

## **Publications Trend of Different Novel Drug Delivery Systems during 1980-2012: A Pilot Study Using Pubmed Search Tool**

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**Abstract:** *The main objectives of this project is to explore and record the trend or pattern of scientific research articles conducted on different novel drug delivery systems, over the last 32 years (1980-2012) and try to explain possible reasons that lead to such trend. Pub Med, has been used as a standard website to search for scientific articles, using different keywords related to the above mentioned topics. Published research articles on different novel drug delivery systems were recorded and analyzed to study their trends. Bar-charts showing the annual number of published articles, the total number of articles that has been published, as well as graphs showing the publications growth rates during (1980-2012), were constructed, to show the trend of such research. Analysis of the collected research articles, over the entire period of study, have indicated that research articles on novel drug delivery systems especially nanoparticles, liposomes, microspheres, and buckyballs have shown a clear escalating pattern in recent years.*

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### **I. Introduction**

Some most recently introduced novel drug delivery systems were chosen in this research, including: liposomes, dendrimers, nanoparticles, muco-adhesive drug delivery systems, buckyballs, hydrogels system, micelles & therapeutic radiopharmaceuticals.

Nanoparticles are small colloidal particles which are made of non-biodegradable and biodegradable polymers. Their diameter is generally around 200 nm. The two types of nanoparticles are nanospheres, which are matrix systems; and nanocapsules, which are reservoir systems composed of a polymer membrane surrounding an oily or aqueous core.

These systems were developed in the early 1970s. This approach was attractive because the methods of preparation of particles were simple and easy to scale-up. The particles formed were stable and easily freeze-dried. Due to these reasons, nanoparticles made of biodegradable polymers were developed for drug delivery. [1,2] while Liposomes they are phospholipid vesicles were first described decades ago by Bangham et al [3]. It has been shown that phospholipids spontaneously form closed structures when they are hydrated in aqueous solutions. Such vesicles, composed of one or more phospholipid bilayer membranes, can carry aqueous or lipid drugs, depending on the nature of those drugs. Because lipids are amphipathic (both hydrophobic and hydrophilic) in aqueous media. [4] Muco-adhesive delivery systems were present since the early 1980s, the concept of muco-adhesion has gained considerable interest in pharmaceutical technology. [5] The American Society of Testing and Materials has defined it as the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both. Muco-adhesive drug delivery systems prolong the residence time of the dosage form at the site of application or absorption. They facilitate an intimate contact of the dosage form with the underlying absorption surface and thus improve the therapeutic performance of the drug. In recent years, many such muco-adhesive drug delivery systems have been developed for oral, buccal, nasal, rectal and vaginal routes for both systemic and local effects. [6] Therapeutic Radiopharmaceuticals are radio labeled molecules designed to deliver therapeutic doses of ionizing radiation to specific diseased sites. Therapeutic application of radiopharmaceuticals have emerged from the concept that certain radionuclide possessing particulate emission such as alpha and beta radiation or low energy low range electrons possess the ability to destroy diseased tissues. Radioisotopes used internally or externally. [7] For Dendrimers they are highly branched macromolecules that can be subdivided into three architectural components: a central core branched cell, interior branch cells, and branch cells possessing surface groups.

The term dendrimers was coined in the early 1980s by Tomalia et al. [8] Dendrimers are synthesized through a stepwise repetitive reaction sequence, which gives rise to different generations of the same molecule and determines the size and surface functionality of the macro-molecule. The dendrimer microenvironment possesses some interesting properties.

Bucky ball is common for a molecule called buckminsterfullerene, which is made of 60 carbon atoms formed in shape of hollow ball discovered in 1985. Bucky balls and other fullerenes because of their chemistry and their unusual hollow cage like shape extremely stable and can withstand high temperatures, Applications of

bucky balls can rise from drug delivery vehicles for cancer therapy to ultra hard coating and military armor. Bucky balls are becoming powerful antioxidants and also inhibitor of HIV. [9]

Hydrogels are three-dimensional and hydrophilic polymer networks capable of swelling in water or biological fluids and retaining a large amount of fluids in the swollen state.[10] The water content in the equilibrium of swelling affects different properties of the hydrogels: permeability, mechanical properties, surface properties, and biocompatibility. The utility of hydrogels as biomaterials lies in the similarity of their physical properties with those of living tissues. This resemblance is based on their water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids.[11] lastly Micelles which they are aggregates of surfactant molecules dispersed in a liquid having size comparable to colloid dispersions, micelles considered one of the novel drug delivery systems which is important in the pharmaceutical field and is competing with other novel drug delivery systems like hydrogel, dendrimers and muco-adhesive drug delivery systems.

