E-ISSN: 2583-9667
Indexed Journal
Peer Reviewed Journal
https://multiresearchjournal.theviews.in

Received: 05-05-2023
Accepted: 13-06-2023

INTERNATIONAL JOURNAL OF ADVANCE RESEARCH IN MULTIDISCIPLINARY

Volume 1; Issue 1; 2023; Page No. 858-863

Development of nanocarriers for targeted drug delivery in cancer treatment

[1]Jeetendra Kumar Prajapati and [2]Aman Shukla

[1]Lecturer, Department of Pharmacy, Mahakaushal University, Jabalpur, Madhya Pradesh, India
[2]Assistant Professor, Department of Pharmacy, Mahakaushal University, Jabalpur, Madhya Pradesh, India

DOI: https://doi.org/10.5281/zenodo.14614125

Corresponding Author: Jeetendra Kumar Prajapati

Abstract

One way to enhance the pharmacological characteristics of frequently used chemicals in cancer detection and therapy is to employ nanocarriers as drug delivery vehicles for therapeutic or imaging agents. Nanocarriers have emerged as promising options for targeted drug delivery research due to developments in surface engineering of nanoparticles to accept targeting ligands. Nanocarriers are now utilized to treat and/or diagnose several kinds of malignancies, however they are not targeted. Several nanocarriers have been authorized for clinical usage. In addition, other formulations are now being tested in different phases of clinical studies. The benefits of using nanocarriers in cancer treatment were covered in this review, which also looked at a few authorized formulations.

Keywords: Nanomedicine, Liposomes, Nanoparticles, Neoplasms/drug therapy, Drug delivery systems

Introduction

Cancer is a disease characterised by the uncontrolled growth of cells. Tissues with a precancerous lesion undergo a multi-stage process that culminates in the development of a malignant tumour from normally functioning cells. The main factor that determines whether a person may acquire cancer is their genetic composition. Most cancers are caused by exposure to one of three types of carcinogens: physical (like UV and ionising radiation), chemical (like asbestos, tobacco smoke, aflatoxin, arsenic), or biological (like certain deadly viruses, bacteria, or parasites). Worldwide, cancer ranks high among the top killers. Nearly 10 million people lost their lives to cancer in 2020, while 19.3 million people were diagnosed with the disease that year. The worldwide cancer burden is projected to rise by 47%, reaching 28.4 million cases in 2040, according to GLOBOCAN 2020. In 2018, the estimated total cost of cancer care in the US was $150.8 billion. As more innovative and often costly therapies become the norm, costs are likewise projected to rise. Countries with low or medium incomes account for almost 70% of cancer fatalities.

The biology of tumours is complex, ever-changing, and diverse. It evolves with time, posing new difficulties for treatment. To successfully design cancer therapies, one must have an in-depth knowledge of tumour microenvironment and the biology of tumour growth. Surgical resection, chemotherapy, and radiation therapy are effective standard treatments when administered early on. The standard treatment regimen, however, is often ineffectual in later phases. Chemotherapy fails because the cytotoxic agent does not distribute selectively or as desired throughout the body, and because it is not easily transported to the tumour site, necessitating bigger dosages. Anticancer medications may selectively kill cancer cells without causing dose-dependent systemic toxicity if the drug delivery devices are spatially placed correctly relative to the tumour cells and the drug is released by a tumour cell specific trigger mechanism.

Proteins called "TAA" are found on the surface of cancer cells. They separate normal cells from malignant cells. Overexpression of cell surface receptors for many peptides, hormones, and vital nutrients such as folic acid and iron is another hallmark of cancer cells. Some cancer cells have an overexpression of the folate receptor (35–40 kDa). Three distinct isoforms, FR-α, FR-β, and FR-γ, are accessible. In normal tissues, the expression levels of FR-α and FR-β are very low and negligible, respectively. Hematoietic cells are

the only ones that express FR-γ. However, tumours have a substantial overexpression of FR-α and FR-β. Through glycosylphosphatidylinositol (GPI) anchors, they acquire cellular membrane attachment.

