NOVEL SIMULATION OF AUNPS IMPACT IN TARGETING, APOPTOTIC, NECROTIC PROCESS ON SEVERAL TYPES OF CANCER CELL

A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF APPLIED SCIENCES OF NEAR EAST UNIVERSITY

By
SAFA ANMAR AMEEN

In Partial Fulfillment of the Requirements for the Degree of Master of Science in Biomedical Engineering

NICOSIA, 2019

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name:
Signature:
Date:

We as biomedical engineers strive to be the hope of all vulnerable people suffering from diseases …

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ABSTRACT

Cancer is an intricate disease at various levels of cell line and has a lethal effect on human, animals or even plants, which poses a threat to the safety of the life on our planet. The increased incidence and mortality due to cancer lead to attracts attention to the urgent need to treat this disease once and for all. The conventional cancer treatment techniques suffer from adverse effects that affect the individual in undesired way during and after the treatment, in addition to the notable low survival rate that cannot overlook. These circumstances push the science to go to the extreme to improve cancer treatment techniques to eliminate it permanently. Under the difficulties faced by medicine to fight cancer, nanotechnology forms a golden opportunity to improve cancer therapeutic techniques due to the noble properties that nanoparticles exhibit as intelligent, effective and safe anticancer drug delivery systems.

Fuzzy PROMETHEE method has been used to make the optimal decision about a group of nanoparticles to be designed as intelligent drug delivery system. The best choice is evaluated among gold nanoparticles (AuNPs), liposomes, dendrimers, polymeric micelles (PMs) and quantum dots (QDs) depending on a group of designing criteria that involve cost, size, shape , surface charge, ligand type, pH and temperature stimuli, biocompatibility, accumulation ratio, toxicity, specificity, stability, efficacy, adverse effect, and safety factor. The resulting order through the total net flow of the Visual PROMETHEE scenario for the anticancer drug delivery based NPs shows that AuNPs are ranked at the first place followed by all other nanoparticle types. Through this promising study, the ability to enhance the therapeutic effectiveness of cancer treatment techniques can be improved and transferred to a new level efficiently with high scale of patient's safety. By providing a clearer picture to facilitate the path toward the new generation of cancer treatment techniques based on nanoparticles as a controlled anticancer drug delivery via Fuzzy PROMETHEE Technique which may be placed as the state of art as being a pioneer and novel application in this field.

***Keywords*:** fuzzy PROMETHEE; nanoparticles; AuNPs; cancer Nanomedicine; chemotherapy; anticancer drug delivery

ÖZET

Kanser, çeşitli hücre seviyelerinde karmaşık bir hastalıktır ve gezegenimizdeki yaşam güvenliğini tehdit eden insan, hayvanlar ve hatta bitkiler üzerinde öldürücü bir etkiye sahiptir. Kansere bağlı olarak artan insidans ve mortalite, bu hastalığın bir kez ve herkes için tedavi edilmesi gerekliliğine dikkat çekmektedir.Geleneksel kanser tedavisi teknikleri, bireyi göz ardı edikemeyecek kadar düşük hayatta kalma durumlarında, bireyi tedavi sırasında ve sonrasında olumsuz etkileyebilir. Bu şartlar, bilimi kalıcı olarak yok etmek için kanser tedavi tekniklerini geliştirmek için bilimi uç noktalara çekmeye zorlar. Nanoteknoloji, nanopartiküllerin zeki, etkili ve güvenli antikanser ilaç dağıtım sistemleri olarak gösterdiği asil özelliklerinden dolayı tıbbın kanserle mücadelede karşılaştığı zorluklar altında, altın tedavi edici bir yöntemdir. Bulanık PROMETHEE yöntemi, akıllı ilaç dağıtım sistemi olarak tasarlanacak bir grup nanopartikül hakkında en iyi kararı vermek için kullanılmıştır. En iyi seçenek altın nanoparçacıklar(AuNP'ler), lipozomlar, dendrimerler, polimerik miseller(PM) ve kuantum noktaları bir gruba bağlı olarak değerlendirilir. Tasarım kriterleri olan, maliyet, büyüklük, şekil, yüzey yükü, ligand tipi, pH, sıcaklık uyarıcıları, biyouyumluluk, birikim oranı, toksisite, özgüllük, stabilite, etkinlik değerleri yan etki ve güvenlik faktörleridir. Antikanser ilaç dağıtımı temelli NP'ler için Görsel PROMETHEE senaryosunun toplam net akışı vasıtasıyla ortaya çıkan sıra, AuNP'lerin diğer tüm nanoparçacık tipleri tarafından takip edilen ilk sırada yer aldığını göstermektedir. Bu umut verici çalışma sayesinde, kanser tedavisi tekniklerinin terapötik etkinliğini arttırma kabiliyeti, yüksek düzeyde hasta güvenliği ile verimli bir şekilde yeni bir seviyeye aktarılabilir. Bulanık PROMETHEE Tekniği, kontrollü bir antikanser ilaç dağıtımı olarak nanoparçacıklara dayanan kanser tedavisi tekniklerinin yeni gelişim seviyesine giden yolu kolaylaştırmak için bu alanda öncü ve yeni bir uygulama olarak kullanılabilecek.

Anahtar Sözcükler: fuzzy PROMETHEE; nanopartiküller; kanser nanomedikini; AuNP'ler; kemoterapi; antikanser ilaç dağıtımı

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ABBREVIATIONS

ACS: American Cancer Society

AuNPs: Gold Nanoparticles

BBB: Blood Brain Barrier

C60: Fullerenes

CAD: Computer Aided Diagnosis

CCS: Canadian Cancer Society

CDDS: Conventional Drug Delivery System

CNMs: Cancer nanomedicine

CNTs: Carbon Nanotubes

CMC: Critical Micelle Concentration

DDS: Drug Delivery System

EPR: Enhanced permeability and retention effect

F-PROMETHEE: Fuzzy Preference Ranking Organization METHod for Enrichment Evaluations

IDDS: Intelligent Drug Delivery System

INDDS: Intelligent Nanodrug Delivery System

MCDM: Multi Criteria Decision Making

MDR: Multiple Drug Resistance

MPS: Mononuclear phagocyte system

MRI: Magnetic Resonance Imaging

MSNs: Mesoprouse Silica Nps

NCI: National Cancer Institute

NDDS: Nano Drug Delivery System

NIH: National Institute of Health

NMs: Nanomedicine

NPs: Nanoparticles

PET: Positron Emission Tomography

PM: Personalized Medicine

PMs:	Polymeric micelles
QDs:	Quantum dots
RES:	Reticulo-endothelial system
SPECT:	Single Positron Emission Computed Tomography
SPIONs:	Super Paramagnetic Oxide NPs
PROMETHEE:	Preference Ranking Organization METHod for Enrichment Evaluations
WHO:	World Health Organization

CHAPTER 1
INTRODUCTION

1.1. Background of the Study

1.1.1. Cancer Difficulties

Cancer is ranked in second place after heart attack disease as a cause of death around the world. It is one of the most complicated diseases where the symptoms vary from one case to another. As each case is considered an especial rare situation in their properties and signs depending on many factors that overlap with each other. Over the years, the prevalence of cancer, which affects various stages of the age of human beings from the elderly, young people and children and not only human as it affects animals and plants, which makes cancer a serious threat to life.

Taking into consideration the aggregate of cancer causing factors are broad and cannot be limited to a certain number or type of factors as it depends on the quality of the surrounding environment, rates of environmental pollution, individual psychological state, lifestyle, nutrition and etc. All those factors together make the prevention of cancer an urgent need to start building a comprehensive environmental protection system. Also we have to notice that this disease is not limited to the injury of a specific organ in the body, it has the possibility of infecting different organs in the body and begins to spread throughout the whole body from the point where it is started. The extent of cancer danger begin from the second that cancer began to be formed, as the delay of the diagnosis and treatment leads to a difficulties to control cancer. Hence, in this thesis the researcher draw attention to the urgent need to develop highly efficient and effective treatment techniques to eliminate these cancerous cells that make up malignancies and prevent them from spreading to the rest of the body.

Taking a look at the most common conventional therapeutic techniques used to treat cancer, it ranges among surgery, radiation and chemotherapy, and etc. which are determined by the doctors concerned depending on the level of the case and the extent of the outbreak after doing the necessary tests. This shows the importance of early detection and diagnosis to apply the right therapy with accurate targeting and effective treatment to effectively eradicate the

disease. Despite the great progress made in cancer treatment area over the past century, the therapeutic techniques of cancer still experience significant adverse effects on the patient's safety during the treatment and quality of life after treatment and even the survivability rate, which cannot be ignored.

Chemotherapy is the most widely and extremely practiced therapeutic technique despite its significant adverse effects on the patient and for lifespan, as they are chemicals with relative toxicity, in addition to the lack in targeting specificity to the infected areas where the error rate is present, which leading to loss of healthy cells also.

1.1.2. IDDS Based Cancer NMs

Over the last 40 years many of drug nanocarriers were developed and there have been a serious attempts to insert nanotechnology based nanomedicine in cancer management, where a notable improvement in the rate of recovery and survival of cancer patient has been observed according to the (Technology Landscape, 2019). In the past few years, the nanoparticles (NPs) had attracted remarkable attention in the cancer management field. A huge number of experiments are conducted and more than 12000 published papers are observed in the area of nanomedicine in order to move forward in the medical field especially to develop cancer treatment techniques and anticancer drug delivery systems (LI et al., 2017). NPs have shown interesting properties for medical imagining, diagnosis and therapy purposes (Senapati et al., 2018). NPs are providing the medical techniques with noble features of high specificity in targeting, efficient drug delivery systems, monitoring in real time and many other important properties accompanied with the most important goal which is eliminating treatment adverse effect and increasing the effectiveness of therapeutic results (Chen et al., 2017). This leads to revealing the great opportunity offered by nanotechnology to develop and overcome the usual obstacles in the conventional cancer treatment techniques by exploiting the NPs features.

The nanotechnology techniques in cancer treatment applications vary due to the variety of NPs used, where those NPs are compete in showing their noble senses to obtain more effective therapeutic results via exploiting NPs to be used as effective anticancer drug delivery systems.

In this study a group of the best nanoparticles were selected to be engineered and modified as intelligent drug delivery systems (IDDS) for cancer treatment based on what can be deduced from the results of the latest studies and experiments in this field. The gold nanoparticles (AuNPs), liposomes, dendrimers, polymeric micelles (PMs) and quantum dots (QDs)" were involved in parallel with the desired standards needed to design and modify those NPs to be more IDDS for transporting anticancer drugs to the targeted site. The NPs types with the modifying criteria will be discuss in detail in the coming chapters.

This thesis seeks to employ the technique of fuzzy comparison based "fuzzy PROMETHEE" method to make a comparison between a set of the most efficient NPs designed as DDS for cancer treatment. In conjunction with the criteria of engineering and modifications to design NPs to be more IDDS, which involved the cost of synthesizing NPs, desired size and shape , surface charge, ligand type, PH and temperature stimuli, biocompatibility factor, accumulation ratio of NPs in the body, toxicity, specificity, stability, efficacy, adverse effects and safety factor.

1.1.3. Fuzzy PROMETHEE

Fuzzy PROMETHEE, is one of the most effective multi criteria decision making (MCDM) methods. It makes the most difficult comparison and multiple decision making possible, despite the complex and unclear circumstances of the issue. The quality of the performance of fuzzy PROMETHEE technique is due to the ambiguous logic used, which provides the possibility of achieving comparisons of qualitative and non-digital data by converting information it to digital data range between 0 and 1. This technique is a (combination logic) combined of both fuzzy and PROMETHEE logic.

Fuzzy PROMETHEE is a branch of the field of computer aided diagnosis (CAD) (Brans et al., 1986). Fuzzy PROMETHEE technique has been applied in different biomedical field successfully and in cancer management specifically. To make comparisons in many complicated issues such as comparing and ranking different techniques for breast cancer therapies, analyzing different tools of nuclear medicine and rating numerous medical imaging machines such as X-ray instruments and etc. (Ozsahin et al., 2017).

For this study fuzzy PROMETHEE is utilizing to make the decision about selecting the optimal designing criteria for the optimal NPs kind as intelligent anticancer drug delivery system.

1.2. Thesis Problem

Chemotherapy is one of the most commonly used techniques to treat cancer. It was considered an efficient treatment technique despite the disadvantages that experienced by the patient during and after the treatment period. Many of the adverse effects suffered by the patient such as hair loss, fatigue, weight loss, in addition to other internal infections and etc.

The threat of recurrence of a new cancer "secondary cancer" as a result of adverse effects resulting from the impact of conventional therapeutic treatments is one of the most serious problems that threaten the safety of the individual and the chance of survival (LI etal., 2017). Inaccurate targeting of cancer cells leads to harming healthy cells, in addition to the need for high doses of drug because of the inefficient delivery of drug to the targeted site making the treatment more expensive and inefficient. Those are one of the most important weaknesses points that must be solved as soon as possible (Pearceet al., 2017).

All the problems with the chemotherapy technique are due to the fact that these conventional drug delivery systems are not intelligent.

1.3. Aim of Thesis

- This thesis aims mainly to shift cancer treatment techniques to develop a new generation of IDDS based NPs with high-precision therapeutic results via improving the site targeting specificity, controlling drug release, minimizing toxicity and therefore eliminating adverse effect, enhancing patient safety and quality of life after treatment and thus raise survival rates.
- To overcoming the old attenuating circumstances and to solve the problems of CDDS through designing smarter drug delivery systems based nanotechnologies.
- To compare, evaluate and rank the latest updates of anticancer nanodrug delivery systems using fuzzy PROMETHEE technique.

- To determine the most efficient type of nanoparticles to be used as intelligent drug delivery to improve cancer treatment.
- To make the best decision about the designing criteria of intelligent drug delivery system for cancer management.
- To design an economical, efficient and intelligent drug delivery system based the best choice of NPs with the most manifest modification standards.

1.4. Significance of Thesis

- The results of this study will solve the problems of CDDS specifically for cancer treatment and management.
- It will ensure a safer treatment for the patient without suffering from adverse effects and systematic toxicity of therapeutic substances and reduce medicine doses, and therefore minimize treatment cost.
- It will increase the chances of recovery for cancer patients and increase the rate of survival via improving the efficiency of treatment and quality of life after treatment.
- Increase the chances of early detection of cancer and thus prevent the injury with cancer and its' pervasion.
- Raising the diagnostic accuracy of the disease and thus choose the treatment plans best suited to the patient's case in particular using the principle of "Personal Medicine".
- The results of this study will enable the possibility of making the most appropriate choices for designing criteria and make the most accurate and correct decision to design smarter drug delivery systems in order to enhance the therapeutic efficiency and its' results.
- In addition to enabling specialists to monitor the situation continuously in real time and provide them with information directly through the new designed theranostics.
- The result of this study will add a qualitative leap not just to improve the chemotherapy treatment but it will strengthen the medical field quality in general.

1.5. Limitations of Thesis

The data of this thesis were collected based on the results of the latest research and experiments conducted in this context, in order to pave the way for the application of the results of this study really and not only hypothetical. Because of the lack of laboratories required currently in Cyprus in addition to the need for substantial financial support to conduct the necessary experiments related to the study, it is still not possible to apply the results of this study in vitro.

VISUAL PROMETHEE, the best and easily available decision-making software was used to conduct this study. For sure if additional programs are available for decision-making, it would be better to compare the results using more than one program to enhance the validity of the results of this study.

In addition, as a future step if laboratory experiments based on the findings of this study are conducted to design realistic drug delivery models and test those models in vivo, it would be a major step to bring this study closer to the reality to pave the way for its use in medical fields.

1.6. Thesis Question

- Can treatment plans for cancer being enhanced to eliminate systemic toxicity and adverse effects in order to ensure complete patient safety during and after treatment?
- Can smarter drug delivery systems be designed to overcome obstacles of vital barriers and problems of conventional drug delivery systems?
- What is the best choice among nanoparticles types to be used as anticancer drug delivery to answer positively to the two previous questions?
- How its' possible to decide what are the optimal criteria for the designing process of an intelligent anticancer drug delivery systems?
- Why fuzzy PROMETHEE technique is used to make the final decision in this study?

1.7. Overview of Thesis

This thesis consists of six chapters the first chapter is entitled with (Introduction) which included the following sections: background of the study that discussed the cancer difficulties, intelligent drug delivery based nanomedicine, the principle of fuzzy PROMETHEE application. Also the thesis problem, aim of the thesis, significance of thesis, limitation of thesis and thesis question were mentioned.

The second chapter deals with the literature review of what cancer is and its' pathophysiology and causes of cancer, how to prevent cancer injury, how to staging cancer, and how it can be diagnosed? In addition to what are the most prominent types of cancer that are causing new incidence and deaths. The most common types of cancer treatments and what are the conventional drug delivery systems for anticancer drugs were also discussed.

The third chapter deal with topics about intelligent drug delivery systems based cancer nanomedicine and entitled with (IDDS based cancer NMs). It discussed the following sections: what are nanoparticles, nanotechnology, nanomedicine, cancer nanomedicne, nanotheranostic and nanodrug delivery systems for cancer treatment. The researcher also discussed the barriers affect the effectiveness of DDS in cancer treatment, How to establish IDDS and what are the factors associated with the manufacturing and engineering of NPs as IDDS. In addition to what are the generational modifications passed by NPs to develop NDDS to more INDDS for cancer treatment. Also detailed information about the involved NPs in this study is discussed and what are their advantages to be used as IDDS for cancer treatment and management.

Chapter four entitled with (Methodology), the researcher in this chapter gave a comprehensive vision about the steps adopted in this thesis to collect and process the collected information using fuzzy PROMETHEE method. Starting from the strategy used in collecting data and how the researcher selected and evaluated these data. In addition, the researcher discussed what PROMETHEE and F-PROMETHE is in detailed way. Also, the method of how the collected data translated from normal data to fuzzy linguistic variables is mentioned in detail to be processed and evaluated at the end.

The result and finding are presented and discussed in chapter five for each type of the included NPs, where the weakness and strengths were presented for each species. The decision was also made on the choice of the optimal NPs type to be used as IDDS for cancer treatment.
Finally, chapter six included the conclusion and future recommendations about what the result of this thesis offer from positives to be taken to a wider extent in the future.

