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NANOMATERIALS IN RELATION TO THEIR DRUG DELIVERY AND RELEASE MECHANISMS: A REVIEW EXEMPLIFIED WITH SOME HERBAL DRUGS

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ABSTRACT

Nanomaterials have large surface area to volume ratio, tuneable size parameters, more precisely functionalization and structural modification property makes them desirable for biological, chemical, environmental and many other applications. Different types of nanomaterials are presently delineate a beneficiary effect of drug loading and delivery, which enhance the importance of sustained release over direct intake of drug or medicine. Polymeric material and silica material are very abundant in earth in respective to other nanomaterials and widely used in food industry, cosmetics, pharmaceuticals and several other fields.

KEY WORDS: Nanomaterials, Nanocarrier, Mesoporous silica, Aloe vera, Allium sativum, Sustained Release, Antimicrobial property.

INTRODUCTION

Nanotechnology is a very systematic multidisciplinary area of science where the main business deals with some specific materials whose chemical and physical properties can be modulated at nanoscale level (1–100 nm) by applying engineering, chemical science and the ideas of development.[1]

Nanobiotechnology is the convergence topic of interest of engineering and molecular biology. To investigate biological and chemical analysis with better sensitivity and specificity and a higher rate of recognition, this multifunctional nanobiotechnology tools are very useful.[2] For the last few decades engineers have been working for the invention of efficient higher density electronic chips. These devices have reached the feature sizes as small as 20 nm using deep UV-lithography. On the other hand, molecular biologists are also functioning on the field of molecular as well as cellular dimensions for many years. The dimensions size ranges started from several nanometers (DNA molecules, viruses) to various micrometers (cells).[3]

NANOMATERIAL

Nanomaterials are defined as materials having particle size in less than 100 nm at least in one dimension. It has larger specific surface area means larger area to volume ratio. The surface area of any nanoparticle is inversely proportional to the diameter of the particles. Owing to their huge surface area nanomaterials can be used to hold drugs/ herbal values which can be released in a controlled manner to treat different diseases.

Additionally nanoparticles also can migrate within a physiological system in the human body and are capable of crossing heart, lung, gut, brain barrier. This may lead to unexpected and unusual results.

Different classes of nanomaterials that can hold drugs/ herbal values are –

1. Zero dimentional / cluster material
2. 1D nanomaterial
3. 2D nanomaterial
4. 3D nanomaterial

ZERO DIMENTIONAL NANOMATERIAL

Zero dimentional nanomaterials have less than 100 nm diameter denoted by nanoparticles, nanocluster or nanocrystal. All dimensions (x,y,z) are in nanoscale. This nanoparticles may be semicrystalline or amorphous or single 0D nanostructures crystal having dimentions larger than 10 nm. For amorphous material the term nanocluster will be appropriate showing narrow size distribution.

This nanoparticles contain following characteristics

a. Uniform size dispersion also called monosize
b. indistinguishable chemical property and crystal nature. Be metallic, ceramic or polymeric
c. Identical size and morphology
d. Having dispersion property (i.e.no agglomeration occurs)

Presently, different variety of physical and chemical methods has been developed to fabricate 0D NMSs with well-controlled dimensions.[4]

ONE DIMENTIONAL NANOMATERIALS

1D nanomaterials are the nanotubes, nanorods, nanofiber and nanowires. Two dimensions (x,y) of this nanomaterial are at nanoscale, other dimension (z) is micronscale or larger. One dimentional nanomaterial exhibit following features:

a. These materials may be crystalline or amorphous
b. Crystalline also in poly or single state
c. These materials can be as individual materials or embedded in within an additional medium.
d. Metallic, ceramic or polymeric in nature.[4]

TWO DIMENSIONAL NANOMATERIALS

In 2D nanomaterials, two dimentions are not confined to the nanometer range and one dimension is in nanoscale range. These nanomaterials are recently widely used in material research for their many low dimensional features. Besides this 2D nanomaterial with specific geometries reveal some size dependent exclusive characteristics and also used as building blocks for nanodevices. Two-dimensional nanomaterials include nanofilms, nanolayers, and nanocoatings. Following are the features of 2D nanomaterials:

a. These materials may be amorphous or crystalline
b. These 2D structures exploited as single or multilayered structure.
c. These nanoflims, layers, coatings all are integrated in any surrounding matrix.
d. May be metallic, ceramic or polymeric.