Literature Review

Kumari, Preeti *et al*. (2015) [1]. A lot of people have been looking into nanoparticles as a way to deliver drugs recently, particularly for cancer therapy. The pharmacokinetics of the loaded hydrophobic pharmaceuticals were improved by solubilising them in the hydrophobic compartments of the nanoparticles. Nanoparticles also enabled cancer specific medication delivery by active targeting techniques and intrinsic passive targeting phenomena. Therefore, as compared to traditional treatment methods, nanoparticle-drug compositions have the potential to enhance therapeutic effectiveness by increasing the delivered medications' bioavailability, pharmacokinetic characteristics, and safety. With an emphasis on different chemotherapeutic drug delivery methods for cancer therapy, this study aims to provide an overview of different nanoparticle formulations in research and clinical applications. Various nanoparticles, such as liposomes, dendrimers, magnetic, polymeric, and inorganic nanoparticles, are described in depth for the purpose of targeted medication administration in cancer.

Irfan, Fariha *et al*. (2019) [2]. The novel characteristics of nanoparticles have piqued a lot of interest in their potential use as cancer treatments. There are a variety of methods in which nanoparticles with certain characteristics might transport drugs. Although conventional chemotherapy has its place in cancer treatment, nanotechnology has several potential uses in the field. Nanoparticles (NPs) provide a safe and efficient method of medication administration; yet, toxicity is a major concern that might restrict their application. There are a number of variables that may affect the characteristics of nanodrug carriers. The benefits and applications of nanoparticles as a medication delivery method in cancer treatment are the primary topics of this study.

The effectiveness of cancer treatment may be severely hindered by the adverse effects of radiation and chemotherapy. This abstract delves at the possibility of nanoparticle-based tailored delivery systems transforming cancer treatment. Creating nanoparticles with cancer cell recognition and adhesion capabilities has the following consequences, which we address: Improved Medication Delivery: By delivering potent therapeutic payloads directly to tumours, nanoparticles may improve treatment results while decreasing systemic toxicity. Enhanced Localisation: By modifying the surface of cancer cells, nanoparticles may more precisely target markers while causing little harm to healthy organs. Overcoming Resistance: Conventional cancer therapies face a significant obstacle in the form of multi-drug resistance; nevertheless, medicines based on nanoparticles show promise in this area. In the final portion of the study, the research being conducted to put this promising technology into practice is discussed, along with the problems that the sector is now facing.

Singhvi, Gautam *et al*. (2020) [3]. With an annual incidence of 11 million new cases, cancer is the greatest cause of mortality globally. The illness is defined by the uncontrolled proliferation of cells. A lot of research into cancer treatments has focused on medication delivery methods that use nanotechnology. Delivery systems known as nanocarriers are created by reducing the size and form of a substance to the nano-range, which may vary from 1 to 1000 nm. Natural polymeric inorganic magnetic silica-based materials are used to create nanocarriers. The diagnostic, therapeutic, and drug targeting potential of various inorganic nanoparticles, including as liposomes, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, magnetic nanoparticles, and others, have been explored in the context of cancer treatment. By modifying their surface features with particular ligands, nanocarriers may become cancer-specific medication delivery or diagnostic agents, or they can rely on their intrinsic passive targeting mechanism. With targeted nanoparticulate systems, the chemotherapeutic chemical may accumulate more effectively in tumour tissue while causing less harm to healthy cells. Nanocarriers prevent the medication from breaking down and prolong its release. By solubilising or penetrating lipophilic biological barriers, nanocarriers have also been successful in enhancing the pharmacokinetics of hydrophobic medicines that are weakly soluble.

Bhatia, Rohit *et al*. (2020) [4]. Cancer, which has no bounds and may strike any human organ, is among the most pressing health issues of the modern day. Traditional chemo treatments aren't tumor-specific, and they may harm other organ systems in addition to the immune system. Smart nanocarrier systems have come a long way in the last several decades, allowing for intracellular gene-specific targeting and the targeted delivery of medications to a wide range of tumour types. The therapeutic substance may be delivered in defined amounts by these nanocarriers, which can identify cancer cells with little or no injury to healthy cells. The effectiveness of nanosystems is enhanced by their altered physicochemical characteristics, increased bioavailability, and prolonged blood retention. Clinical studies are underway for a plethora of formulations based on nanocarriers. A variety of nanocarrier systems are available, including as polymeric micelles, dendrimers, carbon nanotubes, gold nanoparticles, and liposomes. Mesoporous silica nanoparticles (MSNs), quantum dots, and metal organic frameworks are some of the newer developments in nanocarrier systems. Several drug delivery methods based on nanocarriers and their uses in cancer care have been detailed in this study, with a focus on MSNs.