CHAPTER 2
LITERATURE REVIEW

2.1. Overview

In this chapter the researcher gave a general view about what is cancer? What is the pathophysiology of cancer? How it is formed and develops? What causes cancer? How to prevent the injury with cancer and eliminate the progression of the disease? What are the symptoms and stages of the disease and how it can be diagnosed? The most common and lethal cancer types with their statistics were also discussed. Followed by the most common treatment techniques used to treat cancer in addition to the pros and cons of these techniques. Finally, the conventional drug delivery systems adopted in the treatment of cancer and the constraints that these systems faced were discussed with the weaknesses that need to be addressed and developed in these systems.

2.2. Cancer

The term cancer refers to a group of “heterogeneous diseases” that differ in everything but share the principle only, because all kinds of cancer depends on the same logic regardless the type and everything related to it. “Growth” is the basic process of the human life cycle, and it is also the linking point with cancer and its onset. Cancer is a genetic disease due to deformation of the cell’s DNA for unspecified reasons. When a severe and increasing change occurs in a cell's DNA, the cell is mutate from a normal cell to abnormal cell and then into a cancerous cell. Due of this abnormality in the DNA, mutations appear and they are often caused by the effect of this change, they are not the cause.

2.3. The Cell

The cell is the main unit in the organism of the body. The human body consists of what lies between the trillions of cells, the cells bind together to form the tissues, which in turn form the organs and the organs in turn form the whole system of the human body.

- **Normal cell**, is specialized in its' nature as it is generated to perform its own function and it has a limited life cycle. When it becomes old, it stimulates to do the division process "cellular splitting" in response to a specific signal, to form new young cells to do the same function and then die. The process of programmed cell death is called "apoptosis", which is a natural process as part of the normal growth and development of organisms.
- **Pre-cancerous cell**, are abnormal cells that have undergone a change in their structure. The extent of this change may range from mild to severe. In cases of mild change, probably it can disappear without the need for treatment. However, in the cases of severe change, the cell undergoes a genetic change and the need to treat this change is urgent. If it is not treated, it can be increased and turns the cell into a cancer cell.
- **Cancerous cell**, are abnormal cells subjected to severe genetic changes, which stopped them from performing their main function and start to grow out of control with non-stop, as the cancer cells have the ability to ignore the signal that is directed to stop the division in the absence of the need to divide. The cancer cells affect neighboring tissues and invade them to form blood vessels to feed the tumors they are formed and for waste disposal. These cells also have the ability to avoid the immune system and even have the ability to reprogram the immune system to prevent it from killing cancer cells. All of these properties are completely opposite to normal cells.

2.4. Tumors

A tumor is an abnormal growth of a group of abnormal cells that can be lunched from any part in the body. Not every particular mass or growth in the body can be judged as a malignant tumor, because not all tumors are cancerous.

Tumors divide into two kinds, including malignant tumors and benign tumors:

- **Malignant tumor,** are an irregularly formed mass of a group of cancer cells. The term malignant is used to express it because it grows in a chaotic way for unknown reasons. It also strips the energy of the body and makes it idle due to the exhaustion of the body's energy for the purpose of cancer cell reproduction.

When the tumor begins to grow into adjacent tissues from the point where it starts and spreads to distant parts of the body, it is expressed by the "primary tumor". When cancer cells begin to spread chaotic and form other tumors derived, it called "secondary tumors" and the new tumors is termed "metastatic cancer" and they can be detected by a manual examination by specialists or using X-ray or ultrasound or using other methods.

- **Benign tumor,** is a soft lump with regular shaped made up of a group of non-cancerous cell. This type of tumor is spatially stable and does not spread throughout the body. It can be removed by surgical and often does not reappear after the excision.

2.5. Pathophysiology of Cancer

Pathophysiology of cancer is complex in its' nature from all aspects of causal, diagnostic and mechanism of disease progression. Cancer is a genetic disorder that causes the cell to completely break out of its programmed system. The reason for the complexity of cancer is that the type of genetic disorder in the cell varies from one case to another and in the tumor itself varies from one cell to another.

As the growth of cancer cells increasing, the complexity of genetic changes increases. This makes each cancer case an abnormal and rare condition that is different from its own. Therefore, cancer expresses as a group of "heterogeneous diseases" that differ from each other in everything and share the same concept of nonstop growth in uncontrolled way.

Cancer cells differ from normal cells in everything, including shape, size, functions, un-programmed growth and reproduction. Which affect the tissues and neighboring organs and travels to affect the far organs as well as destroy them resulting in invading cancer cell in the body, blood circulation, lymphatic system and the immune system and begin to form the appropriate outer perimeter to supply the needs of the tumor and cancerous cells under the term of "tumor Microenvironment", which by the recruitment blood vessels to exchange oxygen, feeding and waste disposal and protection cancerous cells as well from their own immune system. All of these processes are related mainly to the role of "miRNAs" in the

complex interactions that occur between cancerous tumor and cells in the vicinity of the tumor (Mandal, 2019).

2.6. Causes and Prevention of Cancer

- **Causes of The Disease:**

What is causing cancer? It is a very hard question to be answered because understanding the causes is an intricacy process. Cancer attributed to many factors that overlap with each other, genetic factors, mutations, family predisposition, surrounding environment, pollution, psychological state of the individual, lifestyle, daily habits, nutrition and etc.

As the cell in the human body are mainly differs in their kinds and jobs, but similar in their basic structure. So, how they are differs? What defines the function and type? Basically all the cells have nucleus in their center, which consist of chromosomes. The chromosomes composed of what is called the genes. Genes are a series of DNA and they are responsible of what the cell is doing, on the other hand the RNA and the protein are responsible to define the type of the cell and its action, in addition to the frequency of cell division and the processes related with it.

As (Rous and Kidd, 1941) described the process of cancer development telling that during the process of cellular splitting the occurrence of errors in the DNA is possible, which leads to DNA changes and resulting the generation of the mutation; this called "The initiation stage". When this change is increase, the damaged cell can transfer into a cancer cell and grow to create tumor, this called "Promotion Stage". But it's not always sure because it also depends on the probability of the case itself, taking into account that not all mutations become carcinogenic, some mutations that result from the disease and not cause it. Those mutations can be related to:

- Unhealthy habits such as drinking alcohol, smoking, and unbalanced nutrition such as dieting lacks for vegetables and fruits and rich in fats and sugars, in addition to the consequences of obesity and health problems.
- Taking medicines especially those that are taken in the long span, specialists should balance between the benefits against harm and what can produce side effects.

- Contaminants and the environmental factors such as the exposure to chemical material and radiation such as the ultraviolet from the sun, environmental pollution of water, air and land, occupational risks like pesticides and by products of the industry. It's believed that this group of factors are affected and related with aging and infecting with viruses risks.

- **Prevention The Disease:**

By discussing the above mentioned carcinogenic factors, it is obvious the urgent need to the creation of an integrated environmental friendly health system to prevent cancer or at least to reduce the chances of injury. This is linked to healthy lifestyle, proper nutrition, abstinence from drinking alcohol and smoking tobacco, as well as environmental protection from contaminants, radioactive and industrial substances, and taking vaccines against viruses. Where, it is clear that the factor of aging with the accumulation of other causes and previous factors are increasing the risk of cancer.

On the other hand the importance of early detection of precancerous conditions to prevent them from becoming cancerous cells through taking the proper drugs to treat them and prevent the development of cancer.

2.7. Symptoms, Diagnosis and Staging of Cancer

- **Symptoms of The Disease:**

The symptoms caused by cancer are many and vary depending on the type of cancer and its severity and the type of the organ that affected. Some symptoms are clear and others cannot be distinguished because cancer in its early stages does not cause pain or clear signs. So the patient should check with the doctor and do the necessary tests in the case of appearance of suspicious signs and not cured within weeks. Some symptoms can be as follows:

- Change in the affected organ and difficulty performing functions.
- Change in the skin of the nipple or breast, or the occurrence of secretions or sense of rigid mass.

- Bladder dysfunction or intestinal problems such as difficulty in labor, defecation or bleeding.
- Changes in mouth, tongue, bleeding, cough and hoarseness for unknown reasons
- Problems in eating such as difficulty in swallowing, stomach pain and indigestion or nausea and vomiting.
- A disruption or an increase in appetite and marked change in weight.
- Dysfunction in the senses such as hearing, vision or taste.
- Excessive sweating, tiredness, facial blemishes, yellowing of the skin or in the white of eyes for unknown reasons.
- Tumor sings like change in the skin, such as the sensation of itching, burning, peeling, cracking of the skin, bruising or redness and not healing wounds non-specific reason.

- **Diagnosis of The Disease:**

If the patient noticed any of the previous symptoms of cancer, he \ she should immediately consult a doctor or "health care provider" about these symptoms, if those symptoms do not heal or disappear within a specified period. In order to ascertain whether these symptoms are the result of a malignant tumor or not, the specialist have to take information about the family history with cancer. Also conducting physical tests may enable them to detect cancer in its early stages. The importance of early detection of cancer lie in making accurate diagnosis and enhancing the therapeutic effectiveness of the disease, thus increasing the chance of patient recovery (National Cancer Institute, 2019).

Depending on the type of symptoms, the specialist determines the required tests such as:

- **Laboratory tests**, which may be blood samples or urine or other fluids from the body associated with cancer disease which called "biomarkers" or "tumor markers", where cancer cells produce these biomarkers in rates higher than those which produced by normal cells, thus it can be referred to cancer. These analyzes are preliminary steps and do not give the final decision.
- **Imaging tests**, the purpose of the imaging tests is to check for a tumor presence or not. If a tumor is detected, the shape of the tumor will be showed and the size and the

extent of the tumor will be measured. There are different devices and techniques used for this purpose such as “CT scan, MRI, Nuclear scan, PET scan, Ultrasound, X-ray and etc”.

- **Biopsy,** to make the final decision about the cancer diagnosis, it’s type and selecting the appropriate therapeutic technique, a biopsy of the tumor tissue is taken using several ways such as endoscopy, needle biopsy and surgical biopsy. The sample of the taken tissue will be detected and described under the microscope by a pathologist to determine whether the tissue is cancerous or not. Then the final report is written to describe the result which is very important in making the final decision.

- **Staging of The Disease:**

The stage of cancer is determined using certain systems at the moment of detecting cancer. The stage does not change even if the cancer develops, but new information will be added.

The process of determining the stage of cancer helps in describing the disease in terms of shape, size and prevalence, as well as the classification of the disease in terms of type depending on the location of the injury and the injured organ; thus help the specialists to better understand the condition of the patient to choose the most appropriate treatment plan to promote therapeutic outcomes and ensure the recovery and survival of the patient (Canadian Cancer Society, 2019).

There is several cancer staging systems such as “TNM system”, which describes a large number of cancers, but not all.

- T referred to the “primary tumor”.
- N referred to “Regional lymph nodes” that affected.
- M referred to “Distant metastasis”, the extent of the spread of the tumor.

The TNM system can be expressed with numbers and letters to describe the stage of cancer, for instance “T1N0MX”: X for “cannot be measured”, 0 for “cannot be found and number 1 to 4 for the size and the extent of spread. In some cases they’re using “Stage 0, Stage I, Stage II, Stage III and Stage IV” for less detailed information.

There is another system for staging cancer which is used for all types of cancer and classify cancer in 5 sorts using the following methods:

- “In situ” express the presence of abnormal cells in the region
- “Localized” cancer is confined to the region from which it start
- “Regional” express the spread of cancer to the nearby tissues, lymph nodes and other organs
- “Distant” indicate the spread of cancer to other parts of the body
- “Unknown” express the lack in sufficient information to determine the stage of the disease

2.8. Types of Cancer

There are more than two hundred different types of cancers, and it should be noted that there are no two cases are quite similar in addition to the different body response to the same disease and treatment, it is as well vary from individual to another as well as depending on the type of cancer.

There are thirteen types of cancer that are considered the most common and potentially lethal according to the United States statistics, where breast cancer tops the list in the first place, followed by lung cancer in second place and in the third place prostate cancer (American Cancer Society, 2019).

According to the yearly assessments data of the “American Society of Cancer”, the prediction of new cancer cases and mortality in the “United states of America” for 2019 is around “1,762,450” for new cancer cases and for deaths “606,88” (Siegel et al., 2019). Also it is announced that “8.2 to 8.5” million all over the world is died due to cancer disease and it is predicted to raise to 22 million by 2035, whereby the (World Health Organization, 2018) declarations.

2.8.1. Common kinds of Cancer and Their Statistics

1. **Breast Cancer**

This type of cancer often affects women of all ages and it comes in the second place in leading death cancer for females. There is no specific cause of exposure to the disease, but there are factors that increase the chances of developing the disease; such as smoking, drinking alcohol and pregnancy for the first time in later ages after thirty in addition to genetic factors and patients' family history with cancer. Breast cancer causes a change in the thickness, shape and size of the breast, pain and cracks in the nipple as well as the formation of mass in the breast. It is recommended to conduct periodic checks to ensure the safety of the individual constantly.

- Annually estimation of new cases for female (268,600) and male (2,670)
- Annually estimation deaths for female (41,760) and male (500)

2. **Lung Cancer**

Lung cancer comes in second place of common types of cancer including bronchial cancer and it is the first leading cause of cancer death. In this type, the lining of the bronchial cells begins to grow out of control, causing accumulation and blockage in the trachea and forming malignant tumor; causes difficulty in breathing, swallowing, severe coughing and other symptoms. It is recommended to stop smoking tobacco and not to be exposed to polluted air, as these factors are the main causes of lung and bronchial cancer.

- Annually estimation of new cases for female (111,710) and male (116,440)
- Annually estimation deaths for female (66,020) and male (76,650)

3. **Prostate Cancer:**

This type is ranked third among the common types of cancer and is the second leading cause of cancer deaths in males. The progression of the disease in this type is very slow and it may take years without any obvious symptoms. Prostate cancer is "cancinoma in situ" Which means that it is confined to the prostate gland area.

Symptoms of prostate cancer include recurrent prostate pain, poor sexual intercourse, bleeding with urine, and change in bladder habits. There is no clear proof of how to prevent prostate cancer, but an individual can protect himself by making healthy choices such as exercise and a healthy diet.

- Annually estimation of new cases for male (174,650)
- Annually estimation deaths for male (31,620)

4. Colorectal Cancer:

This type of cancer is also known as “colon and rectal cancer or bowel cancer”. The development of the disease begins with the formation of benign tumors in the colon or rectum, the threat in these tumors as they can be converted to malignant tumors, so once detected, doctors recommend removing them immediately. The development of colorectal cancer is often genetic and is associated with the patient's family history with the disease and colon infections.

Symptoms of the disease include, pain and difficulty in defecation with bleeding, weight loss and change bowel habits.

To prevent the injury with “colorectal cancer”, the individual should refrain from smoking, avoid obesity, and making healthy diet and exercise.

- Annually estimation of new cases for female (67,100) and male (78,500)
- Annually estimation deaths for female (23,380) and male (27,640)

5. Skin Cancer (Melanoma):

There are three types of skin cancer “basal cell tumor, squamous cell carcinoma and melanoma”, the most common one is the “melanoma”. The development of this type of cancer begins in the pigment cells of the epidermis, known as “melanin cells”.

Symptoms of this disease change in the nature of the skin and the appearance of patches and cracks and swelling of the skin.

Prevention should be avoided exposure to direct radiation such as ultraviolet radiation and X-ray, which are major cause of skin cancer.

- Annually estimation of new cases in general (96,480), for female (39,620) and for male (57,220)
- Annually estimation deaths in general (7,230)

6. **Urinary Bladder Cancer:**

This type of cancer is also known as "bladder cancer or urinary track cancer". This type of cancer affects men often more than women. The most prevalent kind of urinary bladder cancer is "Urothelial carcinoma". The progression of the disease begins from the cells lining the bladder which start to grow and multiply abnormally and thus form a malignant tumor to block the ureter.

Symptoms of the disease are difficult to urinate and bleeding in addition to pain in the lower part of abdomen and back, stress and weight loss. The main causes of this type of cancer are chronic urinary tract infections and smoking.

- Annually estimation of new cases in general (80,470), for male (61,700)
- Annually estimation deaths in general (17,670), and for male (12,870)

7. **Lymphoma (Non- Hodgkin's Lymphoma):**

It is the cancer of the "lymph nodes". There are two types of this cancer "Hodgkin's lymphoma and non- Hodgkin's lymphoma", the second type is the most common. The development of "lymphoma" begins with inflammation of the cells of the lymphatic system, particularly white blood cells.

Symptoms include general weakness, lethargy, severe fatigue, neck swelling, fever and sweating, and significant weight loss.

For the purpose of prevention should avoid exposure to pollutants and chemicals and the prevention of viral infections.

- Annually estimation of new cases for non- Hodgkin's lymphoma for female (33,110) and for male (61,700)
- Annually estimation deaths for non- Hodgkin's lymphoma for female (11,510) and male (8,460)

8. **Renal Cancer (Renal Cell Carcinoma):**

Kidney cancer includes "renal cell carcinoma and renal pelvis cancer". Renal cell carcinoma is the most common type of kidney cancer and its' the main responsible for a large proportion of kidney cancer cases. This type of cancer affects one of the kidneys, specifically the cells lining the pelvis or urinary tubules. Men are two times more likely to develop kidney cancer than

women, as well as the elderly and obese individuals with high blood pressure. Also chance of infection with this type of cancer is increase with the genetic and hormonal factors due to the individuals' family history with the disease.

Symptoms of kidney cancer include fatigue, fever, sweating for unknown causes in the ankle and foot area, urine discoloration and bleeding with urine, weight loss and anemia.

For the purpose of prevention should refrain from smoking, avoid obesity, exercise, following a healthy diet, avoiding exposure to pollutants and chemicals.

- Annually estimation of new cases in general (73,820)
- Annually estimation deaths in general (14,770)

9. Endometrial Cancer (Ovarian Cancer):

This type of cancer affects women in the uterine area and associated organs such as ovaries. It divided into two types "endometrial cancer and ovarian cancer". The second one is the most common type and it comes in fourth place as responsible for most new cancer cases in women. In this type of cancer cells begin to break out of their system and multiply randomly, forming tumors that may be benign or cancerous, often affecting the outer envelope of the uterus.

Symptoms include flatulence, abdominal pain, eating disorders and anorexia, frequent diuresis, in addition to unknown bleeding cause, extreme fatigue and weight loss.

Factors that increase the chance of developing this type of cancer are pregnancy and childbirth in the late post thirties, late menopause, hormonal factors and genetic history of the disease in the family of the individual. Childbirth and breastfeeding are protective factors for endometrial and ovarian cancer.