THREE DIMENTIONAL NANOMATERIALS:

The 3D materials are those where diameters do not confine in nanoscale range. All the three diameters are above the 100 nm range i.e., in macroscale called bulk nonmaterial. These 3D-nanomaterials are composed of nanocrystals arranged in numerous forms and in different

orientations. Due to the large surface area and much absorption capacity nanomaterials are getting importance in the research field and applications. 3D nanomareials with greater porosity is a unique combination to transport molecules or drugs. 3D nanomaterials include the structures like nanocones, nanoballs (dendritic structures), nanocoils, nanopillers and nanoflowers.[4]

0D

Cluster materials

These are zero dimentional, amorphous nanomaterials with large surface area. Amorphous silica synthesized by sol- gel route is a good example of cluster material. Silica gel is bioactive and completely biodegradable with no undesirable effects in the adjacent body tissue or any organ. They also have osteoconductive properties and can get attached with bones.[5] due to porous structure and large surface area they can hold drugs, proteins, peptides etc.[6,7]

Quantum dots

Metallic nanomaterial such as Quantum dots are 2-20 normally nanometer sized crystals[8] but some literature says that it should be firmly below 10 nm[9,10] The diameter of QDs depends on the material used. Usually QD means a whole system where the quantum captivity effect happens. The nature of QDs may be metallic (e.g. Cobalt, Nickel, Platinum, Gold etc)[11] or predominantly based on semiconductor materials. In addition some research says a metalloid QD can also be done such as silicon QD.[12] QDs have some extraordinarily attractive properties because of its quantum captivity nature. In application field especially in biological system solubilisation of QDs is important. With the help of hydrophobic inorganic solvents, water insoluble QDs can be made easily but solubilisation in water requires surface modification.[13]

According to many research cytotoxicity of QDs in in-vitro as well as in vivo studies is a major viable issue for its application. It affects the cell growth by damaging DNA and disturbs normal cell activity by short term (acute) and long term toxicity.[13-17] The level of cytotoxicity depends on several parameters. It includes size of the QDs, dosage of QDs, coating bioactivity, capping materials, surface chemistry alteration and processing parameters.[18-20]

1D

Nanotube or nanowire

Carbon nanotubes (CNT) are the example of 1D nanomaterial. The attractive properties of CNTs which make them a good drug carrier, high aspect ratio, high stability and length in the micron size with high mechanical strength and some extraordinary surface properties like selectivity[21,22]

CNTs are of two types[23]

- SWNTs- Single walled carbon nanotubes made up of single sheet of graphene.
- MWNTs- Multiple walled carbon nanotubes made up several tubes in concentric cylinders of single walled carbon nanotube.

Most attracting thing is the presence of benzene ring which makes it easier for loading drugs that already contain benzene ring in their molecules eg; epirubicin (EPI), doxorubicin (DOX) etc.[24]

2D

Comparing with other nanomaterials the ultrathin 2D nanomaterials particularly single layer nanosheets enables undeniable electronic properties.[25] Atomic thickness of 2D materials exploit features like Mechanical litheness and optical transparency. These features allow them to fabricate highly flexible and transparent electronic devices. Ultrathin thickness and large cross section provide them high specific surface area which help them easily in surface active applications.[25-27] 2D nanosheet, nanolayerd structure have high specific surface area so, they contribute to build functional composites as building blocks.[28-32]

3D

Organic nanomaterial like dendrimers are well branched, nanoscale sized, spherical polymeric macromolecules with many arms emanating from a inner core.[33,34] The central void space is mainly useful for encapsulation of metals, tiny drug molecules or imaging moieties. Besides this the void space also facilitates controlled release of drug molecules. In current decades dendrimers have exposed as very promising carriers in gene delivery to magnetic resonance imaging for development of vaccines, antibacterials, antivirals and anticancer therapeutics.[35-38]

Several polymers are successfully used for sustained and controlled drug delivery at specific target sites which therefore enhance the healing effect plus reduce the side effects.[39]

