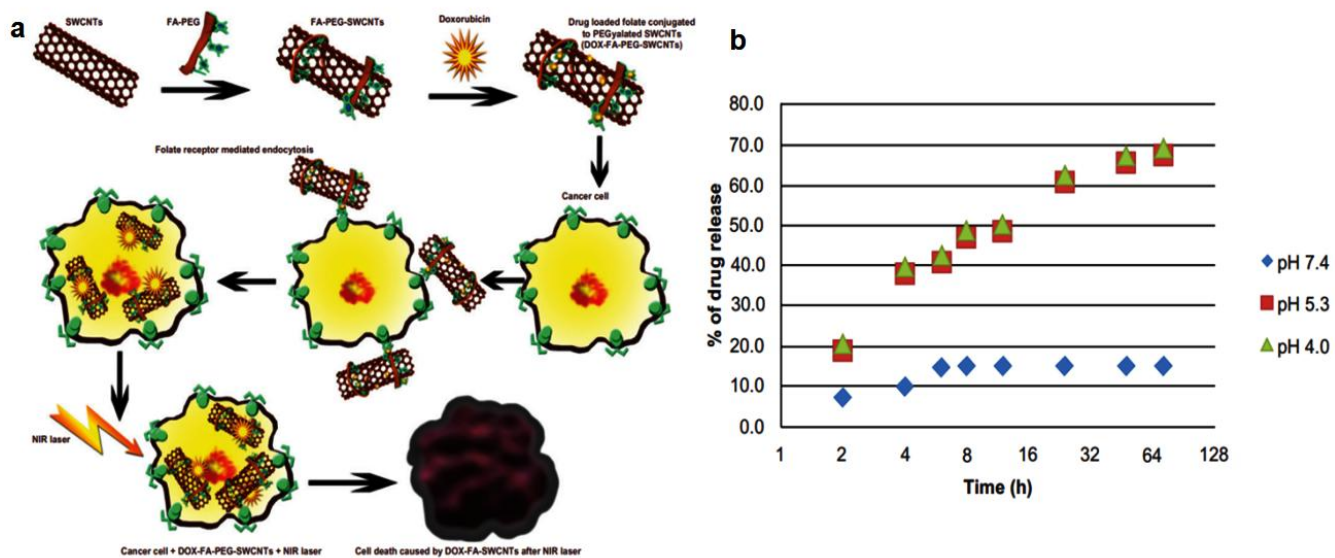
characteristics, extensively investigated for useful applications in last few years, predominantly in nano-delivery and targeting systems regarding drugs. CNTs might be multiwalled (MWCNTs) or single-walled (SWCNTs). Charge on the surface, purity, surface area, distribution of size, morphology, surface chemistry, as well as agglomeration condition of CNTs have significant role in their reactivity. CNTs possess good capability intended for preferred for systems for drug delivery, gene transfer, and cancer treatment (Kaur et al., 2019). They gained significant importance among different nanocarriers because of their biocompatibility, high surface area, in addition to capacities of delivering bulky loads regarding drugs and also biomolecules. Their unique strength, besides flexibility has raised great interest in pharmacological area for number of reasons. Recently, innovative modified CNTs were developed for addressing deficiencies of orthodox CNTs and to create them better nanocarriers (Ravi Kiran et al., 2020, Jha et al., 2020).

CNTs high aspect ratio is accountable for their exceptional penetration in cell, their conductivity is ideal to integrate with muscular and nervous tissues, their large surface area enhances their capability to interact with biological material, their hollow morphology delivers a vast capacity for loading and carrying drug, and their external can be functionalized permitting biological recognition and solubility. Among all desirable features, CNTs modified by polymers are efficient for controlled drug delivery. To fabricate stimuli-sensitive delivery, huge efforts were made, in which drug release is manipulated under specific stimuli reaction (Hasnain et al., 2019). CNTs are valuable in drug delivery nanosystems particularly controllable and targeted delivery of drugs to chosen sites for instance brain, ocular systems, lymphatic systems, and other cancer tissues. They could be adapted with carbohydrates, organic molecules, polymers, or peptides, and then utilized mostly in targeting of cancer and accumulation in tumor for improving their prospective regarding delivery therapeutics (Mahajan et al., 2018).