- Annually estimation of new cases in general (61,880)
- Annually estimation deaths in general (12,160)

10. Blood Cancer (Leukemia):

There are three types of blood cancer "leukemia, lymphoma and myeloma" leukemia is the most common one. The white blood cell starts to grow in uncontrollable way creating abnormal cells in the blood and bone marrow.

Symptoms include anemia, bleeding due to unknown causes, enlargement and inflammation in the liver, spleen, lymph nodes and immunodeficiency.

Prevention required avoiding exposure to radiation and chemicals and industrials, and pay attention to viruses and genetic factors in the individual.

- Annually estimation of new cases in general (61,780), for female (25,860) and for male (35,920)
- Annually estimation deaths in general (22,840), for female (9,690) and male (13,150)

11. Pancreatic Cancer:

Pancreatic cancer is characterized by its rapid development and spread to other organs of the body as the cells of the pancreas tissue begin to grow out of control and spread rapidly. It is supposed to the presence of a certain substance in the human body, which has a great effect with the development of this type of cancer.

Symptoms include weight loss and yellowing of the skin accompanied by pain in the upper abdomen, often the appearance of these signs is slow and cannot be easily diagnosed.

For the purpose of prevention should not drink alcohol as it is a major cause of pancreatic cancer.

- Annually estimation of new cases in general (56,770), for female (26,830) and for male (29,940)
- Annually estimation deaths in general (45,750), for female (21,950) and male (23,800)

12. Thyroid Cancer:

Thyroid cancer is a special type of cancer that affects the "'thyroid gland" in the neck area. Women are more likely to develop thyroid cancer and the risk increases for those who are between 30 and 60 years.

Symptoms include swelling in the neck, difficulty swallowing and eating, voice changes and sore throat for unknown reasons and non-healing.

The causes of thyroid cancer are unclear but the progression of the disease can be linked to an individual's family history with disease, growth hormone imbalance, obesity, exposure to radiation and thyroid infections.

- Annually estimation of new cases in general (52,070)
- Annually estimation deaths in general (2,170)

13. Liver and Intrahepatic Bile Duct Cancer:

It is also called “hepatic cancer” and its’ includes the following types “bile duct cancer (cholangiocarcinoma), hepatoblastoma and hepatocellular carcinoma", the latter is the most common type.

Symptoms include yellowing in the whites of the eye and skin, pain in the upper abdomen, loss of appetite and vomiting and weight loss.

Excessive drinking of alcohol that causes cirrhosis of the liver is one of the most important causes for liver cancer, and infection with a hepatitis B or C.

- Annually estimation of new cases (42,030)
- Annually estimation deaths (31,780)

2.9. Cancer Treatment Techniques

The type of treatment technique used to treat cancer depends on the patient's condition in terms of the type of cancer that the patient has and the extent of cancer spread. After diagnosis, the decision about the type of treatment that the patient needs is made, the duration of treatment and the severity of the treatment mainly depends on the results of the diagnosis. Some cases require one treatment technique such as surgery or radiation or others type of treatments, while other cases may need to combine two therapeutic techniques or more such as surgery followed by chemical doses, radiation or both together as needed.

There are three most common and traditional cancer treatments "chemotherapy, surgery, radiation" and other types of treatments include "immunotherapy, targeted therapy, hormone therapy". In addition to other therapeutic techniques, some are used such as "stem cell transplant, hyperthermia, photodynamic therapy, blood transfusion and donation, laser in cancer treatment" in addition to other procedures in the clinical-trails (National Cancer Institute, 2019).

Over the past decades, therapeutic techniques for cancer have fluctuated between efficiency and deficiency in eliminating cancer cells and tumors due to the adverse effects experienced by the patient after treatment and between the hope and promises to develop these techniques

to get better results to ensure the patients' healing and safety through eliminating the adverse effects.

Traditional and most common cancer treatment techniques and their adverse effects:

Surgery, Specialists resort to surgery in certain cases of cancer such as the cases of having solid tumors. Surgery type varies depending on the patient's condition and type of cancer and the extent of the outbreak (size of the tumor), in addition to the method of surgery itself and the tools used in it. There are other factors that affect the choice of the type of surgery, such as receiving other supportive treatments before or after surgery like chemotherapy or radiation, etc. Taking into account of the mentioned factors, surgery may be a total or partial removal or open surgery depending on the patient's condition and the decision of the specialists and the patient him\herself.

Surgery is considered one of the most safety therapeutic techniques for cancer, as healthy cells do not suffer as much damage as in other therapeutic techniques except the part that is removed. The adverse effects associated with the surgery treatment still present, but it may be less severely depending on the type of surgery. As any surgery accompanied by post-operative pain and fatigue due to the body's attempt to recover. The only serious adverse effect for surgery is the danger of possibility of reforming a new secondary cancer if a very little part or even one cell of cancer is left by mistake. Other adverse effect may be permanent depending on the size of the removed part and the type of organ affected and its' location, such as in cases of uterine or ovarian cancer in women and prostate cancer in men and the consequences of sexual or even affected fertility and reproduction and other functions (National Cancer Institute, 2019).

Radiotherapy, Different radioisotopes with different plans and techniques are used in radiation therapy for cancer, and the type of route, isotopes used and dose intensity are determined based on patient data. The type of radiotherapy used is determined based on the type of cancer that the patient has, its stage, tumor location and size, whether or not the patient

will receive or received supportive treatments in addition to the family's history and the individual's overall health status and his\her age, etc.

Radiation therapy is divided into two types, “external and internal radiotherapy”. External radiation is received by special devices that direct radiation to the tumor area as accurately as possible to minimize the chance of harm to the surrounding or neighboring healthy tissue. As in the case of breast cancer, radiation is directed only to the targeted breast area and not to the entire body.

In the case of internal radiation, the radiation source is positioned inside the body in different ways depending on the state of the radiation source, whether the radiation source is solid, capsules, seeds and etc. Radiation sources are often planted near to the tumor and this method is called “brachytherapy”. If the source of radiation is liquid, the radioactive material is received either orally in capsules, injections or intravenously. Then the radioactive material is travel to the tumor area through the blood and is placed in it, this method is called “systematic radiotherapy”. Each of these methods is used in certain cases and types of cancer (National Cancer Institute, 2019).

The adverse effects of radiation therapy range from mild to severe, from individual to another, depending on the condition of each case, type of cancer, cancer stage, tumor size and its’ site, and intensity of the radiation dose received. Skin problems and fatigue experienced by the patient during and after treatment are among the most common adverse effects and are dealt with by the doctors and the specialist team with the patient. Most adverse effects disappear after treatment and in some cases disappear and return after a period of the treatment. Reconstitution of a new cancer is one of the serious adverse effects that may be experienced by the individual as a result of treatment received in advance and this is one of the risks that should pay attention to.

Chemotherapy, Cancer chemotherapy is considered the most common and effective therapeutic technique by adopting it as a basic therapeutic technique or as a supportive technique with other therapeutic techniques such as surgery, radiation and etc (LaVan et al., 2003) . Chemotherapy is given to the cancer patient in the form of intravenous drugs or via

oral administration in different doses and in different chemical structures according to the type of cancer, the site of injury, the affected organ and the prevalence of the disease. There are many plans for the usage of chemotherapy in the treatment of cancer, as main or supportive therapeutic technique before surgery or radiotherapy for the purpose of shrinking the tumor or inhibiting the spread of cancer cells to increase therapeutic effectiveness; and in other cases after surgery or radiotherapy for the purpose of elimination the remaining cancer cells as a mandatory step or to ensure that the disease cannot spread again as a precautionary plan (Langer et al., 1990).

There are many chemical drugs that are used to treat cancer, which differ in their structures and constituents and each one of them used for a certain case of cancer which differs from other cases. Cancer chemotherapy is a systematic technique that targets cancer cells in a systematic way by carrying the drug and transfer it in the patient's body through the blood circulation to the cancer cell itself. However, despite the intelligence of the basic idea but it has a negative side also that cannot be overlooked; it is the inability of the drug to distinguish between healthy cells and cancer cells.

The principle of action in chemotherapy is based on reprogramming the cellular system in the cancer cells by inhibiting and killing them depending on the "cytostatic and cytotoxic" process. The drug target the cells that grow and multiply rapidly regardless of whether these cells is cancerous or not, which leads to causing a significant adverse effects (Nurgali et al., 2018). Some of these adverse effects are limited to the period of treatment only, such as hair loss, loss of appetite, nausea, thrombosis, severe fatigue, weight loss, change of mental state, various infections, hemorrhage, easy bleeding, altered bowel and digestive habits and many other effects. Some adverse effects may last a few months, others may last for a couple of years or more and some of them last for a lifespan, which affects the quality of life of the individual. And some of those adverse effect lead to a sudden return of cancer outbreak after a few years and the last once is very serious and it is necessary to find an effective solution ends up with solving this serious problem.

Chemotherapy technique has been somewhat effective in previous decades, but for the current time and with the development of science the need to overcome the mentioned circumstance

by developing chemotherapy becomes urgent for the purpose of more effectiveness therapeutic results in order to curing the patient without any undesirable adverse effects.

2.10. Conventional Drug Delivery System (CDDS)

Chemotherapy is one of the most important and most common therapeutic techniques whether adopting it as a basic therapeutic technique or to support other cancer treatment techniques. The importance of chemotherapy is due to the fact that it targets free cancer cells that were not detected during the diagnosis for "metastasized cancer" cases, in addition to the targeting of solid tumors "localized cancer"; unlike surgery and radiation treatment, which target only localized tumors.

On the other side chemotherapy suffer from serious defects which cannot be ignored. The inaccurate distribution and unregulated release of the drugs causes a decrease in therapeutic efficacy, in addition to the disability of these anticancer drugs to distinguish between cancerous cells and healthy cells. The latest is one of the biggest disadvantages of chemotherapy as these drugs are designed to attack fast growing cells and multiplication as a cancer cell, in the other hand, those drugs are also attack healthy cells that fast growing and multiplying such as hair cells and other cells and this is the reason for the hair loss while receiving chemotherapy in addition to the patient suffering from other adverse effects as a result of targeting other healthy cells. In addition, the ability of cancer cells to develop their immunity against chemical drugs "multiple drug resistance (MDR)", which leads to the ineffectiveness of chemotherapy after a period of time maybe during the treatment or after a short or long time after the treatment; which may lead to reconstruct another new cancer "secondary cancer" as adverse effect of chemotherapy. With the continued recording of new cases of cancer and registering new death of cancer patients, it becomes urgent to find a solution to the previous problems and defects. From here began the journey of researches to develop chemotherapy to be more effective and smartness.

In the next chapter, the researcher discuss the usage of nanoparticles (NPs) to develop smarter chemotherapy, which is one of the most promising and intelligent techniques that offer the

possibility to solve the aforementioned problems, by employing NPs in drug delivery systems as smart anticancer drug delivery systems.

CHAPTER 3
IDDS Based Cancer NMs

3.1. Introduction and Overview

This chapter will discuss topics related to nanotechnology, nanomedicine (NMs) and the role of nanoparticles as theranostics all in the area of cancer management and treatment. And in a more precise sense, the researcher will discusses the role of nanoparticles as drug delivery system (DDS) for cancer treatment and how these systems can be developed from conventional drug delivery system (CDDS) to more intelligent drug delivery systems based NPs (INDDS). With the aim of overcoming the various obstacles and weaknesses are experiencing by the CDDS. Each type of nanoparticle that involved in this study, their features and behavior are discussed before and after the modifications decorating process and how the behavior is change due to applying these modifications, in addition to the weaknesses and strengths of each type, to fully exploit the unique features offered by these NPs as efficient and safe IDDS.

3.2. Nanoparticles (NPs)

They are ultrafine particles with sizes ranging from one to a hundred nanometers, which makes them characterized by noble characteristics that distinguish them from other fine particles. The history of NPs back to the early of ninth century in the “Mesopotamian” region, when “artisans” used these ultrafine particles in manufacturing of glassware to make them look more brightening. With the development and progress of science began to describe these NPs in a more precise and clearer scientific way to begin the journey of NPs research and experiments that have revolutionized in many areas. One of the most important fields that have been significantly affected by the revolution of nanoparticles is the field of medicine and its techniques, where nanoparticles have shown countless advantages and benefits in this area. The most prominent of these features is the usage of NPs in “ biomedical imaging and monitoring in MRI studies, creating fluorescent biological labels, protein DNA structure, genetic and tissue engineering and etc” in addition to their effectiveness in the field of “

pharmacokinetic, gene therapy, gene delivery system". Last but not least, the usage of NPs in drug delivery systems and distortion of tumors with drug or heat which is the aim and object of this thesis. Different kinds of NPs have been employing as anticancer drug delivery systems, for instance : polymer materials like dendrimers, polymeric micelles and etc., different types of Si based structure like mesoprouse silica NPs (MSNs) and metal structure like silver, gold, super paramagnetic oxide NPs (SPIONs), and etc. in addition to different kind of carbon nanotubes (CNTs), Fullerenes (C60) and Quantum dots (QDs), liposomes , and etc.

3.3. Nanotechnology

Known as the "nanotech" in short terms, it is a branch of science that deals with the engineering and designing objects in very accurate sizes with a scale ranging from 1 to 100 nanometers. The "nanometer" term is used to express the scale of nanotechnology.

The idea of nanotechnology was launched by "Richard Feynman" in his lecture at 1959, which titled with "There's plenty of room at the bottom" (Feynman, 1960) and from that moment the idea of nanotechnology began. It was paradigm shift for all the levels of science because of the noble characteristics offered by this technique. These properties are attributed to the nanometer scale sizing, which has very tiny sizes, in which the properties of the materials differ in its biological, chemical and physical terms (Teli et al., 2010).

The noble properties of nanoparticles are attributed to have larger surface volume area in addition to the effect of quantum factors; which gives nanoparticles their noble properties, such as mechanical, electrical, optical and magnetic properties according to the "National Science and Technology Council" (2004).

Nanotechnology is therefore a promising technology for the development, enhancement and construction of systems with high precision and efficiency characteristics in various fields.

3.4. Nanomedicine (NMs)

Nanotechnology applications in the field of health and medicine termed with "nanomedicine". According to "European technology platform on nanomedicine" (2005), NMs science deals

with the exploitation and usage of the noble properties of the material that created on the nanoscale size in many fields of medicine.

It also adds that the applications of nanotechnology in the field of medicine is promising for its promotion and development in the field of early detection and prevention of diseases and providing accurate treatment in addition to reduce the cost of health care via the exploitation of physical, biological and chemical properties of NPs (Satalkar et al., 2015).

3.5. Cancer Nanomedicine (CNMs)

CNMs is defined as the optimal use of the special and noble qualities shown by nanoparticles in the field of cancer treatment in order to deal directly with the cancer cells on the cellular nanoscale (Kemp et al., 2015). Exploiting the physical, biological and chemical properties of nanoparticles and employing them as therapeutic agents in addition to the purposes of diagnosis and monitoring is achieved through engineering and designing nanoparticles with special specifications and standards to obtain the desired behavior in order to achieve more accurate targeting of cancer cells and high therapeutic efficiency without undesired adverse effects.

3.6. Nanotheranostics

Nanotheranostic is the science that integrates multiple medical applications into one strategy. This strategy is applied in the field of nanomedicine by exploiting the unique features of nanotechnology. In order to integrate monitoring, diagnostic and therapeutic agents in one structure by employing nanoparticles that provides the possibility of conducting this technique. Specifically, for the purpose of “cancer management and treatment”, “patient stratification”, “drug release monitoring”, “imaging guided focal therapy” and “post treatment response monitoring” (Chen et al., 2017).

3.7. Nano Drug Delivery System for Cancer Treatment (NDDS)

Each cancer case is a special case in terms of how to deal with it as diagnosis, treatment, monitoring and control. Where, each case is completely different from the other, although it

has the same principle and this is the reason of why cancer is described as not identical, but it is alike as well. Therefore, the process of targeting and treatment of tumors and free cancer cells accurately with high therapeutic efficiency without harming the healthy cells and adverse effects is a difficult task elusive.

To overcome these obstacles, each case of cancer must be dealt with a treatment strategy that is consistent specifically with the data of this particular case. This type of curing can be known as “personalized medicine (PM)” (Vogenberg, 2010).

Traditional therapeutic techniques for cancer are unable to provide this type of high specificity of treatment, while nanomedicine techniques are a promising opportunity to achieve this aim. Nanomedicine is considers as an important shift and evident development, not only in the field of cancer management but for other various types of diseases; due to the possibility of accurate treatment, early diagnosis and continuous monitoring without any surgical intervention. Thus the techniques of nanomedicine platform with the noble properties it provide, can achieve the optimal cancer treatment by high specificity targeting and less toxicity or even without any systemic toxicity.

The synthesis and design of nanoparticles as carriers of anticancer drugs should be engineered to optimize their noble qualities as intelligent drug delivery systems (IDDS). Nano drug delivery systems can avoid and solve the problems of the traditional drug delivery systems such as inaccuracy of targeting, irregular distribution of the drug, dissolution and undesirable drug release during traveling through the blood to target the desired cancer cell (Rizvi and Saleh 2017). Nano drug delivery systems (NDDS) offers the possibility of determining and concentrating the dosage of the drug without the need for high doses, and reduce the systematic toxicity by ensuring that nanoparticles are not accumulated in the body and eliminated outside the body after finishing their duty.

It is possible to say that by doing the desired engineering and modifying process for the nanoparticles to be used as drug delivery system with the optimal parameters that will affect the behavior of those NPs, it is possible to exploit the noble properties of NPs in order to achieve the right therapeutic technique to the right target.

3.8. Barriers Affecting the Drug Delivery System

One of the main reasons why it is difficult to target cancer cells accurately and efficiently is the biological barriers faced by therapeutic anticancer drug delivery systems such as:

- "Hepatic, renal and immune clearance, Reticulo-Endothelial System (RES) or Mononuclear Phagocyte System (MPS) and Macrophage internalization" (Aderem et al., 1999); which affect the nanodrug delivering and therapeutic efficiency making its blood circulation time shorter by cleaning them and accumulate with the anticancer drug in the bone marrow, liver or spleen and etc. (Abuchowski et al., 1977) (Hossen et al., 2018) .
- Degradation due to the "Serum Protein Absorption" (Elwing, 1998) (Shen et al., 2016).
- The phenomenon of "Enhanced Permeability and Retention (EPR)" effect, which is one of the microenvironment tumor tissue characterization in which the tumor tissue is rich in leaked blood vessels (Blanco et al. 2015).
- One of the main obstacles to treat brain cancer is the "Blood Brain Barrier (BBB)", due to the structure nature that allow less than 2 % of the molecules to pass (Pardridge, 2005).