The polymeric micelles possess an excellent ability to solubilize poorly water-soluble drugs and increase their bioavailability. This was repeatedly demonstrated for a broad variety of drugs, mostly poorly soluble anti-cancer drugs, with micelles of different composition.

In addition, micelles, due to their small size demonstrate a very efficient spontaneous accumulation via the enhanced permeability and retention effect in pathological areas with compromised vasculature. [12]

## II. Methodology

### 2.1 Study Design

PubMed, that comprises over 22 million citations for biomedical literature from MEDLINE, life science journals, and online books, has been used as a standard website to search for scientific articles that has been published over the last 32 years (1980-2012). Using different key words, the search was classified and confined to five main topics which then subdivided to different groups.

### 2.2 key words used

Novel drug delivery systems	Key Word
Liposomes	liposomes drug delivery
Nanoparticles	nanoparticles
Dendrimers	dendrimers
Microspheres	microspheres
Mucoadhesive drugs	mucoadhesive drug delivery
Radiopharmaceuticals	therapeutic radiopharmaceutics
Hydrogel	hydrogel
Buckyballs	buckyballs
Micelles	micelles

### 2.3 Data Analysis

#### 2.3.1 Data extracting

According to the key words listed above, all relevant published articles during 1980-2012 were collected, classified and tabulated on annual bases. The total number of published articles, and publication growth rates were determined and tabulated.

#### 2.3.2 Graphical presentation

Bar-graphs of the annual number of published articles, the total number of published articles, and the peak year for the number of published articles were constructed. In addition graphs of the total number of published articles and publications growth rates were plotted.

#### 2.3.3 Publications growth rates

The publications growth rates for the routes of administration, modified release tablets and novel drug delivery systems were calculated according to the following formula:

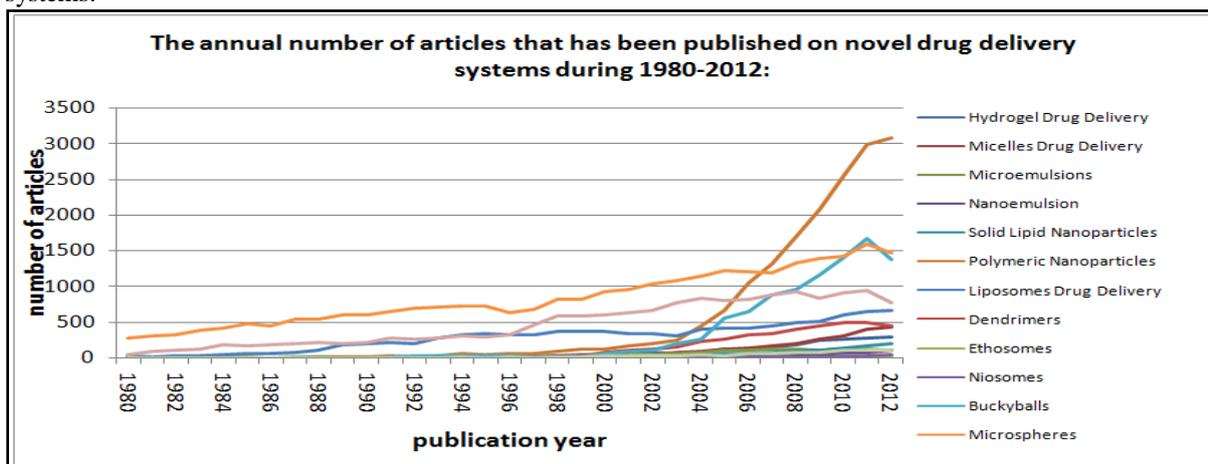
$$\frac{\text{End value}}{\text{Start value}} \times \frac{1}{\text{number of years}} - 1$$

All the years were divided into groups, each 4 years considered as a one group.