Recent advances in nanoparticle technology for cancer therapy

In this portion, we will look at the bigger picture of the IP landscape as it relates to the advancement of nanoparticle technology that targets cancer. This research also provides a trend in patent filings broken down by nation in the last few years, which may be used to assess the rate of technical development in a certain area.

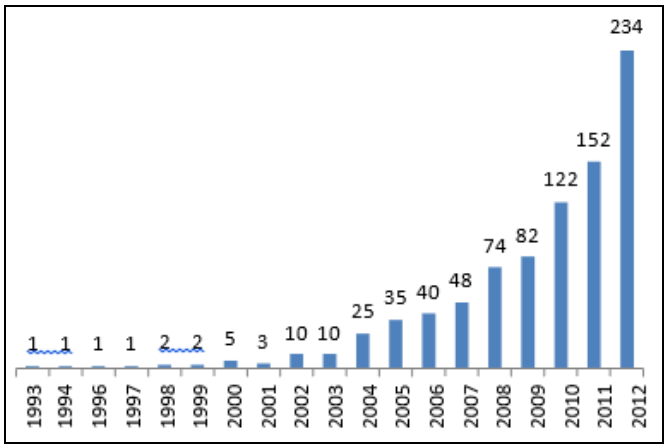

Fig 1: Trends in patent filings by year

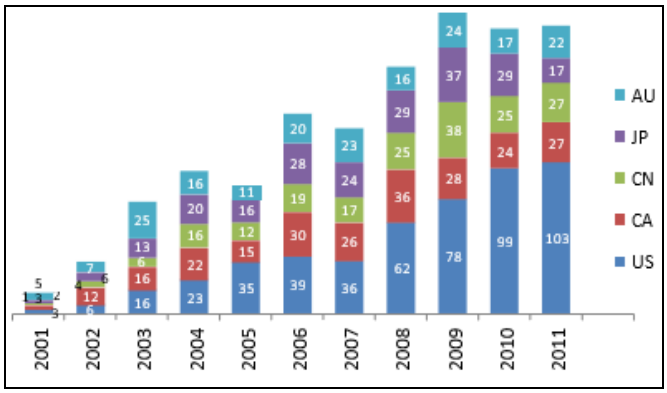

Fig 2: Distributed patents by country based on previous year's filings

Nanoparticle technology that targets cancer has been the subject of an increasing number of patent applications, as shown in Figure 1. The worldwide growth in research activity in this area, with the United States accounting for a disproportionately large number of patent filings, is shown by the rapid rise in the trend. In comparison to the 111% growth rate from 2005 to 2008, the cumulative % growth rate from 2009 to 2012 is over 185%. Based on recent patent filings, Figure 2 illustrates the distribution per nation. Japan, China, and Canada all exhibit mild increases in patent filings throughout the years, in contrast to the obviously exponential rise shown in the US. Also, the filing pattern in Australia has been very stable, even though it was a big participant in 2001.

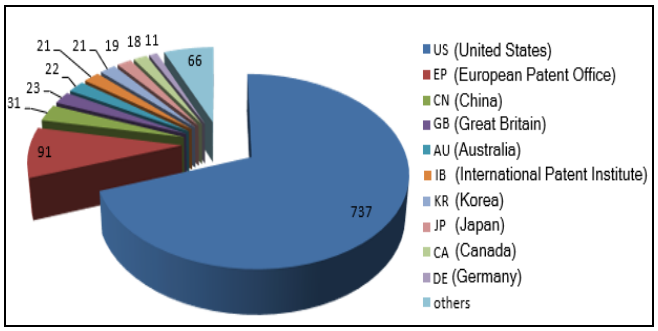

Fig 3: Distribution of priority countries

Figure 3 displays the results of a regional examination of priority patent application submissions. A visual representation of all nations with a high concentration of research activity is provided by the pie chart. Since the majority of our significant assignees, including prestigious colleges, are located in the United States, it is not surprising that this country accounts for almost three quarters of all priority patent applications. There are 91 priority patent applications filed by EP, putting them in second place.