There are a lot of systematic barriers which lead to low targeting specificity, drug biodegradable and leakage causing uncontrollable drug release, solubility causing drug delivery instability and short blood circulation time (Tran et al., 2017). In addition to other obstacle such as encapsulating capacity and binding drug problems, concentrating the drug in the targeted site and low biocompatibility (Cho et al., 2008).

Through this perspective its clear how difficult to face the obstacles faced by drug delivery systems to target cancer cells. And the cancer cells ability to develop immunity against drugs over time to protect their DNA, thus maintain their ability to copy themself and reproduce new cancer cells, or even travel to other areas in the body to reactivate them self and reform secondary cancers.

To face these obstacles, a "multidisciplinary strategy" must be adopted to apply for the drug delivery systems. To this end, medical nanotechnology specifications can be exploited to integrate nanotechnologies combined with exploiting the characteristics of "tumor

microenvironment" to create intelligent anticancer nanodrug delivery systems (Albanese et al., 2012). Like "Weinberg and Hanahan" termed, one of the most promising current methods to improve the efficiency of cancer targeting and treatment today is to exploit the characteristics of full range of cancer biomarkers to distinguish between healthy and cancerous tissues, by employing this set of biomarkers in the use of multiplex nanomedicine technologies (Tran et al., 2017).

3.9. Establishing Intelligent Nano Drug Delivery System (INDDS) with Specificity for Cancer Cells Targeting

To establish intelligent drug delivery system, three main points are required, illustrated in the figure (3.1) bellow:

1) Choosing the optimal NPs kind to carry and deliver the therapeutic agents to the specific targeted site.

2) Providing the system with a specific cancer cell targeting technique by functionalizing the NPs surface.

3) Utilizing stimuli techniques to control the therapeutic agents release at the desired targeted site.

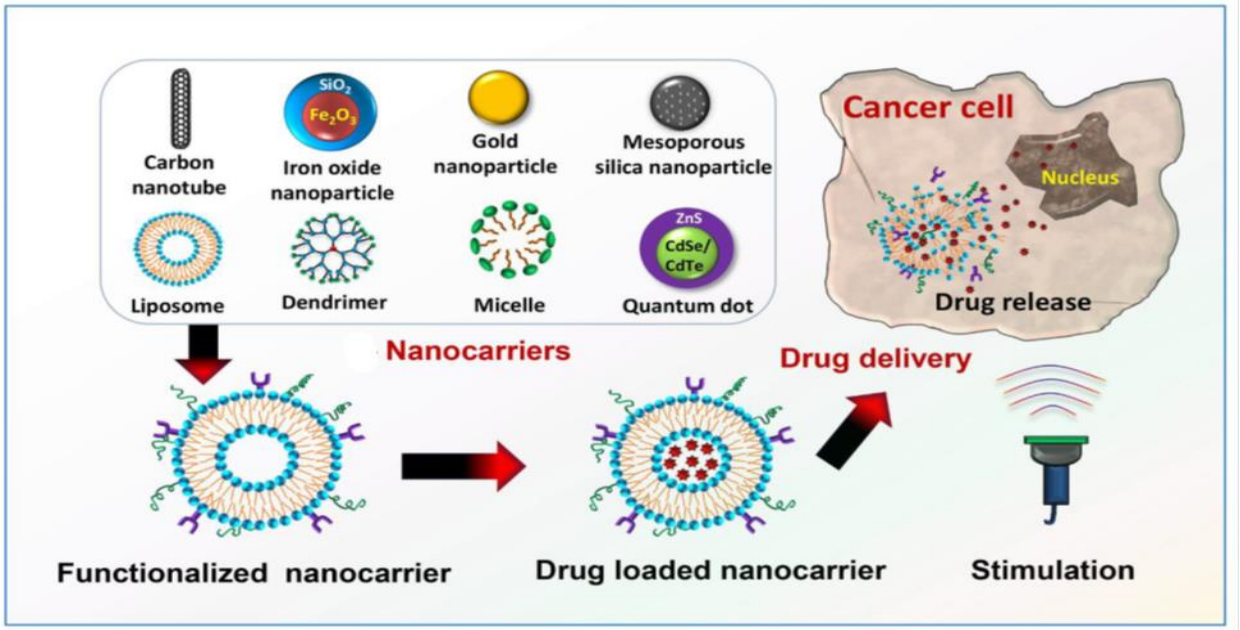


Figure 3.1: Intelligent nano drug delivery system (INDDS) for cancer treatment and management (Hossen et al., 2018)

3.10. Factors Associated with Manufacturing and Engineering Nanoparticles as Intelligent Anticancer Drug Delivery System

To achieve the three conditions for the construction of anticancer intelligent drug delivery systems (IDDS), we have to design nanoparticles based drug carrier according to the following criteria:

- **Size**: most studies have showed that nanoparticles with size smaller than 10 nanometers but larger than 4 nm have less toxicity or no toxicity in some species (Sun ET AL., 2014) (Alley et al., 2010).
- **Shape**: The nanoparticles are designed as carriers of the drug in various forms such as cube, star, rod, plate or sphere, by observing the results of studies and experiments it is obvious that the sphere (core shell) NPs are the least toxic and the most receptive for cell internalization to enter inside the cancer cell with no problems (Sun ET AL., 2014).

- **Temperature and pH stimuli factors**: There are many external and internal stimuli factors that can induce nanoparticles to release the drug at the exact targeted site. Internal stimuli involve “pH, temperature, enzyme, redox, and etc.” and external stimuli involve “magnetic, photo, and ultrasound” factors (Qiao et al., 2018).

  The acidity and thermal (heat) factor are among the most common factors that exploit the properties of the cancerous environment to induce releasing the drug into the target cancer cell (Qiao et al., 2018). Temperature can exploit the nearby increment brought about by the pathological condition for tumor and aggravation. Also, the pH factor of cancerous tissue is known to be low and more acidity around (5.6-7.0) while the pH of healthy tissue is ranged about (7.4) according to the study of (Vaupel et al., 1989) (Ferdous et al., 2012).
- **Surface charge and ligand type**: when the nanocarrier surface charge with a neutral or negative charge and binding the loaded molecules physically with non-covalent ligands, it give a longer blood circulation time, more stability and keeping the drug from leakage, avoiding unwanted dissolution, and reducing toxicity effects (Qiao et al., 2018).

Through the usage of therapeutic agents against cancer loaded with modified nanoparticles, the optimal modification parameters of the nanoparticle such as size, shape, surface charge, type of bonds used such as amino acids or peptide molecules, etc., and the type of coverage used. All these factors will affect the rate of compatibility with the patient's body and the rate of accumulation of nanoparticles in the body after the release of the drug and the effects of systemic toxicity. On the other hand, support and improve the accuracy of cancer cell targeting and stability of drug delivery to the target, raising therapeutic efficiency in addition to enhancing patient safety by reducing the proportion of undesirable side effects during and after the treatment.

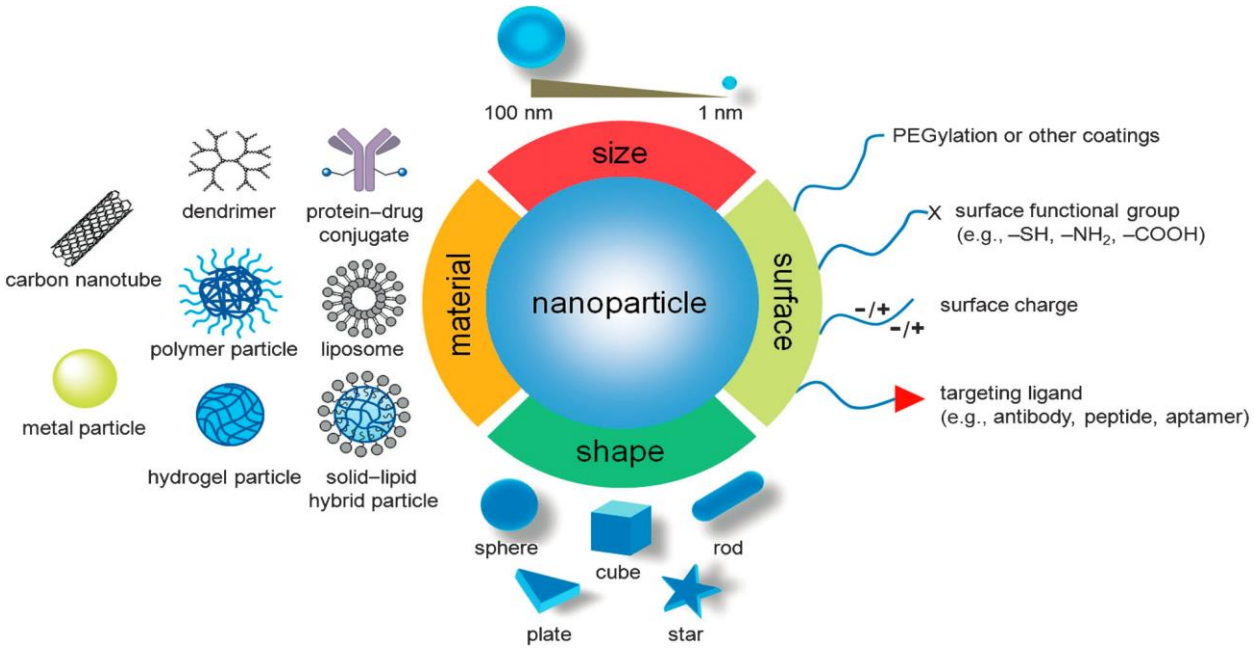


Figure 3.2: Illustrations of the criteria and bio-physicochemical properties related to modifying NPs as intelligent anticancer drug delivery system (Sun et al., 2014)

3.11. Modifying and Engineering Nanoparticle Generations as INDDS

The development in modifying and engineering the NPs as drug delivery system has been practiced in three generations:

- First generation: focused on the chemistry of the surface particles, mainly modifying the NPs surface charges to improve the biocompatibility and limit the toxicity (LI et al., 2017)
- Second generation: the NPs were functionalized with biocompatible polymers (e.g. PEG) to prolong the NPs in the blood circulation (Conde et al. 2012).
- Third generation: developed the environmental responsive polymer to improve the drug delivery efficacy (e.g. pH and temperature changes) (Poon et al., 2011)

By integrating these three generations into one integrated design process, it's possible to design smarter systems for CDDS. Attempts are now being made to modify and design nanoparticles as IDDS for cancer treatment and management as shown in the figure below.

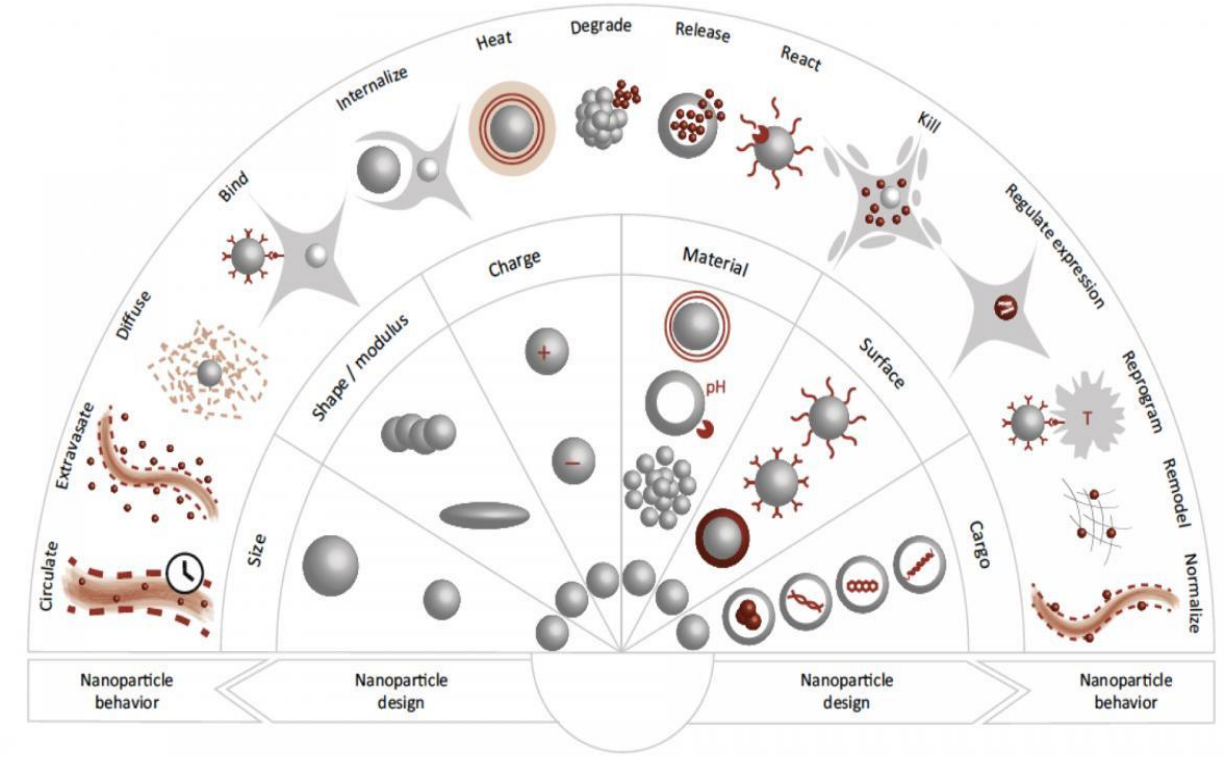


Figure 3.3: A plan to design and modify nanoparticles as smarter anticancer drug delivery system by incorporating the design standards of the three modifying generations and observing the impact of these standards on the behavior of nanoparticles (Marble Center for Cancer Nano medicine, 2019)

3.12. Types of Common Nanoparticles Used as an Intelligent Drug Delivery Systems for Cancer Treatment

Different types of nanoparticles have been used as anticancer drugs carriers (therapeutic agents) for chemotherapy. The types of nanoparticles used for chemotherapy are classified into two main classes, organic nanoparticles and inorganic nanoparticles.

Unluckily, not all the types of nanoparticles qualify as intelligent carriers for anticancer treatments, they are classified based on their behaviors as drug carriers compared to the standards required for designing intelligent drug delivery systems of anticancer drugs.

The following are some of the most common nanoparticles that are nominated as intelligent drug delivery agents:

3.12.1. Gold Nanoparticles (AuNPs)

Gold nanoparticles (AuNPs) are one of the inorganic nanoparticles specifically of the metallic nanoparticles type with a colloidal structure. AuNPs are considered one of the most important types of nanoparticles that have been employed in various medical fields because of their bright properties starting from the stages of synthesis and modification reaching to the interesting results of their uses in medicine, specifically for cancer treatment (Ying Kong, 2017).

AuNPs peaked interesting attention due to their manifest properties advantages which includes:

- Easy to synthesis with suitable cost and has the flexibility to be modified in controllable manner of nanoscale sizes ranging from 1 to 100 nm with different desired shapes such as “spherical, rod, cage, cubic, star”, and so on. The electrical and optical properties are related to modifying AuNPs with the desired size and shape (Verssim et al., 2016).
- AuNPs possess high “surface volume ratio” about (5nm\20%; 1nm \100%), in addition to their excellent biocompatibility and very low or even nontoxicity effects (Hainfeld et al., 2005).
- The great capability of surface functionalization with different types of drug with targeting bond, whether if it is covalent or non-covalent bonds due to the presence of negative charge (Fratoddi et al., 2015).
- Brilliant properties due to the “microscopic quantum tunneling” and their special surface impact with the ultra nanosizes (Kumar et al., 2013).
- Due to the capability of AuNPs to load diagnostic and therapeutic agents in the same structure, they can be used as nanotheranostics which make them promising anticancer theranostic agents (Chen et al., 2017).

The resilient “physical, chemical, electronic, optical, sensing and biomedical properties” of the AuNPs make them very interesting choice to be used in different nanomedicine and biomedical aspects such as “diagnosis, monitoring, therapeutic agents in drug delivery, molecular imaging and biosensing” specifically for cancer treatment (Kong et al., 2017). Also,

since AuNPs are most suitable for use as anticancer drug delivery with minor non-covalent modifications, ability to carry various drug molecules with high capacity and controllable drug release via internal stimuli like “pH and temperature changes” or external stimuli like “light”, their importance has been pronounced more strongly in the field of drug delivery.

In short, all the previous nanofeatures make the AuNPs the most stable anticancer nanocarriers\ drug delivery system due to their high specificity for the tumor or free cancer cell site with controlled dispersion (Elahi et al., 2018). In addition to their long blood circulation time and nonsystematic toxicity as a result of their ability to be cleaned with urine, makes them an attractive destination in the anticancer drug delivery studies (Conde et al., 2012) (Hossen et al., 2018).

3.12.2. Liposomes

Liposomes are organic nanoparticles specifically one of the lipid nanoparticles type. They are occurs in natural way as phospholipids nanovehciles\ carriers. “Alec D. Bangham” at 1960’s discovered the liposomes for the first time with a group of students, and they illustrate that those NPs are “lipid vehicles” composed of phospholipids as a cell membrane, which consist of “lipid tail of a fatty acid, cholesterol and polar head group”. For the first time, “Gregory Gregordians” at 1973 described them and showed that when those phospholipids are immersed in an aquatic medium, the liposomes are behave as self-assembled bilayer nanovehicles\ carriers. Liposomes manufacturing is consider as a very expensive process. Liposomes have spherical shape with bilayer membrane, and nanosize around 20 or 50nm to many micros. Liposomes have an empty cavity inside it, where drugs or DNA or other molecules can be loaded and sent inside the patient body (Hossen et al., 2018).

On the other hand, using liposome as drug delivery system without modifications face serious challenges specifically for anticancer drug delivery (LI et al., 2017), such as:

- Short blood circulation time, toxicity and removal difficulties from the patient body.
- Problems in uncontrollable distribution, instability, drug loading problems and rapid drug release.