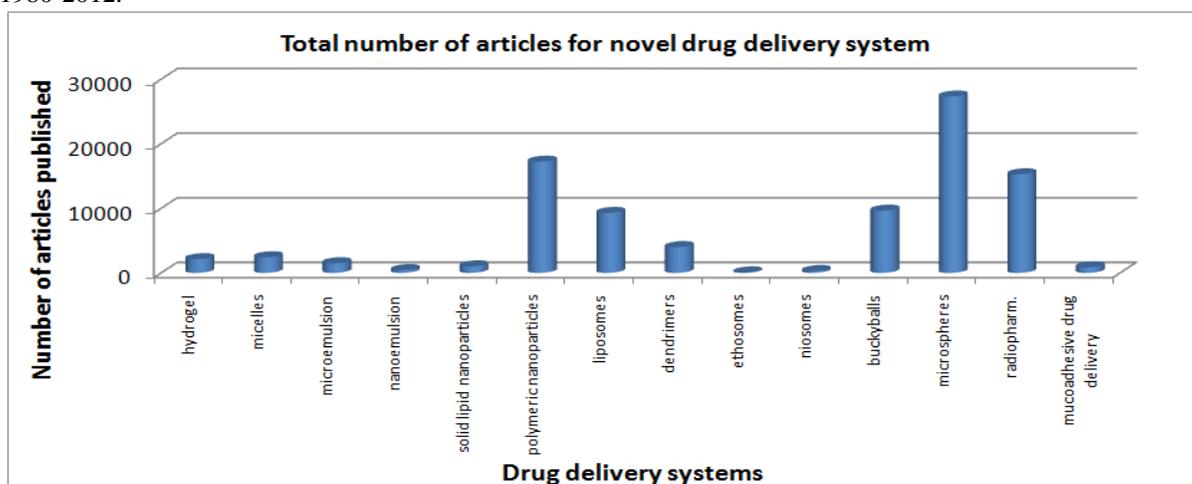
So if we consider the first group is 1980 -1984, the end value is 1984, the start value is 1980, number of years is 4. The publications growth rate obtained was presented in three dimensional graphs.[13]

### III. Results

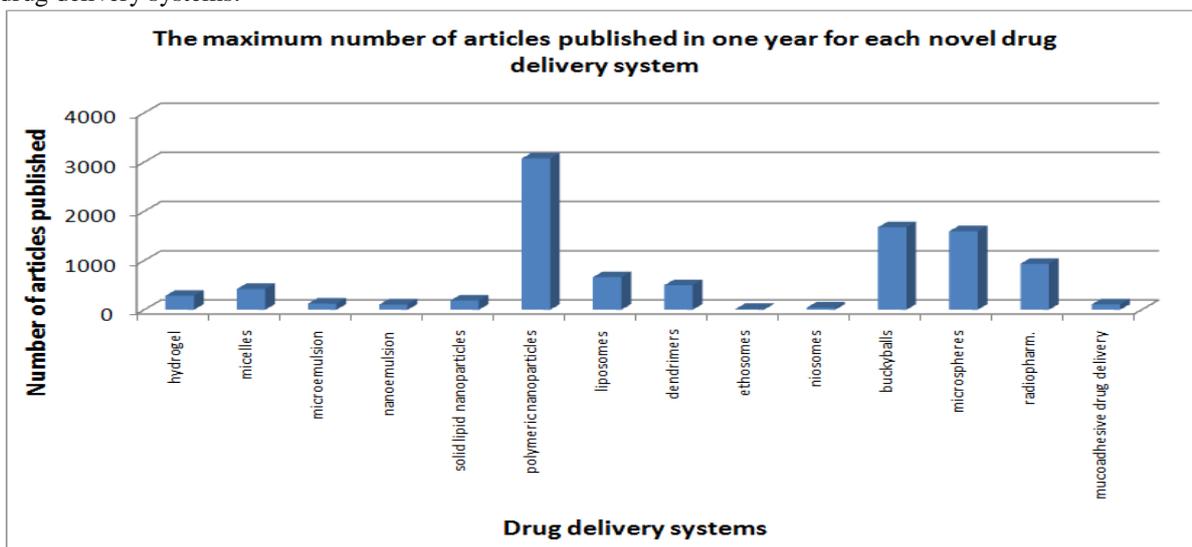
The annual and total number of articles that has been published on novel drug delivery systems during 1980-2012: The following graph shows the annual number of published articles for different novel drug delivery systems:



The following bar chart shows the total number of published articles for novel drug delivery systems during 1980-2012:

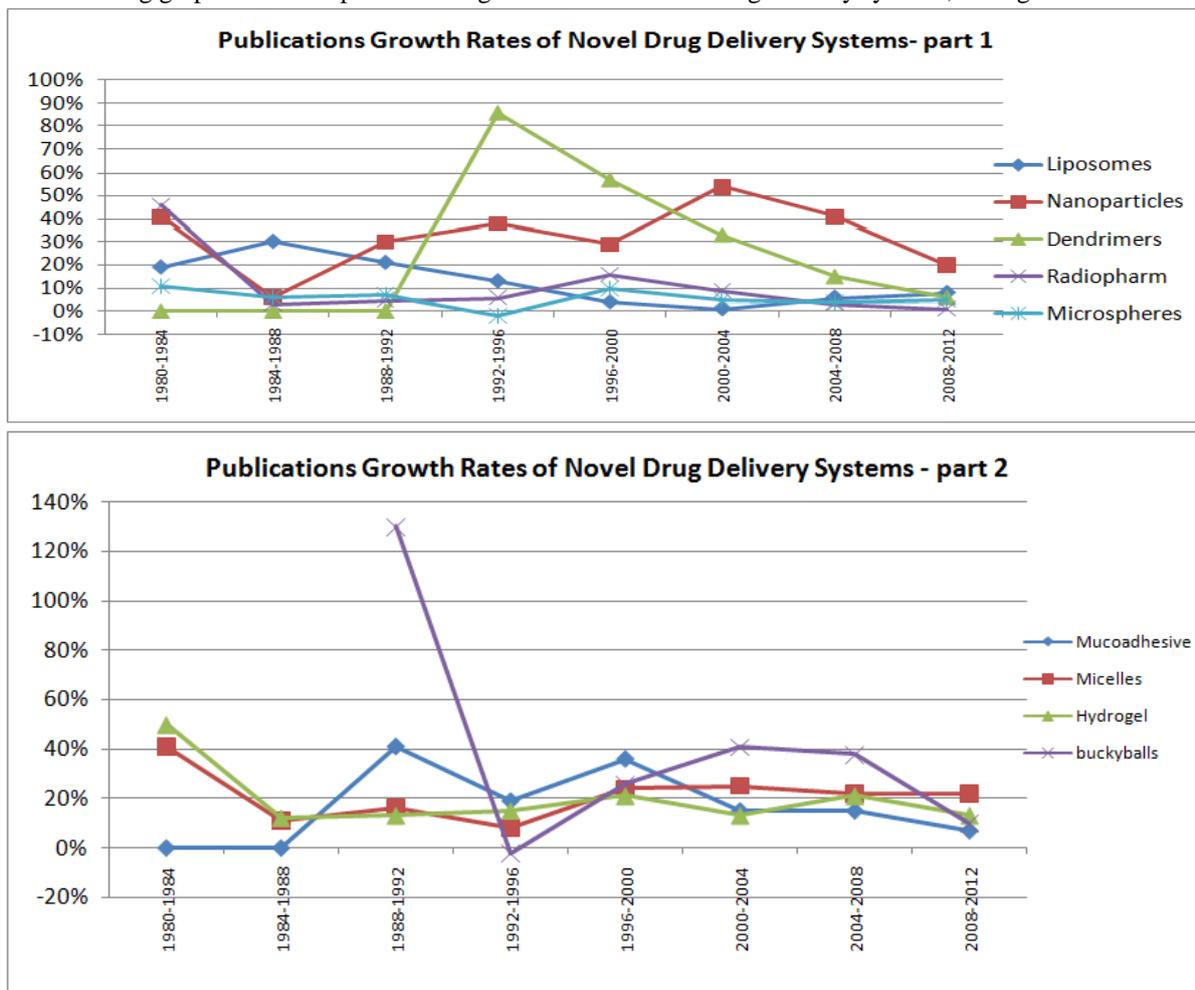


The following bar-chart shows the maximum number of articles that have been published in one year for novel drug delivery systems:



**Publications Growth rates of novel drug delivery systems, during 1980-2012:**

The following graph shows the publications growth rates of novel drug delivery systems, during 1980-2012:



**IV. Discussion**

**Liposomes**

Liposomes are a novel drug delivery system which consists of an aqueous core entrapped by one or more bilayers composed of natural or synthetic lipids. Liposomes composed of natural phospholipids are biologically inert and weakly immunogenic, and they possess low intrinsic toxicity. Further, drugs with different lipophilicities can be encapsulated into liposomes: strongly lipophilic drugs are entrapped almost completely in the lipid bilayer, strongly hydrophilic drugs are located exclusively in the aqueous compartment, and drugs with intermediate logP easily partition between the lipid and aqueous phases, both in the bilayer and in the aqueous core.[14] The annual published articles for liposomes, showed a progressively and regularly increasing publications pattern, during the entire period of study[figure 3.42]. The total number of publications, during the entire period of study, for liposomes was about 2000[figure 3.52]. The growth rate, on the other hand, showed a clear increase of more than 25% during 1980-1988, followed by a gradual decrease, where it reaches a minimum growth rate during 2000-2004& then started to gradually increase during 2004-2012,with a maximum publications number of 650 in 2012 [ figure 3.51&3.53]. The increase in the publication growth rate during 1980-1988 period reflected that researchers were interested in the newly invented technology, where liposomes although first known during 1960s, but where first experimented as drug delivery systems during 1980s. Liposomes have attracted researchers as they are considered as potential drug delivery systems, being superior carriers and have ability to encapsulate hydrophilic and lipophilic drugs and protect them from degradation also they are considered as biodegradable, biocompatible and with low toxicity [15].