A number of noteworthy technological developments include

Here you may find developments in connection to different types of nanoparticles and other technological fronts. Here, patterns indicate an increasing need for a certain nanoparticle type; what proportion of the market share does this kind of nanoparticle have compared to other technological leaders?.

Nanoparticles derived from polymers

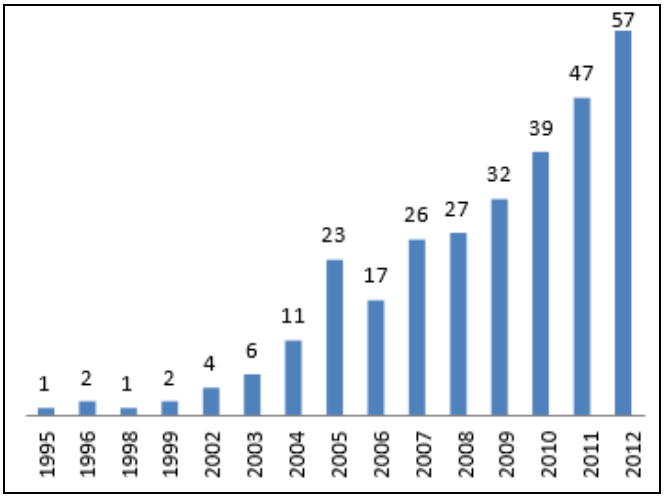

Fig 4: Patterns in the distribution of patents for nanoparticles made of polymers

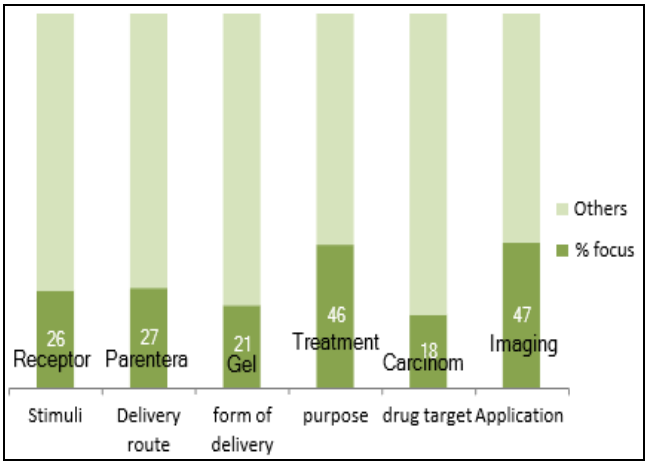

Fig 5: Ratio centering on different heads of technology

Figure 5 displays the most popular combinations of polymer-based nanoparticles with other technological heads, and Figure 4 demonstrates the exponential growth in the usage of these particles for targeted medicine delivery to malignant cells. For instance, the study reveals that gel, with its high absorption and gel strength, is the best delivery method for polymer-based nanoparticles.