Yet these obstacles can be overcome by modifying liposomes and functionalizing their surface, so it's possible to exploit their unique properties advantages as nanodrug delivery system (Khanna et al., 1970), such as:

- Preventing the undesirable drug leakage or drug releasing.
- Preventing loaded drug from degradation.
- Utilizing different types of targeting ligands to activate liposomes to discriminate the cancer cell from other cells (Noble et al., 2014).
- Enhancing the duration of action by prolonging liposomes time in blood circulation.
- Exploiting the ability to stimulate anticancer drug delivery based liposomes to the exact target site using different stimuli factors such as "light, pH or temperature changes" (Lee et al. 2017).
- Liposomes are also Nanotheranostic agents due to their ability to carry both diagnostic and therapeutic agents, making them promising anticancer theranostic agents (Petersen et al., 2012) (ZunniVahed et al., 2017).

All the mentioned advantages are a result to the nature of liposomes structure that makes them more biocompatible than other manufactured materials, their ability to be modified with the desired size and shape; in addition to the capability of functionalizing liposomes surface to improve their therapeutic efficiency and for limiting the adverse effect and systematic toxicity.

3.12.3. Dendrimers

Dendirmers are one of the organic nanoparticle, they are manufactured class and self-assembled polymeric materials. "Buhleier et al and Tomalia et al" started to manufacture dendrimers at 1970-1990 (Buhleier et al., 1978) (Tomalia et al., 1985). Dendrimes have nanosize scale around 1 to 100 nm. The structure of dendrimes can be described as dense branched polymers with 3D planned structure. They are consists of three main sections including the core, the branches with the active (functional) groups. These active groups on the surface control and adjust the physiochemical properties of the dendrimes with peak surface functionality (Buhleier et al., 1978). Dendrimes have unique properties due to their special structure and nanoscale size, including (Jackson et al., 1998) (Qunin et al., 2003):

- Dendrimers have good biocompatibility.
- High ability for encapsulating drugs.
- Have monodisperse nature with adsorption capability.
- Can improve the drug accumulation at specific targeted site.
- Can bind to other molecules to adjust their solubility.

Those special characteristic make dendrimers an interesting choice to be used for anticancer drug delivery as therapeutic and diagnostic agents (Khopade et al., 2002) (Tao et al., 2013). Due to their ability to load different kinds of drug molecules inside the dendrimers cavities physically with non-covalent bonds or even by linking them on dendrimers surface chemically using covalent bonds which is the most stable way (Quintana et al., 2002) (Kutuzov et al., 2007).

Despite the unique features of dendrimers, those nanostructures have some problems and serious obstacles that need to be solved by applying the suitable modifies in order to employ them as anticancer drug deliver successfully (Mukerjee and Chan, 2002) such as:

- The undesirable leakage of the carried drug molecules.
- Poor specificity in drug release causing adverse effects.
- Difficulties in controlling the drug release to the target site which limit the therapeutic efficiency.
- Undesirable cytotoxicity and immunogenicity.
- Difficulties in synthesis and modifying dendrimers.

3.12.4. Polymeric Micelles

Polymeric micelles (PMs) are organic nanoparticles they are “amphiphilic molecules” compound of copolymers. Polymeric micelles have spherical shape with “core shell” structure and nanosize scale about 1 to 100 nm (Bhatia, 2016).

They are manufactured at “critical micelle concentration (CMC)”, when the polymeric micelle immersed in a hydrophilic solvent, they are acts as self-assembled. Polymeric micelles consist of two parts the core which is the hydrophobic part and the corona which is the hydrophilic part, this order known as “direct polymeric micelle” (Shin et al., 2016) (Cagel et al., 2017).

Polymeric micelles consider as an excellent drug delivery system (DDS) because of their unique nanofeatures (Bhatia, 2016) (Croy et al., 2006) such as:

- PMs nanosizing scale and their desired spherical shape.
- High stability at physiological terms.
- Reasonable solubility.
- Preventing drug degradation.
- Specificity in drug releasing at the target site.
- Ease in surface functionalization.
- Ability to carry and load the drug molecules via electrostatic interactions.
- High encapsulating ability around 94%.

The capability of modification to limit the toxicity and enhancing the accuracy of targeting in order to improve the therapeutic efficacy makes the polymeric micelle a suitable choice to be used as anticancer drug delivery system (Croy et al., 2006) (Park et al., 2008).

To improve the specificity of targeting and releasing drug with the desired dose, targeting ligands with stimuli factors should be used to modify polymeric micelles (Husseini et al., 2007). Such as "folic acid, antibodies, peptides, carbohydrate and etc." for targeting ligands, and for stimuli PMs it's possible to use "pH gradient, temperature change, ultrasound, enzymes and oxidations"; as the PMs with thermo stimuli factor at "lower critical solution temperature (LCST) or with pH stimuli around 5 can release about 80% of the loaded drug with rapid degrade (Tao et al., 2013). For more PMs efficient improvement in cancer therapy and diagnosis, the "co-delivery technique" is used in multifunctional micelle (Seo et al., 2015). On the other side, it should be noted that by crossing the "critical micelle concentration" (CMC) the balance between the blood and PMs will be shattered and the micelles will face a challenge of undesirable interactions; so it is important to make the proper modifications in order to avoid this hurdle (Cajot et al., 2013) (Sutton et al., 2007).

3.12.5. Quantum Dots

Quantum dots (QDs) are inorganic nanoparticles they are nanocrystals, having spherical "core shell" shape with 3D structure and nanosizing scale range between 1 to 100 nm (Petersen et

al., 2012). Quantum dots are “fluorescent semiconductor” nanocarriers, compounding of the inorganic core with the aquatic organic shell and capping material (Ghasemi et al., 2009).

Quantum dots have ultra-small core diameter around 1 or 2 to 10 nm, with the desired spherical shape that gives them unique nanofeatures (Lee et al., 2017), such as:

- The extremely nanosize gives QDs the possibility to be used for drug delivery systems.
- Multilateral chemo surface properties permit different modification.
- Photo-physical features make the QDs an attractive destination for monitoring applications.

The special nanofeatures of quantum dots have been exploited to some extent as diagnostic and monitoring agents at the real time using QDs brilliant photo stability and enormous agitation by “UV light” (Ghasemi et al., 2009).

Many modifications carried out on quantum dots to enhance the circulation time in the blood and the intracellular process for the purpose of monitoring and bio-imaging at the real time. QDs utilized as diagnostic agents in “MRI, tissue fluorescence imaging and cell labeling” applications and as therapeutic agent for cancer therapies (Bailry et al., 2004).

Quantum dots employed as anticancer drug delivery in vitro study, by developing prostate cancer in a group of laboratory mice. They modified the quantum dots using special targeting ligands and functionalizing factors. The result showed that quantum dots accumulated in the targeted cancer site by exploiting the cancer microenvironment features of “permeability and retention (EPR)” effect (Gao et al., 2004).

However, there are limited studies about quantum dots which make the usage of quantum dots is kind of difficult. Some of these studies indicate that quantum dots have some serious hurdles related to the toxicity due to their precipitation in the atriums of heart and lungs (Bathia, 2016).

3.13. Advantages of using NPs as Intelligent Drug Delivery System IDDS for Cancer Treatment

1- Intelligent drug delivery systems (IDDS) based nanoparticles can load the anticancer drug and release it with the desired dose at the targeted site by distinguish cancer cells

with high precision targeting using stimuli effects by making the necessary modifications and functionalizing the nanoparticles which is something not possible to do with conventional drug carriers (Peer et al., 2007).

2- The IDDS based NPs characterize with the ability to avoid the biological barriers effects and overcome the obstacles circumstance to accumulate the anticancer drug in the cancer cells (Liu et al., 2016).
3- The IDDS based NPs can recognize the little variation between the cancer cells and healthy cells, therefore they can achieve high therapeutic efficacy with very low or even no toxicity and adverse effects in some types of NPs which is something impossible to achieve with the CDDS (Brahami et al., 2017).
4- IDDS are economic system due to the unique properties of specificity of targeting, releasing drugs with the right doses to the right targeted site, in addition to the immunity against the bio-filtering systems inside the body and enhancing the circulation time in the blood; so there is no need for additional probable drug doses (Brahami et al., 2017).
5- The unique qualities showed by NPs through exploiting the nanosize, desired shape, nanostructure, high "surface to volume ratio" offer high efficiency for cancer cell targeting, diagnosis and treatment by embedding different agents at the same time (Petros et al., 2010).
6- The NPs have the capability to be functionalized with different kind of ligands, which gave the ability to attach various "molecules of drugs, genes and contrast agent" and bind to the cancer biomarkers with "specific delivery" and "desirable biodistribution" (Zhang et al., 2010).
7- Cancer medicine based nanotechnology offers therapeutic agents with the range of nanoscale size, which achieve and provide set of dosage drug with group of advantages to overcome the "multiple drug resistance (MDR)" problem. Such as increasing therapeutic efficacy with lower doses and reduced drug resistance, enhancing drug stability with high solubility and dissolution rate, increasing therapeutic action, raising

the oral bioavailability, decreasing nutrition variability and patients variability and etc. (Bathia, 2016).

8- The development of nanomedicine in the field of cancer management led to the possibility of integrating diagnosis, treatment and monitoring at real time all in one physical structure under the term of (theranostic agents), which increases the efficiency of diagnostic and therapeutic opportunities and even the possibility of preventing the spread of the disease through early detection (Chen et al., 2017).

Ultimately it can be concluded that intelligent drug delivery systems (IDDS) based NPs have the ability to solve the problem of conventional drug delivery systems (CDDS).

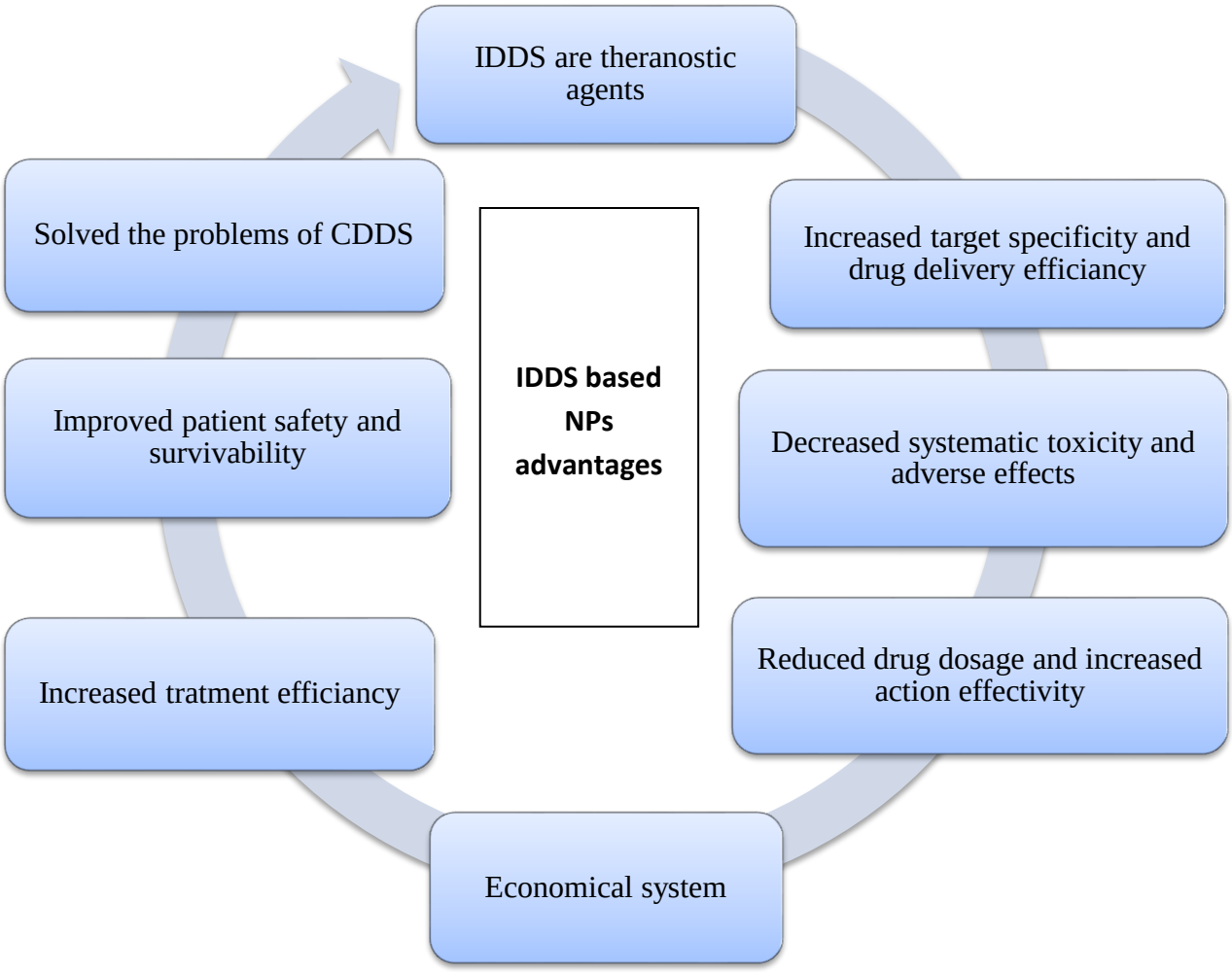


Figure 3.4: Advantages of intelligent drug delivery system based nanoparticles

CHAPTER 4
METHODOLOGY

4.1. Overview

In this chapter the researcher discussed the strategy used in data collection for this study and electing criteria for designing anticancer IDDS. The method used for evaluating simulation was (PROMETHEE and F-PROMETHEE) which has been discussed in detailed in this chapter to evaluate the optimal NPs types to be the best choice for designing IDDS in parallel with the designing criteria. In addition to the fulfillment electing optimal NPs as anticancer IDDS and how the collected criteria data of NPs alternatives have been translated to fuzzy linguistic variables.

4.2. The Strategy of Data Collection Used in the Study

As a first step, information was collected about the types of nanoparticles used as carriers for cancer drugs depending on the opinions of scientists about the studies that curried out in this field and the results of the related laboratory experiments were studied by the researcher also.
It was found that there is a wide variety of nanoparticles that have been employed in cancer management for various therapeutic, diagnostic and monitoring purposes as “nanotheranostics”. The main objective of this study is to select the optimal nanoparticles as intelligent carriers for anticancer drug and by following the results of the latest studies and experiments conducted in vivo on mice, rabbits and other organisms in vitro. Five types of nanoparticles that have been used as anticancer drug delivery were selected by the researcher for their remarkable characteristics and bright behavior towards both the free cancer cells and cancerous tumors including AuNPs, liposomes NPs, dendrimers NPs, PMs NPs and QDs NPs.
As a second step, the optimal criteria for the design of an intelligent drug delivery system have been selected. It is a set of complex and overlapping criteria in terms of the synthesis process cost and the standards of the method and its impact on the patient in addition to the efficiency of the results given. This step is the basis for the selection of nanoparticles required in the first step, where fifteen standards have been identified, some of which are directly related to the

safety and survival of the patient and the other is the basis of the first section but secondary to the patient's safety. The latter group of standards is not related to the safety and survival of the patient or the NPs design method, therefore, less important but is also essential and indispensable.

The fifteen criteria for designing an intelligent anticancer drug delivery system involve the synthesizing cost of NPs with the desirable standards to design smart NPs, the NPs shape and size, pH and temperature effects as stimuli factors, surface charge to control the internalization to the target cell without problems, ligand type to bond the desired agents, biocompatibility and accumulation rate of NPs, in addition to the toxicity ratio, specificity, stability, efficacy, adverse effect and patient safety factor.

During the third step, in order to make the decision about the optimal NPs type to be chosen as an intelligent anticancer drug carrier based on the desired set of criteria, the application of fuzzy PROMETHEE was used.

4.3. Election Criteria for Designing Anticancer IDDS

The accurate selection of criteria in the manufacture of nanoparticles as anticancer drug carriers significantly affects the pharmacological effectiveness and therapeutic efficiency in addition to the adverse effects and toxicity that can be generated. In order to exploit the noble features of NPs as a result of nanosizing and nanostructuring of these particles, the correct criteria for the modification and decoration of NPs must be chosen to optimize them as intelligent drug carriers. The physicochemical, electromagnetic, mechanical, optical and other effective nanofeatures in the medical field can be directly influenced by a certain set of manufacturing factors.

The mechanism of modification and activation of nanoparticles as intelligent drug carriers is a process governed by the standards that must be adopted during the manufacturing nanoparticles according to the pathophysiological specifications of the disease to which the drug was transferred and treated as a strategy to exploit the specifications of the disease against itself to eliminate it as in the case of cancer.

In the process of designing, modifying and activating nanoparticles as carriers of anticancer drugs, the appropriate shape and size are selected, as well as the most appropriate synthetic structure for the selected nanoparticles. Nano surfaces are then activated with different kind of bonds physically or chemically to load the cargos and prolong the circulation of the NPs in the blood. The surface is charged with a positive or negative charge to increase the portability of loading drug particles and to control the cellular insertion of drug carriers into the cancer cell without exposure to biological barriers or other problems. In order to increase the targeting accuracy, external or internal stimuli are used to stimulate the degrading process and release the drugs inside the target cancer cell. Temperature variation factors due to cancer infections and different pH levels of the cancer medium are the most important factors in this stage. By determining the design and modification criteria, it's possible to achieve the controlling the drug's loading capacity, adjusting the required dosages, increasing the stability and accuracy of targeting, prolonging the blood circulation time cycle, in addition to avoiding systemic drug cleaning problems. Upon reaching the target cancer cells, nanoparticles spread around the cancerous tumor and begin to enter the cancer cells to begin the stimulation process to release drug dose into the cancer cells. The drug begins to interact with cancer cells kill it and reprogramming the affected area and returning it to the normal system without any toxic effects or harm to neighboring healthy cells as shown in the figure (4.1) below.