**Nanoparticles**

Nanoparticles are one of the recent drug delivery systems, where they started to appear in literature in 1988. Its defined as ultra-small objects with dimensions measured in nanometres (nm). Nanoparticles typically have at least one dimension less than 100nm in size. The annual published articles for nanoparticles, showed a

progressively regularly increasing publications pattern, during 1988 till 2012, and a maximum publication number of 2500 in 2012 [figure 3.43 and 3.53]. The total number of publications, during 1988 till 2012, for nanoparticles, was about 13000 [figure 3.52]. The growth rate, on the other hand, showed a clear increase of about 40% during 1996-2000, followed by another similar increase during 2004-2008. [figure 3.54]. Such high publication growth rates, reflected researchers interest in such newly invented technology. Nanoparticles have received such attraction from researchers, as their methods of preparation are simple. In addition, they are stable and easily freeze-dried and are able to achieve with success tissue targeting of many drugs (antibiotics, cytostatics, peptides and proteins, nucleic acids, etc.). In addition, nanoparticles were able to protect drugs against chemical and enzymatic degradation and were also able to reduce side effects of some active drugs.[16]

### **Microspheres**

Microspheres have been covered as an oral modified release dosage form but another research has been done for the numbers of articles that has been published for microspheres in order to be compared with novel drug delivery systems as a novel drug delivery, the microspheres system is an attractive novel drug delivery system if its compared to the novel drug delivery systems as observed in the results [figure 3.51], it's the second novel drug delivery system from the total number of articles that has been published from 1980 – 2012 [figure 3.52] Microspheres nowadays is having different pharmaceutical applications such as ophthalmic, nasal, oral, buccal, per-oral, gastrointestinal, vaginal, transdermal, colonic drug delivery and for gene delivery also as a diagnostic tool.[17]

In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.[18]

### **Dendrimers**

Dendrimers are the most recent drug delivery systems, where they started to appear in literature Only in 1996. It can be defined as large, synthetically produced polymer in which the atoms are arranged in many branches and sub-branches radiating out from a central core.