Gold Nanoparticle

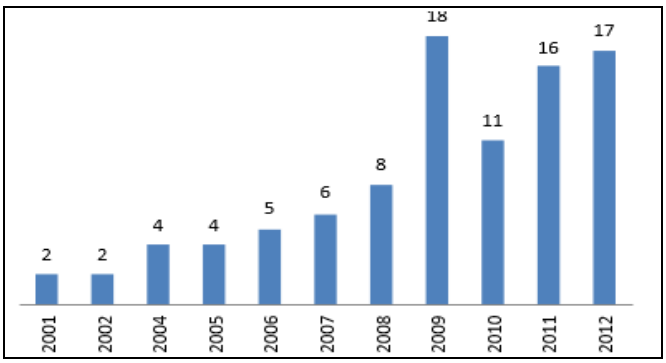

Fig 6: Pattern of patent distribution for a certain form of gold nanoparticle

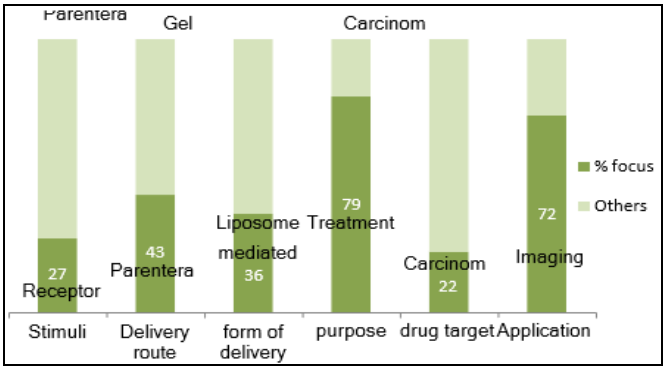

Fig 7: Ratio centering on different heads of technology

Figure 6 demonstrates that the use of gold nanoparticles for the transport of drugs to cancer cells has been growing at an exponential rate in recent years. Figure 7 displays the most popular pairings of gold nanoparticles with different types of technological heads. Liposome mediated administration of gold nanoparticles is favoured, according to the study, since liposomes are non-toxic, biocompatible, and boost stability via encapsulation. Many groundbreaking research on the use of gold nanoparticles in cancer therapy, published around 2009 by colleges like MIT and Stanford, etc., may explain the sharp uptick in patent applications that year (source).

Assignee analysis

Important assignees' locations

In Figure 8, we can see the top ten assignees working on cancer treatments that use nanoparticles for targeted medication delivery. For this study, we only look at one family member at a time. Universities such as MIT, UC Berkeley, and UT have a significant impact on the pharmaceutical industry, which includes behemoths like Abbott, Abraxis Bioscience (CELGENE Corp.), and Immuno light. Our research indicates that the United States is home to all of the main assignees. One of the companies that has done extensive study in this area is Abraxis Bioscience, a subsidiary of Celgene Corporation. They have revealed that they employ albumin-stabilized nanoparticles in their targeted drug delivery system. Prominent academic institutions own the vast majority of the technological patents.

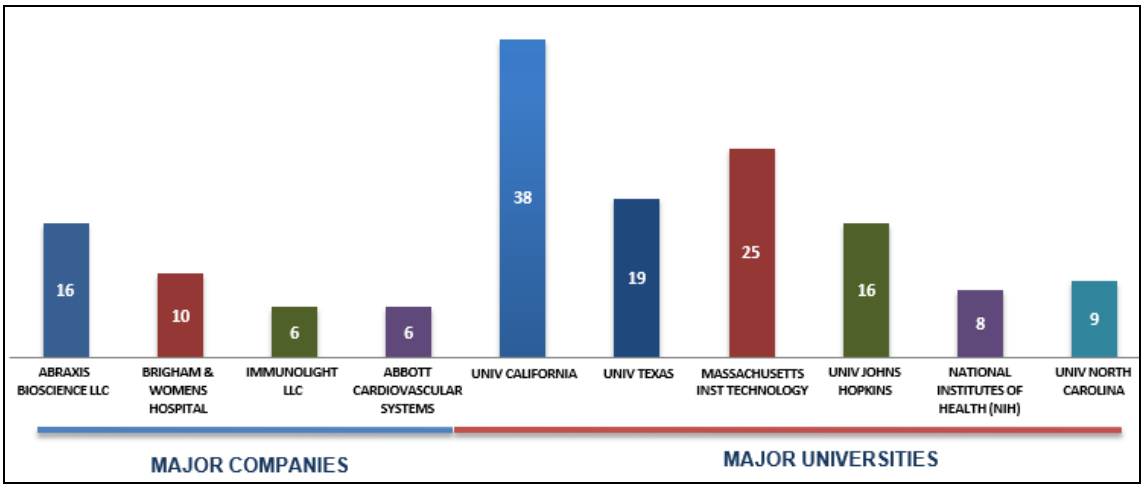

Fig 8: Various patents held by leading assignees in the area of cancer therapy using nanoparticles for targeted medication delivery systems.