SWCNTs had been employed as a nanocarrier of immunomodulatory antiviral drug, isoprinosine for improving anti-nervous necrosis virus (NNV) activity. Results showed that drug effectively defended SSN-1 cells from NNV infection. Percentage of apoptosis was pointedly reduced after treatment by drug. Likewise, drug displayed intense anti-NNV activity inside zebrafish, with IC50 (inhibitory concentration at half-maximal activity) values of about 86.44 and 52.47 mg/L, later to exposition to drug for three and five days, correspondingly. Isoprinosine therapy signified improvement of immunity towards NNV infection. SWCNTs based delivery system along with BSA and drug after internalization in SSN-1 cells, showed general distribution in larvae of zebrafish. These nanocarriers had strong anti-NNV reactivity compared with naked drug. Results indicated that SWCNTs has possible usage value for controlling viral diseases (Zhu et al., 2019b). Carboxylic functionalized SWCNTs loaded with Flutamide (anticancer drug) were explored for drug delivery performance. Results verified energetic constancy and showed that adsorption of drug on CNTs is physical. Hydrogen bonds between Flutamide and the carboxylic group play an important role towards stabilization of configurations under consideration. Results from simulation proved that molecules of drug are adsorbed strongly on surface of nanotube and possibly employed as delivery carrier for drug (Kamel et al., 2018). Doxorubicin (DOX), SWCNTs, in addition to hydroxyl- and carboxyl-functionalized SWCNT (*f*-SWCNTs) were investigated to fabricate, enhances, and increases CNTs nanocarriers for drug delivery systems. Hydrogen bonds between molecules of DOX and *f*SWCNTs performed a vital role than pure CNTs in fixation and adsorption studies in addition to their thermodynamic energy. Theoretical evaluation of the results showed that doxorubicin drug on pristine and functionalized SWCNTs can be employed as drug nanocarriers (Karimzadeh et al., 2021). Photothermal impact of SWCNTs with anticancerous doxorubicin is validated to target and accelerate annihilation of

cancerous breast cells (Fig. 15a). Nanocarriers regarding directed delivery for drugs were established for killing breast cancerous cells selectively with biofunctionalized polyethylene glycol and SWCNTs loaded with DOX and bonded to folic acid. *In vitro* drug release analysis displayed that drug binds at pH value of 7.4 and get released at lower pH only, that is lysosomal pH of 4, typical pH of tumor (Fig. 15b). Sustained drug release out of SWCNTs was perceived for 3 days. In near-infrared (NIR) region, SWCNTs possess intense absorbance and biological systems are also extremely transparent. Such optical characteristics regarding SWCNTs paved the way to specific photothermal ablation aimed at treatment of cancer. *In vitro* testing's revealed the effectiveness of laser cancerous cell killing, without harming normal healthy cells. On combining laser with DOX-SWCNTs, there is an increase in killing of cancerous cells of breast. Therefore, these nanocarriers, containing drug, laser in addition to SWCNTs, seems promising with large therapy effectiveness besides reduced side effects meant for cancer treatment (Jeyamohan et al., 2013).



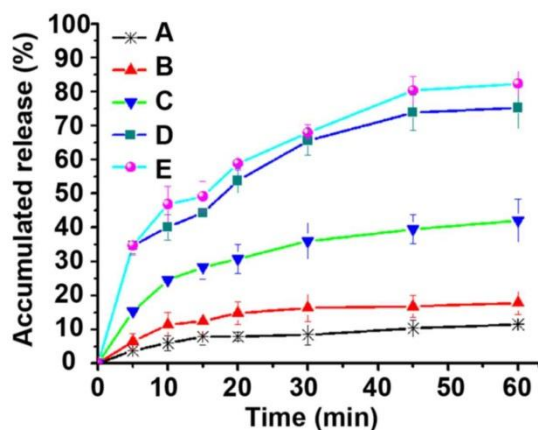
**Fig. 15.** a. Representation of a nanosystem consisting of SWCNTs, biologically functionalized by PEG (polyethylene glycol), bonded to folic acid (FA); loaded with DOX (doxorubicin) with

photothermal treatment to selectively kill cancer cells. b. *In vitro* DOX releasing profile from DOX-FA-PEG-SWCNTs in PBS at pH values equal to 4, 5.3, and 7.4. Reprinted from (Jeyamohan et al., 2013) with permission from Dove Medical Press.