The annual published articles for dendrimers, showed a progressively and regularly increasing publications pattern, during 1996 till 2011 with a slight decrease in 2012 and a maximum publication number of 500 in 2011 [figure 3.45 and figure 3.53]. The total number of publications, during the entire period of study, for dendrimers, was about 4000 [figure 3.52]. The growth rate, on the other hand, showed a sharp increase of more than 80% during 1996-2000, which is the maximum publication growth rate compared to other novel drug delivery systems [figure 3.54]. The high publication growth rate during 1996-2000 period, reflected researchers interesting such newly invented technology. Dendrimers have a high degree of molecular uniformity, specific nano-size and shape characteristics, such properties have led to their commercial use for gene therapy, immunodiagnostics and variety of other biological applications that offers researchers the possibility to work with a tool for well-defined scalable size [19].

### **Therapeutic Radiopharmaceuticals**

Therapeutic radiopharmaceuticals are radio labeled molecules designed to deliver therapeutic doses of ionizing radiation to specific diseased sites. Therapeutic application of radiopharmaceuticals have emerged from the concept that certain radionuclide possessing particulate emission such as alpha and beta radiation or low energy low range electrons possess the ability to destroy diseased tissues. Radioisotopes are used internally or externally. If the radio isotopes is used externally or implanted in sealed capsules in a tissues, the dose could be terminated by removal of sources, but if given internally as unsealed sources they cannot be recovered [20].

Therapeutic radiopharmaceuticals although conventional are considered very important and are still attracting researchers. The annual published articles for radiopharmaceuticals, showed a somewhat progressively increasing publications pattern, during the entire period of study, and a maximum publication number of 920 in 2011 [figure 3.46]. The total number of publications, during the entire period of study, for radiopharmaceuticals, was about 14500 [figure 3.52 and 3.53]. This figure locates radiopharmaceuticals at top rank of novel drug delivery systems ladder. The growth rate, on the other hand, showed a clear increase of about 46% during 1980-1984, followed by another 10% increase during 1996-2000 [figure 3.54]. The high total number of publications as well as the high publication growth rates, reflect researchers interest in radiopharmaceuticals. The high publication growth rate during 1996-2000 may be attributed to the introduction of new therapeutic radiopharmaceuticals for treating bone cancer, neuroendocrine cancer, metastatic abdominal cancers, leukemia and blood cancers, prostate cancer and other persistent cancers [21]. Such researchers trend is strengthened by the BIO-TECH Report #350 regarding the sales of therapeutic radiopharmaceuticals in USA, where the sales of therapeutic radiopharmaceuticals were \$244.9 million in 2012. In addition rapid growth is anticipated over the next 5-6 years. By 2020, therapeutic product sales might reach \$5.8 billion [21].

### **Micelles**

Micelles are aggregates of surfactant molecules dispersed in a liquid having size comparable to colloidal dispersions. Micelles as a drug delivery system has taken the researchers attention during the period 2006 – 2012 [ figure 3.47], that's why micelles considered one of the novel drug delivery systems which is important in the pharmaceutical field and is competing with other novel drug delivery systems like hydrogel, dendrimers and muco-adhesive drug delivery systems. [Figure 3.53].

The justification for this system can be that polymeric micelles possess an excellent ability to solubilize poorly water-soluble drugs and increase their bioavailability. This was repeatedly demonstrated for a broad variety of drugs, mostly poorly soluble anti-cancer drugs, with micelles of different composition.