Major Inventors

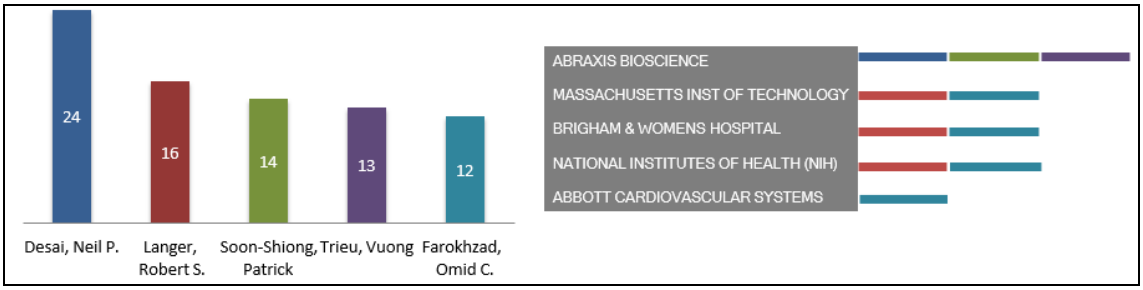

Fig 9: Comprehensive patent portfolio of leading innovators in the area of cancer therapy employing nanoparticles for targeted medication delivery

Figure 9 displays the top ten assignees in the area of cancer therapy via targeted medication delivery utilizing nanoparticles. For this study, we only look at one family member at a time. Major assignees in the field may be traced back to most of the inventors mentioned above. Three of the five main inventors have named Abraxis Biosciences as the designated assignee for their patent applications. Some of the top assignees from the patent portfolio of inventor Omid C. Farokhzad include Abbott Cardiovascular Systems, the National Institutes of Health, Massachusetts Institute of Technology (MIT), and Brigham and Women's Hospital.