An electrical-sensitive transdermal delivery system of drug was developed by matrix of semi-interpenetrating network of polymer along pentaerythritol triacrylate and polyethylene oxide. To enhance electric sensitivity, MWCNTs were employed. Drug release investigations were performed in various electrical voltage conditions. There is an increase in release of drug with high electric voltages applied to the system. This is because of the exceptional electric conductance of CNTs used as additive. The proposed device intended for drug release comprises polymer network dissolved in CNTs effects, thus discharging drug. Hence MWCNTs improved the sensitivity of developed system aimed at transdermal delivery of drug (Im et al., 2010). CNTs can be modified with diagnostic and therapeutic agents. The CNTs fabrication as nanocarriers loaded with drug opens way for their engagement as nanovectors into cells. Cisplatin, platinum-based chemotherapeutic drug was embedded in to SWCNTs and investigated for *in vitro* drug release. The cisplatin release under physiological conditions was analyzed to predict CNTs role in blood from where they are transported to tumor site. For preventing non-selective as well as non-specific cellular uptake and subsequent side-effects, it is essential cisplatin release happens in cytoplasm, not before reaching cells. The restriction on the viability regarding prostate (PC3 and DU145) cancerous cells from cisplatin encapsulated CNTs showed efficacy of developed delivery system. This is a forward step towards CNTs usage as anticancer nanocarriers in human body, though filled composite was not uniform in all its portions (Tripisciano et al., 2009). A drug delivery system based on CNTs was developed integrated with two anti-cancerous drugs (mitoxantrone and doxorubicin). The developed system possesses high chemical and biological

stability, higher capacity to load drug and specific *in vivo* therapy of cancer by active targeting approach. pH-dependent release of drug within buffer solutions was demonstrated and verified uptake of nanocarriers by cells and intracellular release of drug by confocal microscopy. Therapeutic effectiveness regarding system in cell viability analysis displayed that CNTs with only drug are less efficient than free drugs; however, bonding of folic acid as targeting molecules considerably improved efficiency and selectiveness of system. Free forms of drug are extremely operative for *in vitro* investigations owing aqueous dispersibility besides membrane penetrability. CNTs loaded with drug are precise compared with free drugs, permitting continued release, that reduces side effects related to drugs in animals and clinical examinations. Generally, CNTs have potential to be used as multimodal system for delivery of drugs and overcome many problems come across in this area concerning biomedical application (Heister et al., 2012).

MWCNTs loaded with poor soluble dipyridamole (DDM) with different rates to load drugs (10, 25 and 50%) were evaluated along with impact of drug-loading efficacy on release from MWCNT-DDM system (Fig. 16). Results showed the change of state of DDM in CNTs, with increasing loading of drug loading, from amorphous to crystalline form. Correspondingly, rate of DDM release get reduced with increasing rate of drug-loading of nanocarriers. In short, MWCNTs based delivery hold promising prospective as nanocarriers to load DDM for preventing thrombosis in patients having or valvular or vascular disease (Zhu et al., 2019c).



**Fig. 16.** Dissolution releasing profiles of (A) DDM, (B) DMP, (C) DM-50, (D) DM-25 and (E) DM-10 in weak-basic medium (pH 6.8). DDM, dipyridamole; DMP, MWCNT-DDM physical mixture. Reprinted from (Zhu et al., 2019c) with permission from PubMed Central.

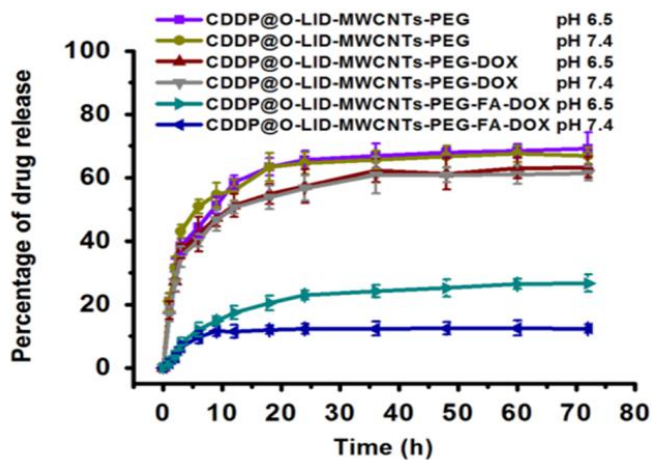
SWCNTs were investigated as Droxidopa carrier by quantum mechanics measurements for gaseous medium and dynamic molecular simulation in aqueous medium. SWCNTs were modified as carboxylated CNTs and then loaded by Droxidopa. The process of adsorption was methodically analyzed by means of density functional technique. Results showed effective loading of drug by intense chemisorption along energy of adsorption of about  $-0.714$  eV. Improved solubility of SWCNTs and consequently enhanced bioavailability as well as less toxicity possibly is attained via carboxylated SWCNTs loaded with Droxidopa. This is an effectual drug nanocarriers that overcomes limitations regarding Droxidopa and assist targeting (Yoosefian and Jahani, 2019). Alginate and chitosan modified SWCNTs based system for drug delivery; loaded with curcumin (CUR) has also been investigated. Modified SWCNTs presents high efficacy concerning drug loading and persistent release of drug. System with CUR incorporation in modified SWCNTs was investigated for *in vitro* release to foresee perception of release of entrapped CUR out of modified SWCNTs depending on pH. A continued release of drug was preserved at pH of 5.5 and 7.4 for hrs. Prominently, cumulative CUR release increases