In addition, micelles, due to their small size demonstrate a very efficient spontaneous accumulation via the enhanced permeability and retention effect in pathological areas with compromised vasculature. Micelle specific targeting to required areas can be also achieved by attaching specific targeting ligand molecules (such as target-specific antibodies, transferrin or folate) to the micelle surface.[12]

The annual published articles for micelles, showed a very scarce publications during 1980 till 1990, where the total number of publications was only 29. During 1991 till 2000 the publication number

Continued to be scarce. From 2001 till 2012, the annual published articles for micelles started to clearly escalate, until they reached a maximum of 422 in 2012.[Appendix 5 and figure 3.47].

The total number of publications, during the entire period of study, for micelles, was about 2430 [Appendix 5 & figure 3.52]. This figure locates micelles at a lower rank compared to other novel drug delivery system. The publications growth rate, on the other hand, showed a sharp increase of about 41% during 1980-1984, then started to decline during 1984-1996 & then increase to an average of 23% during 1996-2012 [Table-3 appendix 6 & figure 3.55]. The high publication growth rate during 1980-1984, reflected researchers interesting the newly invented technology during that period.

### **Buckyballs**

Buckyballs is a newly introduced term that can be defined as any molecule composed entirely of carbon, in the form of a hollow sphere, ellipsoid or tube. An important area of research in modern material nanoscience concerns carbon-based materials, among which fullerenes take one of the first places. by photo-irradiation we can excite Fullerene from ground state to  $1C_{60}$  and this is done by photo-irradiation, This property of fullerenes renders them potential photosensitizers for their use in photodynamic therapy (PDT). Many fullerene conjugates with different functional groups possessing biological affinity to nucleic acids or proteins, are being investigated for anticancer activity [22,23]. They found that, mono-cationic fullerene is highly effective photosensitizer for killing cancer cells by rapid induction of apoptosis after illumination. [24]. Buckyballs are considered to be the world's most efficient radical scavenger and are described as radical sponges. The major advantage of using fullerenes as medical antioxidant is their ability to localize within the cell to mitochondria and other cell compartment sites, where in diseased states, the production of free radicals takes place.[25] The annual published articles for bucky balls, showed a lack of publications during 1980 till 1990. During 1991 till 2000 the publication number continued to be scarce. From 2001 till 2012, the annual published articles for bucky balls started to clearly escalate, until they reached a maximum of 1676 in 2011. The total number of publications, during the entire period of study, for bucky balls, was about 9649 [Table VIII, Appendix 5 & figure 3.52]. This figure locates bucky balls in a fourth position, after nanoparticles, microspheres & radiopharmaceuticals. The publications growth rate, on the other hand, showed a sharp increase of about 130% during 1988-1992, then started to decline sharply during 1992-1996 to a very low value of only -2% & then increase to an average of 26% during 1996-2000 to reach a value of 41% during 2004-2008 & then decline to 10% during 2008-2012 [Table VIII, appendix 6 & figure 3.55]. The high total number of publications together with the high publication growth rate during 1988-1992, reflected researchers interest in the newly invented technology during that period.

### **Hydrogels**

Hydrogels are two- or multi-component systems consisting of three-dimensional network of hydrophilic polymer capable of swelling in water or biological fluids and retaining a large amount of fluids in the swollen state [26]. Hydrogels have been extensively studied as drug delivery devices due to their excellent capacity of absorbing water and their swelling and permeability characteristics that enable them to undergo structural changes in response to different physical, chemical, or biological stimuli for which they have been named "intelligent" or stimuli-responsive drug delivery systems. Hydrogels loaded with drugs can be administered via variety of routes such as the buccal, nasal, vaginal, oral and transdermal. [27] and [28]. The annual published articles for hydrogels, showed a lack of publications during 1980 till 1983. During 1983 till 2004 the publication number continued to rise slowly. From 2005 till 2012, the annual published articles for hydrogels started to clearly escalate, until they reached a maximum of 286 in 2012.[Table V, Appendix 5 and figure 3.49]. The total

number of publications, during the entire period of study, for hydrogels, was about 2151 [Table V, Appendix 5 & figure 3.52]. This figure locates hydrogels in a trailing position among other novel drug delivery systems. The publications growth rate, on the other hand, showed a sharp increase of about 50% during 1980-1984, followed by a sharp decline during 1984-1996 to a very low value of 13% & then increase to an average of 21% during 1996-2000 and then decline again to 13 % during 2000-2004 & then rise to 21% during 2004-2008 followed by a third decline of 13% during 2008-2012 [Table-3 appendix 6 & figure 3.55]. The relative high total number of publications together with the high publication growth rate during 1980-1984, reflected researchers interest in the newly invented technology during that period.