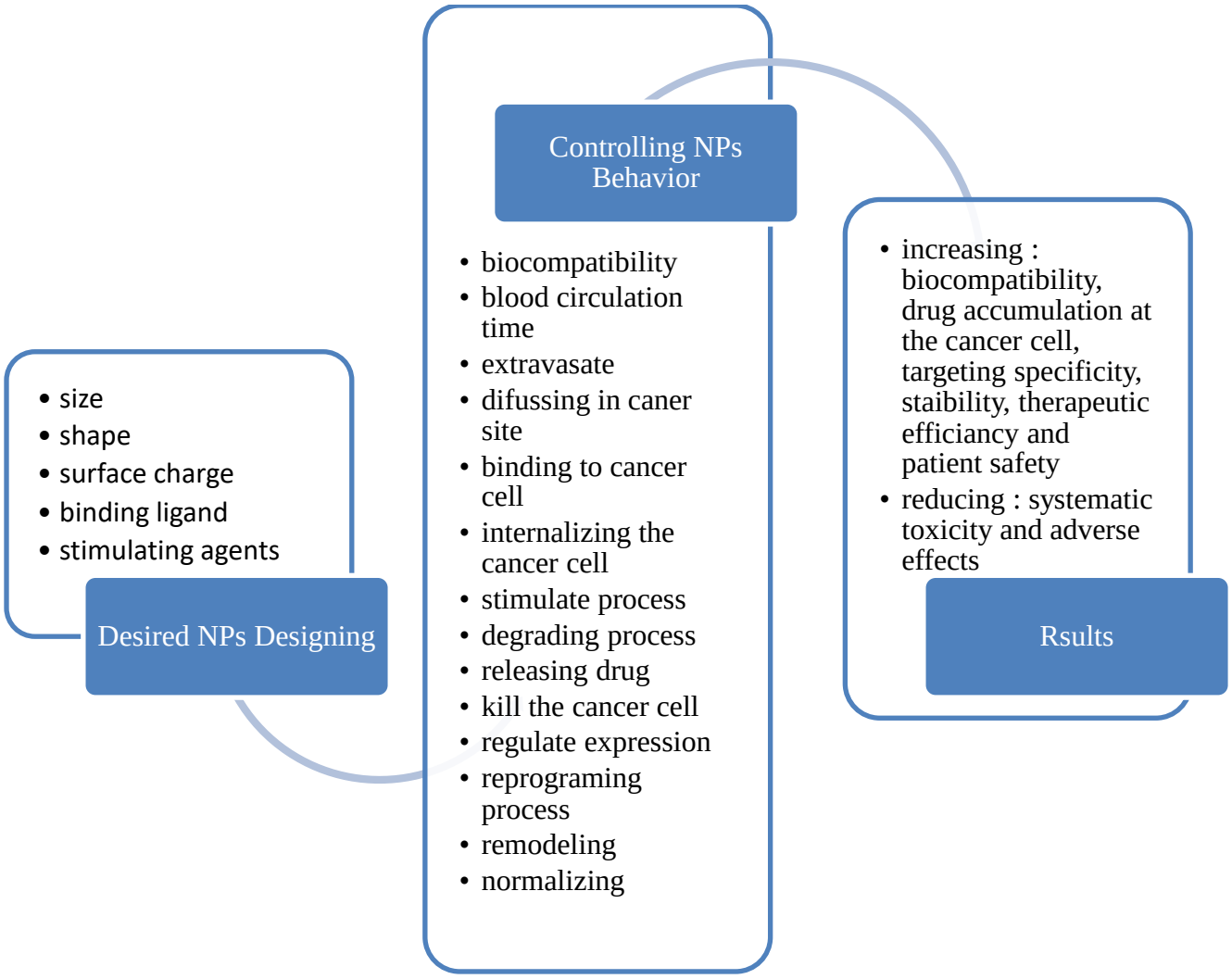


Figure 4.1: Designing and modification standards for IDDS and the principle of their working mechanism with the expected results

4.4. PROMETHEE and F-PROMETHEE

PROMETHEE method is a multi-criteria decision-making (MCDM) technique and it consider one of the great ways to compare, rank and evaluate a group of alternatives due to the nature of the fuzzy in the process of decision making. PROMETHEE method prepared by (Brans and Vincle, 1985), (Brans et al., 1984) and (Brans et al., 1986) and it termed from “Preference Ranking Organization METHod for Enrichment Evaluations” (Senvar et al., 2014).

This method handles excellently to make a comparison and classification of a range of selections according to specific criteria (Bilsel et al., 2006), (Albadvi et al., 2007) and (Tuzkaya et al., 2010). What distinguishe the PROMETHEE method from other methods is the range of advantages it offers, such as being an easy and friendly way to use and apply to complete the process of classification between alternatives. The method was successfully implemented to design problem-solving plans in reality. PROMETHEE I offer partial classification and PROMETHEE II offer the possibility of total classification of alternatives with accurate and satisfactory results (Ulengin et al., 2001).

First step in the PROMETHEE method is the evaluation process, where alternatives are evaluated according to a set of criteria that are determined by the decision maker. In addition to the need for two types of information, the first is information that determines the relative importance of standards, called the (criterion weight); the second type of information is to determine the preferred function of each criterion associated with the set of alternatives that are determined by the decision maker as well according to the theory and hypothesis of the decision maker (Macharis et al, 2004) as shown in the figures below with notice that all the PROMOTHE figures are retrieved from (Brans et al., 1984) and (Brans et al., 1986).

a	$g_1(\cdot)$	$g_2(\cdot)$	$\cdots$	$g_j(\cdot)$	$\cdots$	$g_k(\cdot)$
a_1	$g_1(a_1)$	$g_2(a_1)$	$\cdots$	$g_j(a_1)$	$\cdots$	$g_k(a_1)$
a_2	$g_1(a_2)$	$g_2(a_2)$	$\cdots$	$g_j(a_2)$	$\cdots$	$g_k(a_2)$
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
a_i	$g_1(a_i)$	$g_2(a_i)$	$\cdots$	$g_j(a_i)$	$\cdots$	$g_k(a_i)$
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
a_n	$g_1(a_n)$	$g_2(a_n)$	$\cdots$	$g_j(a_n)$	$\cdots$	$g_k(a_n)$

Figure 4.2: Evaluation table

$g_1(\cdot)$	$g_2(\cdot)$	...	$g_j(\cdot)$	...	$g_k(\cdot)$
w_1	w_2	...	w_j	...	w_k

Figure 4.3: Criteria importance weight

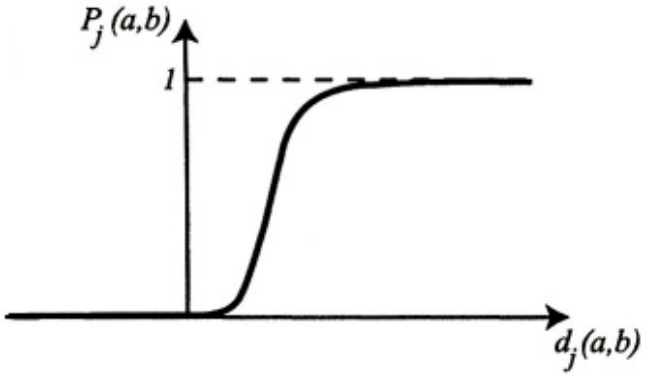


Figure 4.4: Preference function

There are set of different preference functions to qualify conflicted criteria that a decision maker can use including “usual function, linear function, level function, U-shape function, V-shape function, and Gaussian function”. The preference function can indicate the difference between two alternatives of specific criteria as (a) and (b) within a preference degree from (0 to 1) as it shown in the figures below.

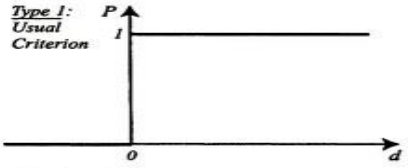
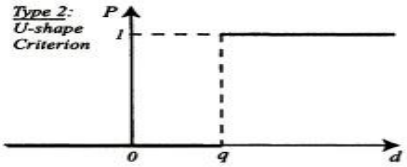
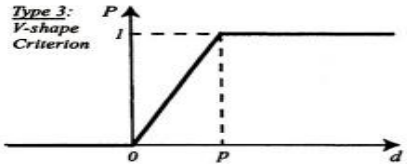
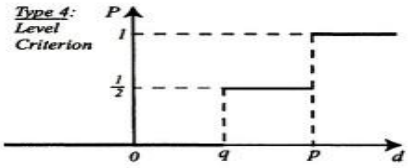
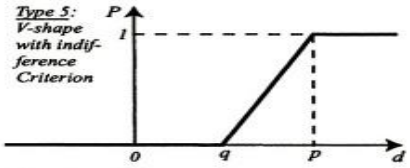
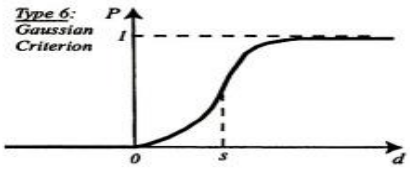
Generalised criterion	Definition	Parameters to fix
	$P(d) = \begin{cases} 0 & d \leq 0 \\ 1 & d > 0 \end{cases}$	–
	$P(d) = \begin{cases} 0 & d \leq q \\ 1 & d > q \end{cases}$	q
	$P(d) = \begin{cases} 0 & d \leq 0 \\ \frac{d}{p} & 0 \leq d \leq p \\ 1 & d > p \end{cases}$	p
	$P(d) = \begin{cases} 0 & d \leq q \\ \frac{1}{2} & q < d \leq p \\ 1 & d > p \end{cases}$	p, q
	$P(d) = \begin{cases} 0 & d \leq q \\ \frac{d-q}{p-q} & q < d \leq p \\ 1 & d > p \end{cases}$	p, q
	$P(d) = \begin{cases} 0 & d \leq 0 \\ 1 - e^{-\frac{d^2}{2s^2}} & d > 0 \end{cases}$	s

Figure 4.5: Set of different group of preference function

Geldermann et al. (2000) and Brans et al. (1986) summarize the requisite procedure for the algorithm PROMETHEE method as follows:

Step (1): defining the general preference function f_k for each criterion as $p_k(d)$

Step (2): defining the relative importance weight for each criterion, where the criterion with higher weight is more important and vice versa

$$w^T = (w_1, \dots, w_k) \qquad (4.1)$$

By normalizing weights using:

$$\sum_{k=1}^{K} w_k = 1 \qquad (4.2)$$

Step (3): specifying the outranking relation π for each alternative a_t, $a_{t'} \in$ A equation;

$$\begin{cases} AXA \rightarrow [0,1] \\ \pi(a_t, a_{t'}) \end{cases} = \sum_{k=1}^{K} w_k . \left[p_k \left(f_k(a_t) - f_k(a_{t'}) \right) \right] \qquad (4.3)$$

Step (5): In the following two equations (T) represents the number of alternatives to determine the positive and negative outflow force, since the preference for positive outflow alternatives:

For the positive outflow a_t:

$$\Phi^{+}(a_t) = \frac{1}{T-1} \sum_{\substack{t'=1 \\ t' \neq t}}^{n} \pi(a_t, a_{t'}) \qquad (4.4)$$

For the negative outflow $a_{t:}$

$$\Phi^{-}(a_t) = \frac{1}{T-1} \sum_{\substack{t'=1 \\ t' \neq t}}^{n} \pi(a_{t'}, a_t) \qquad (4.5)$$

Step (6): In PROMETHEE I, the higher positive outflow and lower negative outflow describe the optimal alternative choice a_t, when a_t is outstanding compared to $a_{t'}$ $(a_t P a_{t'})$

$$\begin{cases} \Phi^{+}(a_t) > \Phi^{+}(a_{t'}) \; and \; \Phi^{-}(a_t) < \Phi^{-}(a_{t'}) \; or \\ \Phi^{+}(a_t) > \Phi^{+}(a_{t'}) \; and \; \Phi^{-}(a_t) = \Phi^{-}(a_{t'}) or \\ \Phi^{+}(a_t) = \Phi^{+}(a_{t'}) \; and \; \Phi^{-}(a_t) < \Phi^{-}(a_{t,} a_{t'}) \end{cases} \qquad (4.6)$$

If positive and negative outflows match the analysis then partial classification is used, where PROMETHEE I weighs the potential possibility of incomparalibilty ($a_t I a_{t'}$) of the outflows.

$$(a_t I a_{t'}) \text{ if: } \Phi^{+}(a_t) = \Phi^{+}(a_{t'}) \;\; and \;\; \Phi^{-}(a_t) = \Phi^{-}(a_{t'}) \qquad (4.7)$$

In case of a_t is outstanding to $a_{t'}$ with respect to the positive outflow, both alternatives are incomparable $(a_t R a_{t'})$ and the reverse applies to the negative outflow.

$$(a_t R a_{t'}), \text{if} \begin{cases} \Phi^{+}(a_t) > \Phi^{+}(a_{t'}) \; and \; \Phi^{-}(a_t) > \Phi^{-}(a_{t'}) \\ \Phi^{+}(a_t) < \Phi^{+}(a_{t'}) \quad and \; \Phi^{-}(a_t) < \Phi^{-}(a_{t'}) \end{cases} \qquad (4.8)$$

Step (7): PROMETHEE II offer a total ranking via the netflow. A high netflow for $a_t$indicates that a_t is outstanding to $a_{t'}$

$$\Phi^{net}(a_t) = \Phi^{+}(a_t) - \Phi^{-}(a_t) \qquad (4.9)$$

Thus that can conclude that the optimal alternative is the one with superior Φnet (a_t) value.

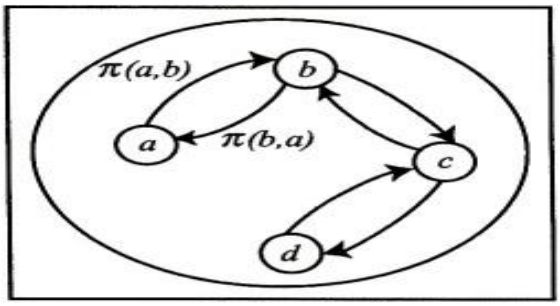
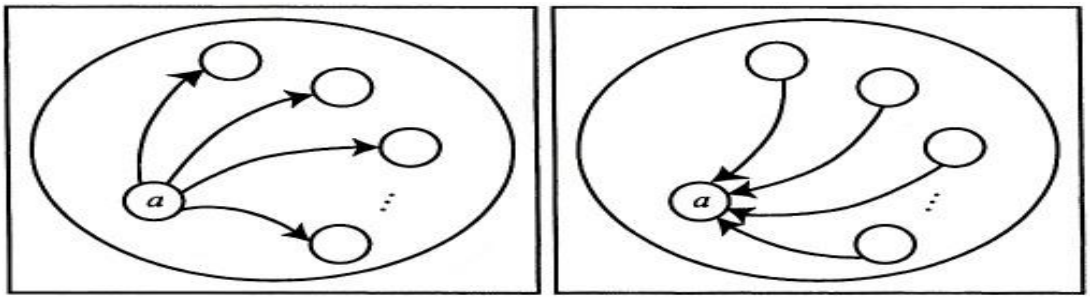


Figure 4.6: PROMETHEE outranking flow graph



(a) The $\phi^+(a)$ outranking flow. (b) The $\phi^-(a)$ outranking flow.

Figure 4.7: Positive and negative PROMETHEE outranking net flows

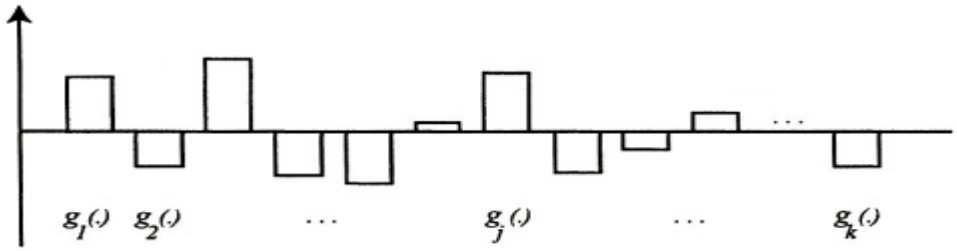


Figure 4.8: Resulted profile of the alternatives

F-PROMETHEE solved the problem of comparing index between fuzzy numbers by taking the average of the F-numbers which proposed by Yager (1981) and termed with his name as "Yager's index". The triangular fuzzy numbers is resulted by taking

the center of weight values based on Yager index (Goumas and Lygerou, 2000; Bilsel et al., 2006) which is used in this study. The traingular fuzzy number (TFN) is presented with $F\sim = (n , a , b)$ and expressed in the following equation as :

$$F\sim = (n – a, n, n + b) = (3n – a +b) / 3 \quad (4.10)$$

Until recently, few researches were applied fuzzy PROMETHEE as methodology for their study such as: Goumas and Lygerou (2000), Ozgen et al. (2000), Geldermann et al. (2000), Ulengin et al. (2001), Bilsel (2006), Chou et al. (2007), Tuzkaya et al. (2010), those study considered as the first attempts to use fuzzy PROMETHEE method.

Nowadays, there are many studies that have been successfully applied in the field of decision making on various types of complex issues in various fields including engineering, medicine, economics etc. Since the focus of this study is exclusively in the field of biomedical engineering, the researcher was briefed on many successful applied studies in the field of implementing fuzzy PROMETHEE and MCDM in biomedical engineering, especially in the studies related to cancer management. One of the studies carried out by (Uzun Ozsahin et al., 2017) included a decision-making process on six cancer treatment techniques “chemotherapy, radiation therapy, surgery, immune-therapy, hormone therapy and hadron therapy” using fuzzy PROMETHEE and MCDM. The study resulted in a preference for surgery technique with a net flow value equal to (0.5262).

In a second study, this technique was used to select the optimal technique for creating nuclear medicine images among a range of techniques that included “Ordered Subset Expectation Maximization (OSEM), Origin Ensemble (OE), List Mode-OSEM (LM-OSEM) and Filtered Back Propagation (FBP)”. The study resulted in a preference for the FBP technique with a net flow equal to (0.0031), (Uzun Ozsahin et al., 2018).

In a third study, this method was applied to assess and classify a range of imaging devices used in nuclear medicine, which included “Single Positron Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), SPECT/CT, PET/CT and PET/MRI”. The study resulted in a preference for the PET device with a net flow equal to (0.0005), (Uzun Ozsahin et al., 2017). In addition to conducting other evaluative studies using fuzzy

PROMETHEE method to make a decision about the favor device for medical X-ray imaging and choosing the optimal technique for the treatment of breast cancer by (Ozsahin et al., 2018) and (Uzun Ozsahin et al.,2018) respectively.

4.5. Evaluation of IDDS Designing Criteria Based Fuzzy PROMETHEE Logic

To achieve a successful evaluation for the comparison process of selecting optimal NPs type as anticancer IDDS to end up with accurate results of the decision-making process. The triangular fuzzy linguistic preference scale was used via applying Yager's index to defuzzify each criterion values and applied these values to "PROMETHEE GAIA" decision lab software with "Gaussian preference function" for analysis, in order to accomplish the decision-making process towards electing the optimal nanoparticles by adopting the standard measures (criteria) of the designing process via defining the weights of significance for each criterion starting with the most important down to the least important taking into account the amount of influence resulting from the importance of each criterion towards achieving the objectives of the study.