at pH 7.4 from 28.6% to about 91.2% at 5.5 pH in 72 hrs. Such pH stimulated release offers selective release in different conditions and mainly useful for targeting cancer with acidic environment. The anti-cancerous prospective was established consuming lung A549 adenocarcinoma cells of humans as model system. Different cell cultural assays verified the inhibition of proliferation of cancerous cell by persuading apoptosis (Singh et al., 2018).

Dox-linked glycoblock copolymers with CNTs were designed as efficient nanocarriers for targeted drug delivery. Carboxylic acid adapted CNTs were further functionalized by poly(1-O-methacryloyl- $\beta$ -D-fructopyranose-b-(2-methacryloxyethoxy)benzaldehyde)-Py/Dox and alkynyl decorated CNTs by poly(1-O-methacryloyl- $\beta$ -D-fructopyranose-b-(2-methacryloxyethoxy)benzaldehyde)-N3/Dox. Their biocompatibility, aqueous dispersibility, besides hybrid-CNTs (glycoblock copolymer decorated CNTs interactions with cancerous cells get improved through functionalization. The hybrid-CNTs having chained fructose along folic acid moieties apparently transport anticancerous drugs proficiently in cancerous cells (MDA-MB-231 and MCF-7), later to recognition and bonding to analogous receptors. Such functionalized CNTs with anticancerous drug holding fructosylated glycoblock copolymer are promising for targeting delivery of drugs to cancerous cells of breast (Omurtag Ozgen et al., 2020). MWCNTs are effectual drug nanocarrier. MWCNTs were modified with polyethylene glycol (MWNTs-PEG) and after that loaded with doxorubicin. Thermodynamic investigations presented spontaneous DOX adsorption on nanocarrier as well as exothermic in nature. The cumulative DOX release from nanocarriers of MWNTs-PEG depends on pH. Releasing rate at 5.5 pH was much greater in contrast to release at 7.4 pH. Releasing curves display fast release initially, followed by persistent release that remained continued for long time. Thus drug release depending on pH from MWNTs possibly employed in systems aimed at delivery of drugs due to

the acidic environment of tumors (Farahani et al., 2015).

A new system to deliver drug aimed at cancer therapy was developed using MWCNTs as nanocarriers. MWCNTs were loaded with anticancerous drugs, doxorubicin (DOX) and cisplatin (CDDP). The efficiencies for loading DOX and CDDP were 192.67% and 84.56, respectively. Particularly, later to CDDP encapsulation in nanotubes, FA (folic acid), PEG (polyethylene glycol), along with DOX were utilized for blocking CDDP leavings at various levels. pH-responsive DOX and CDDP release was verified by adapted characterization technique. In conclusion, anticancerous activity of system on MCF-7 cancer cells was examined and combined impact was investigated. Excluding system with FA at 7.4 pH that presented short fast release and comparatively shorter persistent release, all additional five releasing profiles displayed short fast releasing phase with prolonged persistent releasing phase (Fig. 17). This work delivers a foundation to develop an innovative antitumor therapy combining photothermal and chemotherapy (Yang et al., 2017).



**Fig. 17.** Releasing profile of CDDP from CDDP@O-LID-MWCNTs-PEG, CDDP@O-LID-MWCNTs-PEG-DOX, and CDDP@O-LID-MWCNTs-FA-PEG-DOX at various values of pH. Reprinted from (Yang et al., 2017) with permission from Springer Nature.