The utility of hydrogels as biomaterials lies in the similarity of their physical properties with those of living tissues. This resemblance is based on their water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids.[29]

In addition, they present mechanical properties which are suitable for a specific application, which along with their characteristics of being made up of bio-stable or biodegradable devices, it makes these elements very versatile and with very diverse applications.

Soft contact lenses are one of the most widely used applications of hydrogels and the applications of hydrogels as materials for tissue replacement is possible use for replacing articular cartilage stands out. The importance of this use is obvious if we consider the millions of people who suffer from degenerative joint diseases, which make it necessary to have effective treatments available to repair cartilage damaged by pathological processes or from injuries.[30]

### **Mucoadhesive Drug Delivery Systems**

Mucoadhesives are drug delivery systems that are composed of muco-adhesive polymers that adhere to the oral and gastrointestinal mucosal membranes, increase drug concentration gradient at the absorption site and therefore improve bioavailability and specificity of systemically delivered drugs[31]. Muco-adhesives are relatively recent drug delivery systems, where they started to appear in literature in 1984. The annual published articles for muco-adhesives, showed a somewhat progressively increasing publications pattern, during 1990 till 2012, and a maximum publication number of 49 in 2008 [figure 3.51]. The total number of publications, during 1984 till 2012, for muco-adhesives, was about 523 [figure 3.52]. The growth rate, showed a clear increase of about 55% during 1988-1992, followed by another 22% increase during 1996-2000. [figure 3.55]. Such high publication growth rates during these periods, reflect researchers interest in such somewhat recently invented technology. Muco-adhesives has received such attraction from researchers, because of their major advantages of increased residence time of the drug at the absorption site that leads to increase in the bioavailability of the drug. In addition the invention of novel muco-adhesive polymers such as lectins, bacterial adhesions and thiolated polymers have increase target specificity of such delivery systems [31].

## **V. Conclusion**

Analysis of the collected published articles, over the entire period of study (1980-2012), has shown that: Novel drug delivery systems are progressively attracting researchers and providing a continuously innovation area to satisfy the market needs and to overcome the limitations of the oldest systems.

Nanoparticles represent a promising and fast-growing field. This is principally due to their simple methods of preparation, in addition of being stable and able to achieve with great success tissue targeting of many drugs. In addition, nanoparticles were able to protect drugs against chemical and enzymatic degradation and were also able to reduce side effects of some active drugs.

Although recently introduced, bucky balls, is ranked third among other novel drug delivery systems, after microspheres & radiopharmaceuticals, because of the diversity of its uses.

Therapeutic radiopharmaceuticals, although considered conventional, but still receiving a lot of attraction from researchers. This is because of their specialized role in treating different types of tumors.

The relatively high total number of publications together with the high publication growth rate of hydrogels, during 1980-1984, reflected researchers interest in the newly invented technology during this period.

The annual published articles for micelles, showed a scarce publications during 1980 till 2000. From 2001 till 2012, the annual published articles for micelles started to clearly escalate, and they reached a maximum 2012. According to the total number of publications, during the entire period of study, micelles are located at a lower rank compared to other novel drug delivery system.

Dendrimers, being newly invented, received a paramount attraction from researchers and shall continue to show high publication growth rates in the future, compared to other novel drug delivery systems.

The high publication growth rates showed by muco-adhesives reflected that researchers are interested in such delivery system, as it has potential site specificity that leads to increase residence time of the drug at the absorption site and hence increase drug bioavailability.

The drug delivery technology landscape is rapidly evolving with new classes of pharmaceuticals and biologics fuelling this revolution. The innovation of new drug delivery systems through all the routes of administration is growing rapidly to satisfy the market need and to allow the pharmaceutical technology to move parallel with the technology revolution in all other aspects of life.

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