The weight of significance was determined after analyzing importance of each criterion of NPs involving the NPs size, shape, surface charge, ligand type, PH and temperature stimuli effect and the influence of the biocompatibility, accumulation ratio of NPs in the body and the their toxicity, targeting specificity, stability, efficacy, adverse effect and safety factor in addition the cost of the manufacturing process. The criteria were divided into groups according to importance as follows: first group of criteria include size, shape, surface charge, biocompatibility, accumulation ratio, toxicity, efficacy, adverse effect, safety they were given first class importance due to their direct association with patient safety and were allocated as (very high) weight because of the maximum importance to progress the drug targeting to the target cancer site to enhance the efficiency and safety of the therapeutic technique and therefore, quality of life and survivability of the patient. Second group of criteria included pH and Temperature stimuli factors, ligand type, specificity, stability which were given second class importance due to the indirect association with the safety and survivability of the patient. In the last class, was the manufacturing cost which determined as minimal importance

(moderate class) on the preference of linguistic fuzzy scale where previous criteria are uttermost important in the relative with the recovery, safety and patient survival ratio as shown in the table (4.1) which illustrate the linguistic variables and their corresponding priority weight of criteria and fuzzy numbers for the rating criteria.

Table 4.1: Linguistic variables and their corresponding priority weight of criteria and their fuzzy numbers

Priority weight of criteria	Fuzzy number	Rating of criteria
Very High (VH)	(0.75, 1.00, 1.00)	Size, Shape, Surface charge, Biocompatibility, Accumulation ratio, Toxicity, Efficacy, Adverse effect, Safety
High (H)	(0.50, 0.75, 1.00)	PH, Temperature, Non covalent ligand, Specificity, Stability
Moderate (M)	(0.25, 0.50, 0.75)	Cost
Low (L)	(0, 0.25, 0.50)	
Very Low (VL)	(0, 0, 0.25)	

The priority of the preference function for each criterion was determined by using a scale ranged between (Max\ Min) or (Yes\ No) according the status of the function, as shown in the table 4.2 below.

Table 4.2: Linguistic variables and their corresponding priority preference function of criteria and fuzzy numbers

Priority preference function of criteria	Fuzzy number	Rating of criteria
Max	0.50 - 1.00	Size, shape, pH, temperature, surface charge, biocompatibility, specificity, efficacy, stability.
Min	0- 0.50	Cost, accumulation ratio, toxicity, adverse effect.
Yes	1.00	Non covalent ligand
No	0	

4.6. Fulfillment Electing Optimal NPs as Anticancer IDDS

The data used in this study were collected based on secondary sources, which included a group of the latest studies and experiments using the internationally recognized scientific journals as the main sources of secondary sources, which included a group of international journals such as Elsevier, Springer, MPDI, Research Get, American Association of Cancer Research, Google Scholar and etc. in addition to National Cancer Institute, American Cancer Society, Canadian Cancer Society, World Health Organization and etc. as main sources for the literature reviews. The data collected by the researcher were scrutinized and presented to the specialists and supervisors of the research in order to make an accurate decision regarding the selection of the optimal parameters of the study and taking the approximate rates and values as

the first analytical step of the data, followed by a second analytical step using the fuzzy PROMETHEE method. The application of the fuzzy PROMETHEE visual was used to create a tactic for the criteria and their importance weights and preference function that used in the study to be accurately evaluated in conjunction with the input data.

4.7. Translating Collected Criteria Data of NPs Alternatives to Fuzzy Linguistic Variables

Gold nanoparticles

The cost of manufacturing and modifying gold nanoparticles has been classified as low cost due to the ease of manufacture and the lack of obstacles to modify them with the required specifications (Ying Kong, et al. 2017). Experiments have also showed that designing AuNPs with 5 to 5.4 nm in size makes them exhibit (high) effective behavior with minimal toxic effects as drug delivery (Shen, et al. 2016) (Hossen, et al. 2018), so the researcher classified AuNPs with size around 5 nm as (very good). The core shell shape was classified as (very high) performance. Stimulating factors to control the release of the drug is at its optimal peak when pH stimuli factor is about 4.6 to 5.3 with average equal to 4.9 according to Shen, et al. (2016) and its classified as (very good), in another study we found that the optimal control of the drug releasing is when temperature stimuli factor used with value around 25 to 30 C with average 37C at room temperature (Tyagi et al. 2016) and its classified as (very high), with the use of negative surface charge and functionalizing the surface with physical bond (non-covalent ligands) (Shen, et al. 2016). All of these design criteria made for AuNPs shows an ideal behavior as IDDS with excellent bio-compatibility, (very low) accumulation ratio in the body, systemic toxicity almost negligible, very high target efficiency, excellent stability classified as (very high), (very low) adverse effect and (very high) safety.

Liposomes

The cost of synthesis of liposomes has been classified as (very high) because of the high cost of synthesis and modification of these nanoparticles. The optimize size of modification standard was classified as (average) according to the information mentioned in previous studies as the synthesis volume has no specific scale and low safety (Hossen, et al. 2018). The lipid bilayer nanosphare shape and structure were classified as (moderate). To stimulate the release of the drug, the study of Ferreira, et, al., (2013) showed that a catalytic pH index of 5 to 6 is used in average 5.5 or less which classified as (good). They also used thermal stimuli with value ≤ 40 to 50C which classified as (moderate) due to the need of high temperature degree to release the cargo. For the surface charge it is mentioned in a study conducted by Liu et al. (2015) that the surface liposomes NPs is modified with heavy negative charge which classified as (average) due to the difficulties of this process as well modifying liposomes with chemical bonds (covalent ligands) which considered misfit with the standards of the hypothesis of this study. As a result for aforementioned data the modified liposomes shows (high) biocompatibility due to their nature availability in the body, (high) accumulation ratio of liposomes in the body, (high) systematic toxicity, (high) controlled drug release, improved stability that classified as (high) preference, thus (high) efficacy, (low) adverse effect and (low) safety (LI et al., 2017).

Dendrimers

The process of manufacturing dendrimers NPs is difficult and complicated which make it a high cost process due to this reason the researcher assorted the synthesizing and decorating cost process as expensive (high). It found that the dendrimers can synthesis with very low size rating between 1 to 5 nm (Bhatia, 2016), so the criterion of nanosizing classified as (good). The dense tree branched structure with spherical shape were assorted as (moderate). The pH stimuli factor is around 5 to 6 and it's classified as (good). The thermal stimuli factor is ranged around 20 to 30C and it's classified as (high) performance. The surface charged with positive charge, and due to the resulted toxicity this criteria assorted as (average). The used bond for modification is chemical bonds (covalent ligands) to achieve better loading and targeting. The

biocompatibility classified as (moderate), (high) accumulation ratio in the body, (moderate) toxicity ratio, specificity, stability, efficacy, adverse effect and safety.

Polymeric micelles (PMs)

The cost of manufacturing and modifying PMs is considered relatively an expensive process and it's assorted as (high) cost process. The customized size of modifying PMs has a wide scale ranged between 10 to 100 nm, so the size criteria classified in (average). pH stimuli factor equal to 5 according to the study of (Zhou, 2018), thus classified as (good). Thermal sensitivity found that it ranged between 30 to 39 C and in another case it ranged between 37 to 42 C (Zhou, 2018), consequently it classified as (moderate). To functionalize the surface it charged with slight negative charge according to the study of Lui et al. (2015), so it classified as (good). To enhance the drug loading ability the surface modified with covalent bonds as mention in Bhatia study (2016), thus the ligand type of the PMs assorted as unfit with thesis standards. The PMs with desired modification behave as (high) biocompatibility, (moderate) accumulation ratio and toxicity, (high) specificity and stability, (very high) efficacy, (low) adverse effect and (high) safety.

Quantum dots (QDs)

QDs can be synthesis and modified with suitable cost, so the cost of QDs manufacturing classified as (moderate). The nanosizing scale of QDs range between 2 to10 nm according to (Senapati, 2018) and it can be describe in specific way to be modified for drug delivery purpose, it modify with size ranged between 2.2 to 5.2 nm. QDs with size equal to 5.2 nm consider to be less toxic behave, thus the size criteria classified as (good). QDs are nanocrystal structures that can be modified with core shell shape, therefore the researcher classified shape criterion as (high) performance. To control drug releasing with the usage of pH sensitivity that equal to 5 consider as (good) performance, in addition to thermal sensitivity around 37 C which offer high uptake cellular, thus it classified as (very high) quality criteria. It's possible to modify the QDs surface by charging it with negative charge and covalent linkage which makes the QDs exhibit less toxicity effect, so it's classified as (good) surface charge

performance and (low) toxicity. Due to the aforementioned modifications applied in the studies of (Dey et al. 2011), (Lui et al. 2015) and (Fang et al., 2018) respectively; the QDs had (moderate) compatibility, (high) accumulation rate in the body, (low) systematic toxicity, (high) specificity due to the good accumulation in the target site, (moderate) stability, (high) efficacy, (high) adverse effect due to the deposition of the QDs in the lung and other organs, (very low) safety which is related to the breakthrough the BBB.

The table (4.3) below shows the customized nanoparticles to be designed as intelligent anticancer drug delivery system applied with desired criteria using fuzzy PROMETHEE method. The Gaussian preference function applied through Visual PROMETHEE lab which is a multi-criteria-decision-aid (MCDA). The criteria were abbreviated as follow: pH sensitivity (pH), temperature sensitivity (Temp.), surface charge (SC), non-covalent ligand (NCL), biocompatibility (BC), accumulation ratio (ACC.), toxicity (TO), specificity (SP), stability (ST), efficiency (EF), adverse effect (AE) and for safety factor (SA).

Table 4.3: Customized NPs used as anticancer IDDS accompanied with respective parameters and corresponding visual PROMETHEE values (A)

Criteria	Cost	Size	Shape	pH	Temp.	SC	NCL
Unit	($)	(nm)			(C)		
Preference							
Max\Min	Min	Max	Max	Max	Max	Max	Yes
Weight	M	VH	VH	H	H	VH	H
Preference Fn.	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian
Evaluation							
AuNPs	M	VG	VH	VG	VH	VG	Yes
Liposomes	VH	A	M	G	M	A	No
Dendrimers	H	G	M	G	H	A	No
PMs	H	A	H	G	M	G	No
QDs	M	G	H	G	VH	G	No

Table 4.3: Customized NPs used as anticancer IDDS accompanied with respective parameters and corresponding visual PROMETHEE values (B)

Criteria	BC	ACC.	TO	SP	ST	EF	AE	SA
Unit	%	%	%	%	%	%	%	%
Preference								
Max\Min	Max	Min	Min	Max	Max	Max	Min	Max
Weight	VH	VH	VH	H	H	VH	VH	VH
Preference Fn.	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian
Evaluation								
AuNPs	VH	VL	VL	VH	VH	VH	VL	VH
Liposomes	H	H	H	H	H	H	L	L
Dendrimers	M	H	M	M	M	M	M	M
PMs	H	M	M	H	H	VH	L	H
QDs	M	H	L	H	M	H	H	VL

CHAPTER 5
FINDINGS AND DISCUSSION

5.1. Visual PROMETHEE Result

The visual PROMETHEE scenario provided full net flow for the purpose of ranking the customized NPs as anticancer IDDS, in regard to determined designing criteria under the effect of determined importance scale. The visual PROMETHEE scenario offered a total net flow of outranking ranged from positive outranking flow to negative outranking flow passing by net flow. The range from the net flow point to the positive outranking flow recognize the progressive performance of NPs as IDDS for anticancer treatment, whilst the range from the net flow point to the negative outranking flow recognize the descending performance as shown in the table (5.1) bellow.

Table 5.1: Visual PROMETHEE scenario results total outranking flows of the alternative NPs designed as IDDS for cancer treatment

Rank	Nanoparticles as Intelligent Anticancer drug delivery	Phi	Phi+	Phi-
1	AuNPs	0,1428	0,1428	0,0000
2	Polymeric Micelles	0,0280	0,0511	0,0231
3	Quantum dots	-0,0467	0,0225	0,0692
4	Dendrimers	-0,0593	0,0111	0,0703
5	Liposomes	-0,0649	0,0110	0,0759

The NPs classification result for IDDS designing described in the above table via total outranking flow of the Visual PROMETHEE scenario shows that the gold nanoparticles (AuNPs) assorted in the 1st place with both highest net flow and positive outranking flow equal to (0,1428) and with zero negative outranking flow, the polymeric micelles (PMs) assorted in

the 2nd place with net flow (0,0280), positive outranking flow equal to (0,0511) and negative outranking flow equal to (0,0231). In the 3rd placed the quantum dots nanoparticles (QDs) which had net flow equal to (-0,0467), (0,0225) for positive outranking flow and (0,0692) for the negative outranking flow. The dendrimers assorted in the 4th place with net flow (-0,0593), positive outranking flow (0,0111) and negative outranking flow (0,0703). For the last place it was taken by the liposomes nanoparticles with net flow equal to (-0,0649), positive outranking flow (0,0110) and negative outranking flow (0,0759).

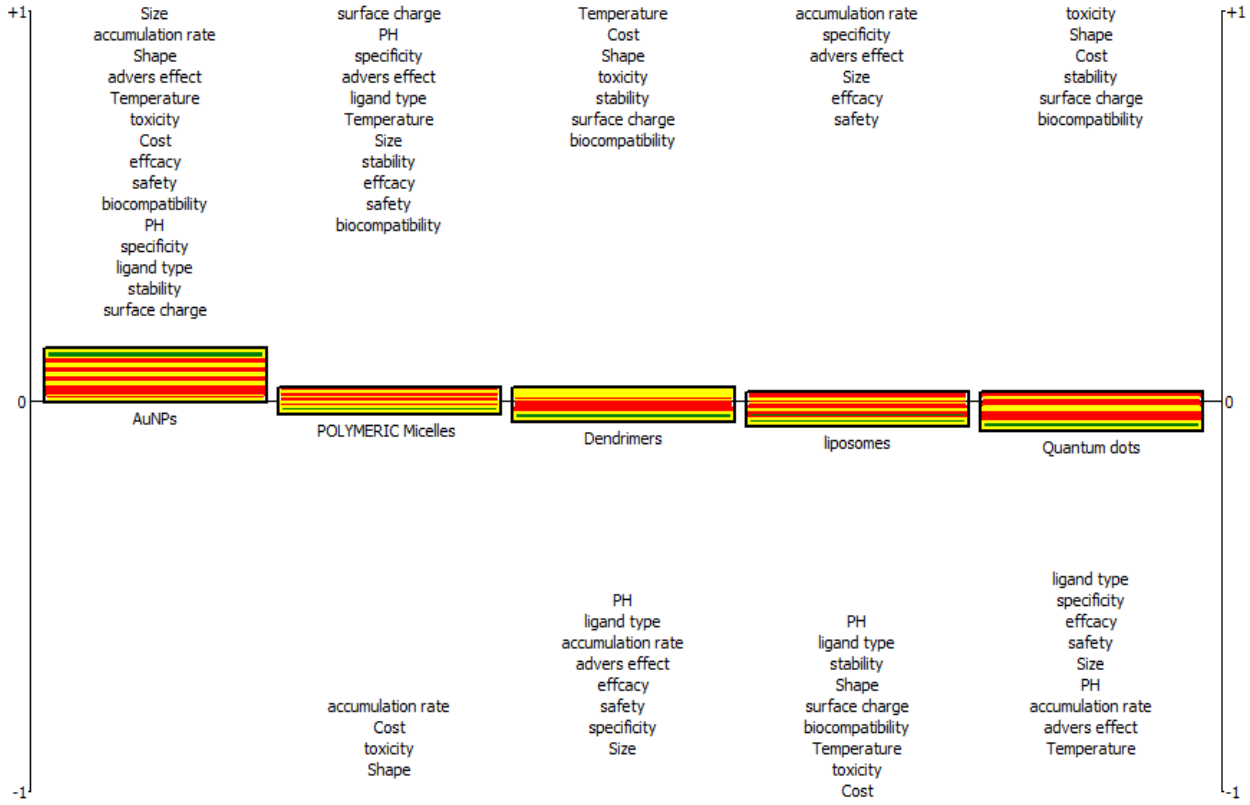


Figure 5.1: PROMETHEE rainbow ranking illustrating the criteria for each alternative NPs with their positive and negative outranking flow

AuNPs was ranked in the first place due to the classification of it's all design criteria as very good modification choices which can result high performance as IDDS for cancer treatment

with almost no disadvantages if the desired decorating process is best done, while other NPs even with applying the desired decorating processes they still have undesired behaves to employ as anticancer drug delivery system.

The following figures show the action profile for each type of NPs alternatives separately:

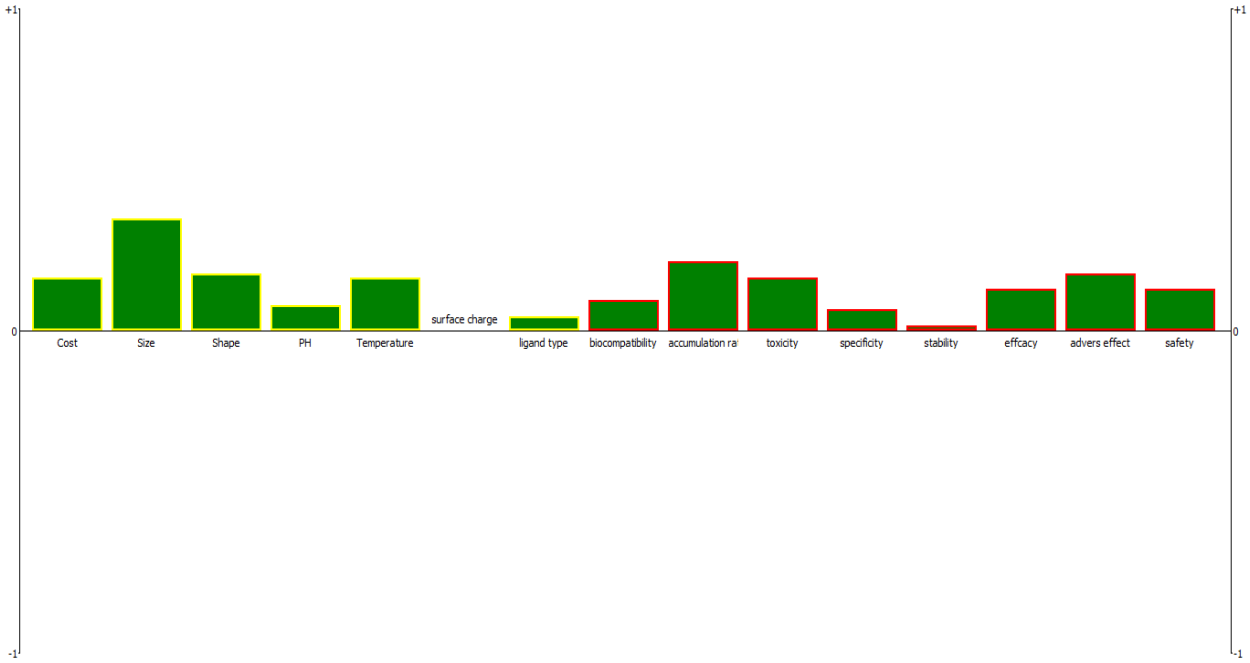


Figure 5.2: Action profile for AuNPs

The resulted action profile for AuNPs shows that all the determined design criteria to manufacture and decorate gold nanoparticles are well performance. Starting with the cost factor it's affordable as it shown in the figure above. For the size factor it's very good choice and well performance followed by the shape, thermal sensitivity, accumulation ratio with good biocompatibility and pH sensitivity. For the surface functionalization factors the non-covalent ligand is tolerable performance with moderated surface charge performance. The mentioned decorating factors result in good biocompatibility, good targeting specificity and high

therapeutic efficiency with reasonable stability. No systematic toxicity and adverse effect with high ratio of patient's safety.