#### 4. Comparison between different nanosystems for drug delivery

Nano drug delivery systems are moderately novel however speedily emerging field where nanomaterials are utilized for delivery of therapy agents to particular targets in controllable manner. Nanocarriers offer manifold benefits to treat human chronic diseases to specific site through targeted delivery of particular medicines. In recent times, exceptional applications regarding nanomedicine (biological, chemotherapeutic, immunotherapeutic agents etc.) have been developed to treat several diseases. Nanocarriers are the bridge between physical and biological sciences by applying different nanostructures with different phases to develop effective nano based drug delivery systems (Rudramurthy et al., 2016).

Inorganic, organic, and polymeric nanocarriers are recurrently investigated to design particular nanosystems for delivery of drugs. Particularly, drugs with low solubility and have less ability of absorption are labeled with such nanocarriers. Though, effectiveness of nanocarriers differs depending upon shape, size, along with additional intrinsic chemical/biophysical properties (Watkins et al., 2015). Organic nanocarriers particularly, polymeric nanocarriers display features that are idyllic for proficient nanovehicle aimed at therapeutic delivery. Due to their higher biocompatibility in addition to biodegradability, different synthetic polymers for instance polyethylene glycol (PEG), poly-L-lactic acid (PLA), polyvinyl alcohol (PVA), and poly(lactic-co-glycolic acid) (PLGA), as well as natural polymers, like chitosan and alginate, are widely utilized for nanofabrication of nanocarriers (Obeid et al., 2017b). Polymeric nanocarriers could be synthesized in spherical and capsules form which both are outstanding for delivery of drugs. Similarly, compacted lipid nanocarriers as well as phospholipids counting micelles and liposomes are beneficial for targeted delivery. Inorganic nanocarriers showed potential for drug delivery with benefits like physical and chemical robustness, higher loading ability, less toxicity



besides simple and inexpensive production in laboratory (Khafaji et al., 2019). However only few are accepted for clinical usage, while rest of them are still under clinical trials. Among inorganic nanoparticles, gold and silver and possess specific feature such as surface plasmon resonance, that organic nanocarriers do not own (Majdalawieh et al., 2014). In addition they exhibited numerous benefits for instance better biocompatibility as well as adaptability for surface modification. Though, inorganic nanocarriers showed some problems in contrast to organic nanocarriers like partial penetration inside living cells or tissues due to their inflexible nature (Baeza et al., 2017). CNTs are appropriate for encapsulation of drug attributed to their features regarding surface and dimensions, in addition to their critical physical potentials. The stability and strength of CNTs are employed for their characterization so as to use them as reliable drug carriers (Saad et al., 2012). QDs are advantageous for persistent and controllable release regarding therapeutic agents. Strong photo-stability, narrow emission, wide UV excitation, along intense fluorescence are certain properties that make them appropriate for therapeutic applications (Abdellatif et al., 2022). Nevertheless QDs possess some toxicity that can be lessened after modification of their surface. Hence in a nutshell employing nanocarriers for drug delivery increases bioavailability, decreases dose proportionality, reduces toxicity, and increases drug dissolution rate (Sim and Wong, 2021).

## **5. Future perspectives of drug delivery nanosystems**

Delivery of therapeutic agents using nanocarriers is presently most interesting research field. Considerable research has been done in the field of nanomedicine and several clinical trials have been completed (Pandit and Zeugolis, 2016). Among various diseases, cancer is most common diseases profited by nonmedicinal technologies. Employing different nanocarriers to deliver precise drug amount to diseased cells, with no effect on functioning of normal cells, is

positively an effective trend that will be a future research dome for upcoming eras. The nanocarriers discussed in this review vary in size, some having sizes in nanometers while others are in sub-micrometers. Further research regarding nanocarriers having regular homogeneity, loading and release capacity of drug could be an advance research area. The use of various nanocarriers for therapeutics can prospectively lead towards broader demand of nanocarriers in coming future. The main interest is to fabricate nanocarriers that get absorbed properly inside soft cancer cells and making them vulnerable to radiations used in radiotherapy intended for discriminatory removal.