Major assignees: Technology focus
Nanoparticle type

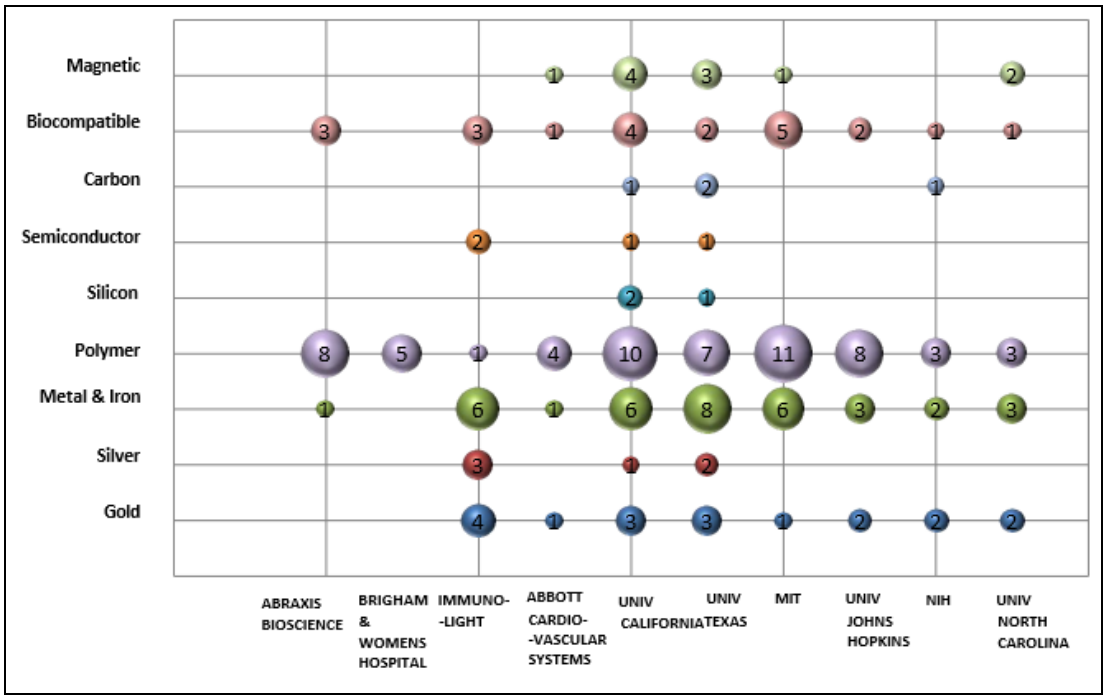

Fig 10: Assignment of patents according to nanoparticle type

In Figure 10, we can see how many patents an assignee has filed for innovations concerning different kinds of nanoparticles that may transport drugs specifically to cancer cells. The number shown above is inclusive of all possible forms of nanoparticles, as a single patent may disclose more than one. Additionally, it can be inferred that the majority of the main assignees use polymer-based nanoparticles as their primary vehicle for drug delivery. Nanoparticles derived from polymers are widely used by Abraxis Biosciences, for instance. Research on almost every kind of nanoparticle may be found at the University of California and the University of Texas. Nanoparticles made of biocompatible materials and gold have recently attracted a lot of attention. Nanoparticles made of carbon and semiconductors also exhibit a white space.

Route of Administration

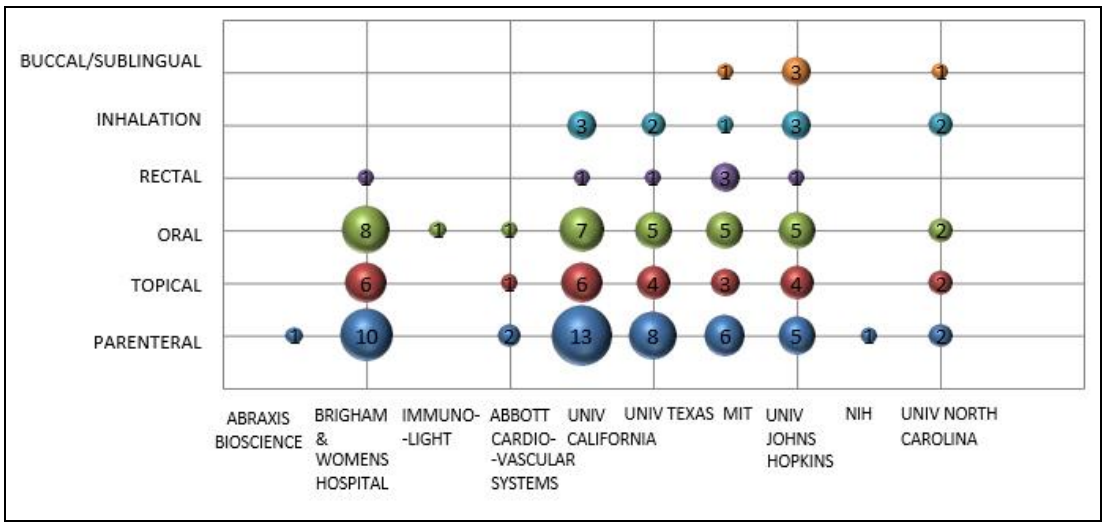

Fig 11: Distribution of patents to assignees based on administrative route

Figure 11 shows that an assignee has filed many patents in the technology pertaining to the different ways that drug-carrying nanoparticles may be administered. Since a single patent might disclose several administrative paths, the count shown above is inclusive of all possible outcomes. The parenteral medication delivery method is the primary emphasis of all the major assignees, as we may also infer. You can see from the image that Johns Hopkins University and MIT have studied every possible administrative approach. The topical and oral routes of medication delivery are also given considerable attention. For nanoparticles delivered as sprays or aerosols, for instance, inhalation is the method of choice for medication delivery since the route of administration is directly tied to the drug delivery form. Additionally, when drugs are administered via the rectal route, a white gap is seen.

Conclusion

Advances in nanoscale imaging and drug delivery systems point to the possibility of creating multifunctional "smart" nanoparticles, which might help bring about personalized and targeted cancer treatments. The potential of many nanoparticles for use in cancer imaging and diagnostics has been investigated. These nanoparticles include carbon nanotubes, dendrimers, polymeric micelles, nanocrystals, and polymeric nanoparticles. In the future, it is possible that multiplex nanoparticles will be able to detect cancer cells, image their location in the body (real-time *in vivo* imaging), selectively kill cancer cells while sparing healthy cells (active targeting and controlled drug release or photo thermal ablation), and track the treatment's progress in real-time.

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