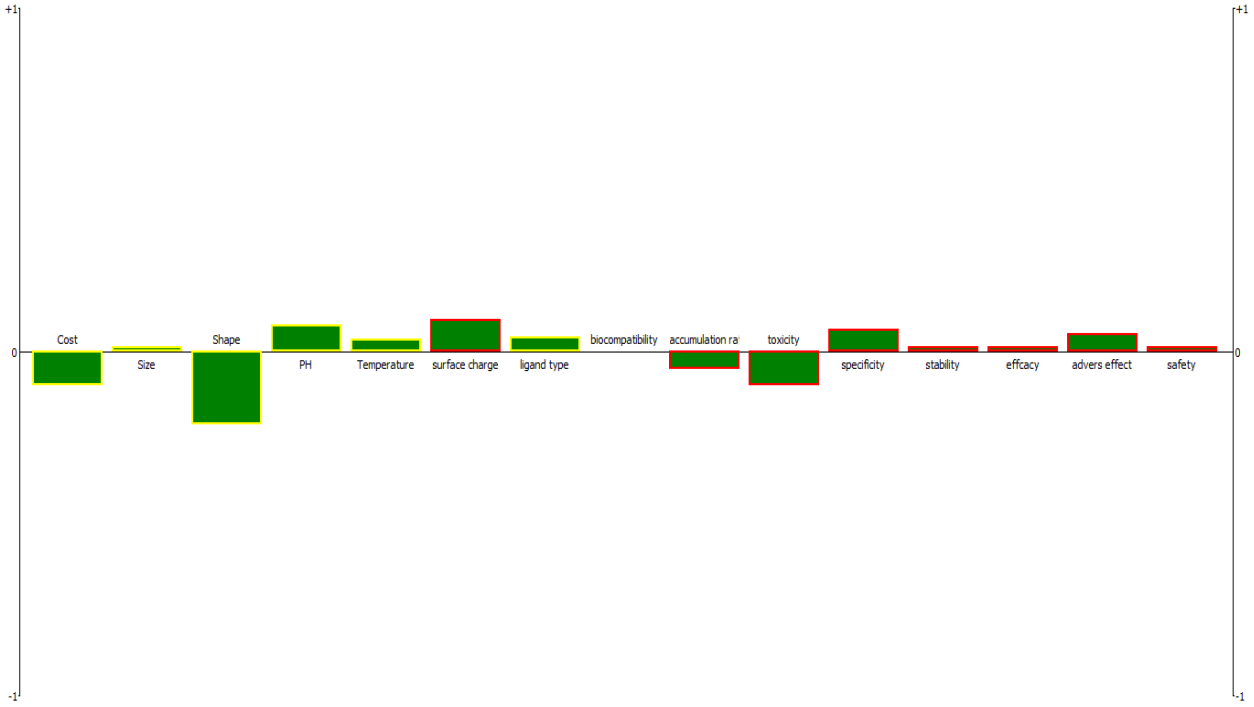


Figure 5.3: Action profile for polymeric micelles NPs (PMs)

For the PMs, the results shown in the action profile figure clarify that the main problem for the PMs is related to determining the shape factor with undesirable accumulation and systematic toxicities, in addition to the unsuitable cost for the manufacturing process. The modified size is moderate interpretation, pH and thermal sensitivity with the surface charge and ligand type functionalization are good performance. The whole modification process results in to moderate biocompatibility, stability and efficiency with good specificity and low adverse effect, and finally tolerable safety factor.

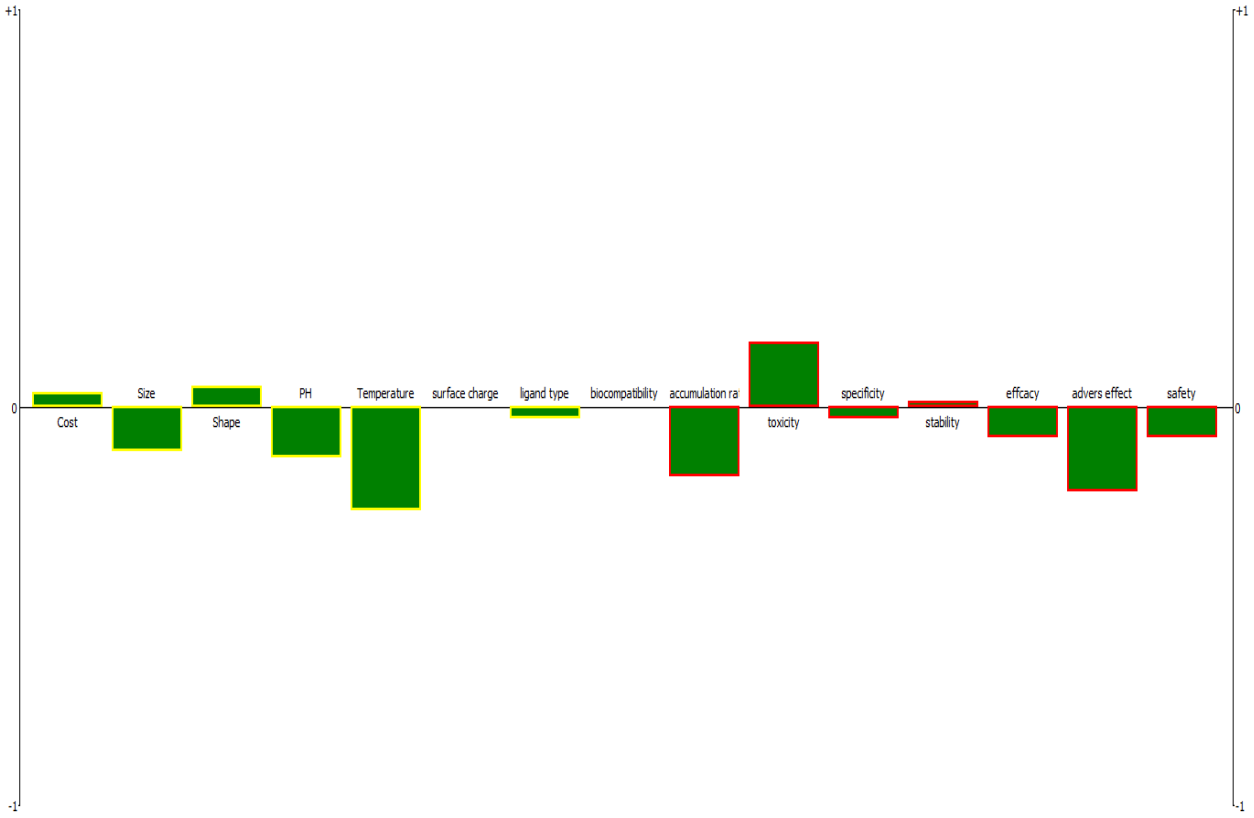


Figure 5.4: Action profile for quantum dots NPS (QDs)

The figure of QDs action profile illustrate that the main deficiency for this type is related to thermal sensitivity and accumulation ratio causing adverse effects and therapeutic deficiency. Followed by undesirable size modifications performance, pH sensitivity and ligand type functionalization with moderated surface charge performance. Result in moderate biocompatibility and stability with weakness in the patient's safety factor.

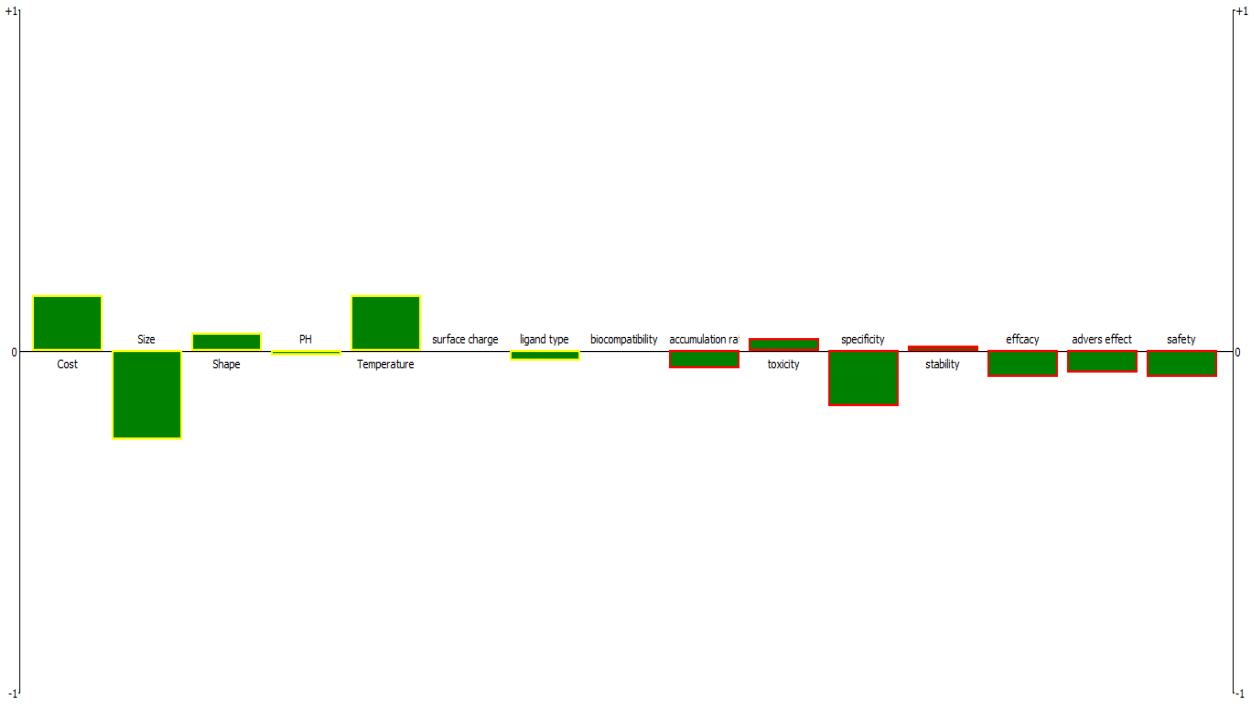


Figure 5.5: Action profile for dendrimers NPs

For dendrimers NPs, the action profile shows that the main problem with this type is related to the modified size performance and targeting specificity causing therapeutic deficiency, followed by undesired accumulation ratio of the dendrimers in the body causing adverse effect and deficiency in patient's safety factor. The cost of dendrimers synthesis factor is good, the thermal sensitivity is well performance and the modified shape is good performance. For the pH sensitivity, surface charge and non-covalent ligand they are moderate performance with different levels. In addition to, moderate level of biocompatibility and stability with tolerable level of nontoxicity.

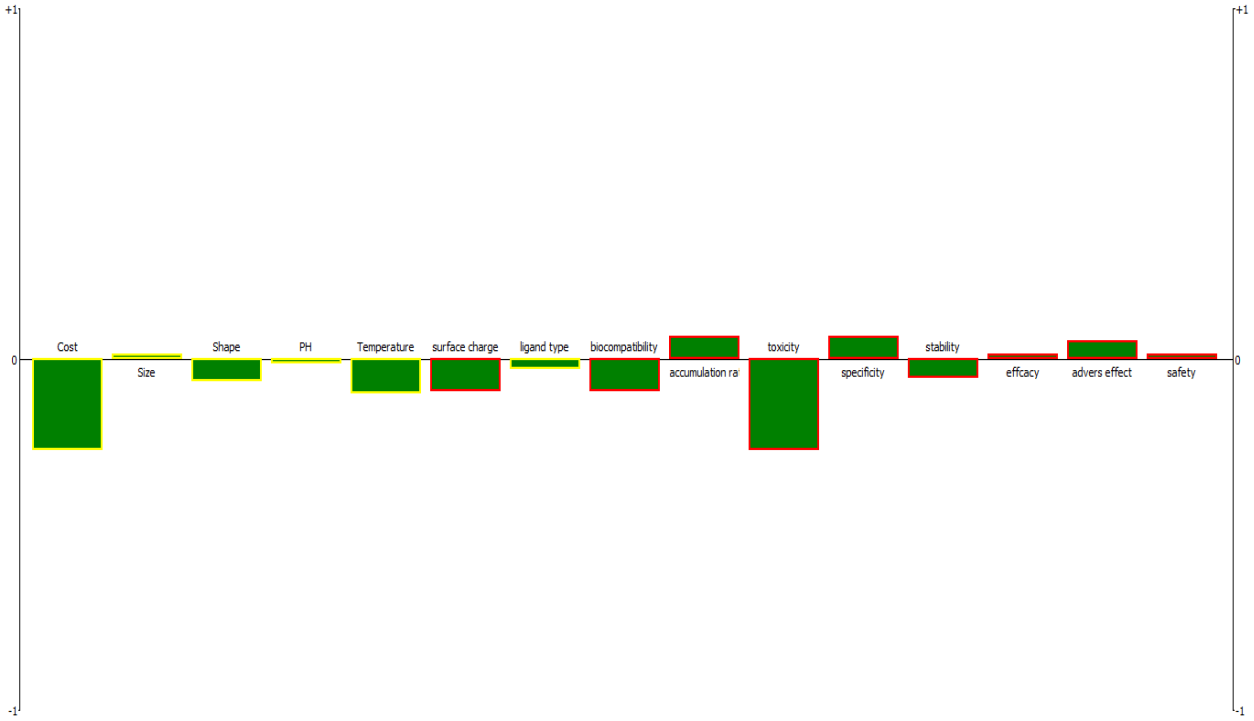


Figure 5.6: Action profile for liposomes NPs

From the evaluative result of the decorating criteria of liposomes NPs and it's respective behave as IDDs for anticancer drug, we can notice that the main problem is limited to high synthesizing cost with high systematic toxicity ratio followed by deficiency in shape factor, thermal sensitivity, surface charge and ligands functionalizing in addition to moderate pH sensitivity with very low effectiveness for size factor. All the results of the designing factors in combination, results in moderate liposome accumulation in the body, moderate targeting specificity, low adverse effect, very low therapeutic efficiency and patient safety.

CHAPTER 6
CONCLUSION AND FUTUR RECOMMENDATION

6.1.Conclusion

In this thesis, the aim of the researcher is to highlight and redirect attention to the suffering of cancer patients during the treatment period and the resulting adverse effects experienced by the patient after treatment and for lifespan. As a result of the weaknesses suffered by conventional therapeutic techniques to treat cancer which considered as relative fairly efficient for cancer treatment regardless its adverse effects, especially chemotherapy, which is the most common treatment for cancer until the present time. This thesis was able to facilitate the way to develop the technique of chemotherapy for cancer treatment by enhancing the therapeutic efficiency for anticancer drug delivery with high-precision targeting of cancer cells and thus ensure the safety of the patient during the treatment and thereafter; thereby raising the quality of life of the individual after receiving the optimal treatment that deal with the individual's condition. In addition to eliminating the chances of developing secondary cancer as a negative result of the adverse effects of traditional treatments, which is one of the most important points to ensure the safety of the individual in the long term after receiving treatment.

The results of this thesis have ensured the advantages mentioned by striving to bring these extremely important goals closer to reality by exploiting the noble advantages offered by nanomedicine and its unique technologies. The study reviewed the optimal nanoparticles that have been used in the area of nanodrug delivery system for cancer management and in line with recent studies, the most efficient nanoparticles were included in this study as alternatives customized choices for anticancer intelligent drug delivery system in contrast with determining the design criteria of anticancer IDDS which in it is turn subject to the factor of importance for each criterion.

Using the fuzzy PROMETHEE method, which is one of the most efficient comparative methods for multi-criteria decision-making MCDM model that deal with the most complex issues with overlapping data in their obstacles circumstance. The customized NPs were compared, evaluated and categorized successfully to determine the optimal option for the

design of a more intelligent anticancer drug delivery system for the purpose of achieving the noble objectives of the study hypothesis. In order to clarify vision and facilitate the prospects towards going with chemotherapy to new level to be more efficient, friendly and safer for the individual via the exploiting of the NPs brilliant qualities. This thesis resulted a remarkable occupation of AuNPs in the first place as the best choice of nanoparticles as an intelligent anticancer drug delivery system regarding to the analytical results of fuzzy PROMETHEE method of AuNPs noble behavior and optimal response to the system design criteria versus the behavioral results as an IDDS.

6.2.Future Recommendations

As a future measure to take advantage of the results of this thesis and take them to farther horizon and closer to the reality applied, the researcher's recommendation can be adopted by the following steps:

First, Use other reliable software and comparative methods for further comparison and evaluation to compare results obtained from different applications and thus the possibility of obtaining more reliable results.

Second, as a next step to this study it is worth to go with these results for laboratory application and experimentation on vivo with the aim of testing them first and then start manufacturing them to be included as effective medical therapeutic as IDDS.

Third, from other point of view including the five types of nanoparticles included in this study, the design process of each type was evaluated separately for each design criterion. The effect of each criterion on the behavior of these NPs as smart drug delivery was analyzed and evaluated considering to the therapeutic efficacy and patient safety in the first place. This led to a clearer understanding of the effects of design standards on the behavior and response of nanoparticles and thus the possibility of easily detecting weaknesses in NPs response during the design process for each species. This has made it easier to detect and solve the designing problems as future measures for each type of nanoparticle.

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