In spite of vast understanding regarding future vision of using nanocarriers in drug delivery system, the real impact of these systems in healthcare is very inadequate even for cancer theranostics. This is a newfangled field of research from the past few years; still main fundamental aspects are being unfamiliar. The essential biomarkers of diseased cells, which permit unconditional targeting with no alteration in normal physiological process is foremost area of future research. Eventually, usage of nanocarriers would progress along with our growing knowledge about diseases at cellular level. Nanocarriers with cellular dimensions to identify biomarker unlock new paths for effective therapy and will result in improvement of nanomedicinal applications. Release of particular drugs in controllable manner at targeted sites, knowledge to assess effect of drug inside molecular level; in addition to theoretical predication models are not being finalized yet. Several studies concerning nanomaterials are focused on biomaterials and appear to be in preliminary stages. Supportive data regarding therapeutic come from *in vivo* studies and comprehensive researches needs significant time along with resources. Evolving worldwide trend for looking precise medicines to treat diseases, future of capable and multi-focused methodology regarding nanocarriers and nanosystems aimed at delivery

technology appears bright.

There exists a desire to develop simple nanocarriers that function in tissue therapy with bursting controlled process. This possibly would be achieved by researchers in future. Along with advantages, however, the risk concerned to nanocarriers to humans as well as to environment needs extensive investigation too. Henceforth, suitable influence of severe besides chronic toxicity of them on both must be examined. As nanosystems for drug delivery are gaining fame, their competitiveness is another research area. Lastly, nanocarriers would evolve continually with advances in their applications.

## **6. Conclusions**

With advancement of material, pharmaceutical, and biomedical sciences, numerous controllable releasing nanocarriers are engaged in systems to deliver drugs. Nanoparticles as carriers for drugs are worthy candidates for targeted delivery because of their easy availability, biocompatible, ease of functionalization, and stability. Such properties permit encapsulation of toxic drugs and direct delivery to cancerous site. Herein, we highlighted some of latest advancement regarding nanocarriers as innovative platforms toward effectual delivery and controllable drug release. Systems to deliver drugs established upon nanoparticles are advantageous to traditional anticancerous drugs by guaranteeing cytotoxicity regarding drugs to only tumor specific sites. The foremost objective regarding effective nano-delivery systems is the reduction of dosage required for particular treatment, consequently dropping the expenses and side effects related to their usage.

Nanocarriers as delivery systems for drugs enhanced bioavailability concerning payloads and attain persistent as well as targeted delivery. Similarly, they effectually decrease destructive impacts between tissue environments and payload. By loading of drug in nanostructured

materials, drug gets protected from decomposition by physiological environment. Mostly inorganic and organic nanocarriers are broadly consumed in delivery concerning drugs and revealed a diversity of harmonizing as well as combined features, which are possibly and profitably used. Among them, organic nanocarriers showed improved characteristics, identical to physicochemical situations in pathological and biological tissues, therefore providing finest biocompatible nanocarriers. Additionally, nanocarriers based on QDs and CNTs also suggest balanced functions aimed at analysis as well as recognition of pathological disorders within diseased organs. Because of significant effect of microenvironment in diseased cells or tissues upon delivery efficacy regarding nanocarriers, the selection of nanocarriers is critical to design competent nanocarriers intended for precise functions. Exceptional characteristics of these nanocarriers controlled operative delivery of drugs, without any side effects, to preferred sites. Before any clinical employment of these nanocarriers, they undergo *in vitro* and *in vivo* analysis for ensuring that they would not be harmful to living tissues. Because of difficulties and uncertainty related to delivery procedure of drugs involved, computational modeling has evidenced beneficial for optimization of nanocarrier design.

Till now, several investigations have been primarily dedicated to fabrication, improvement, in addition to characterization of drug-loaded polymeric nanocarriers. Though, storing and purification approaches of drug-loaded nanocarriers require considerations and investigations. Furthermore, future perceptions in nanocarriers for drug delivery systems should be focused on consuming novel and effective nanomaterials for developing progressive system aimed at drug delivery, thus ranging usages of drug-loaded nanocarriers in pharmacological fields. Presently, computational modeling is not being widely employed in pharmacological sectors because of their low predictability. Mostly models are focused on particular routes for

drug delivery, not whole procedure at diverse scales, i.e. Drug to patient scale. Multistage modeling at dissimilar spatial and temporal scales is unusual. Even though smart drug nanocarriers are more effective for diagnostic and therapeutic applications, still potential durability is needed to be estimated before applying these systems to clinics. For researchers, it is a great challenge to advance preclinical investigations to adaptable and reproducible production for clinical-trial realization. Yet, the ultimate objective of all analysis, investigations, and efforts are patient's treatments. Consequently, a deeper understanding and knowledge involving interaction of nanocarriers with diseased tissues is essential to develop novel and different therapeutic methodologies and procedures established on consumption of smart drug nanocarriers.

### **Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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