Different outer surface modified polymeric nanoparticles and block copolymers can augment the interface significantly among the nanoparticles and the biological atmosphere as a result more cellular uptake, more advantageous bio distribution level and a longer half life occurs.[40]

In general, the detrimental effects of nanoparticles come from various aspects. Usually the combination of surface property like high surface area and intrinsic toxicity of the surface may be reason of harmfulness.[41] Nanoparticles below 100 nm diameter potentially be more deadly for lung tissue (gateway of entry), on the contrary with conventional particles of big size. The nanoparticles can relocate from their deposition site and also change their protein structure which helps them to run away from normal phagocytic cell defences. As a result, an inflammatory and immunological response is triggered by these nanoparticles as well as normal tissue activity may be affected.[42]

NANOCONJUGATE

Here, Tang et al (2015) report a scalable process of fabricating drug-silica conjugated nanoparticles, termed drug-silica nanoconjugates (drug-NCs), which hold monodisperse size distributions and the most advantageous particle sizes are expected as small as 20 nm. It is found that 20-nm NCs are superior to their 50-nm and 200-nm NC analogues by 2–5 and 10–20 folds, respectively, with regard to tumor accumulation and penetration, and cellular internalization.[43]

TYPES OF DRUGS

Drug is a chemical compound, synthetic or natural (usually excluding any nutrients, water, or oxygen), that - by its chemical nature – it can alter bio molecule's structure or working when administered in the body and absorbed.

In daily life people are accustomed to different types of drugs to heal different diseases or physical problems.

Drugs may be categorized into 3 groups:

1. Allopathic drug
2. Homeopathic drug

3. Herbal drug.

USE OF ALLOPATHIC DRUG

Allopathic drugs are not always used in conventional way. There are varieties of drugs which are medicated in sustained release dosage form and results are in a positive range.

Like **Theophyllines** is a sustained release drug for Asthma.
Procardia XL is a sustained release for High blood pressure.

Floxuridine, Mitomycin, Cis-platin are all sustained release for cancer treatment.

Allopathic drug is preferred during surgery for its advantageous effect to eliminate damaged portions from the body. Allopathic drugs are prescribed due to its instant relief action that is why it is used widely in our medicinal world. In accidental cases this medicines are very useful to keep the body in perfect condition.[44]

USE OF HOMEOPATHIC DRUG

Easiness of administration of drug.
One of the main advantage is the high acceptability among children.
Extensively used for its much less side effects.

HERBAL DRUG

Herbs are medicinal plants which have therapeutic agents (also called phytomedicinals) that can be used for controlling different diseases. These herbs can be administered as the whole plant or plant parts or as plant extraction in solvents.[45]

IMPORTANCE OF HERBAL MEDICINES

Medicinal plants metabolites and other natural materials may keep away from the side effects of synthetic drugs, because they actually accumulate within the living cells, seems like our own system.[45,46]

In addition Ayurvedic medicine aims to integrate and balance the body and mind. This balance is believed to lead to happiness and health, and to help prevent illness.

HERBAL VALUE

India is the leading country where production of medicinal plants is in huge quantity. That is why it named as the "Botanical garden of the World".[47] The medicinal plants have high natural therapeutic values against a variety of diseases. And it also supplies raw materials and high quality food for livelihood. Significant amount of works have already been done on these plants for treatment of different diseases like cancer and many plant products have also been marketed as anticancer drugs, depending on their traditional uses and scientific reports (i.e., They are termed as medicinal plants).[47] Because of this reason in both developing and developed countries demand of medical plant is increasing day by day in human welfare.[48]

It is to be expected that dietary constituents, such as garlic, ginger, soya, curcumin, onion, tomatoes, cruciferous vegetables, chillies and green tea, play an important role in protection from cancers. These nutritional agents are thought to suppress the transformative, hyperproliferative and inflammatory processes that initiate carcinogenesis. These nutritional constituents have been classified as chemopreventive agents, and it has been studied broadly about their ability to delay the onset of carcinogenesis. As the source of this chemopreventive are from natural sources, they are considered pharmacologically not hazardous.[49]

In recent times the whole world is interested towards the herbal medicine or phytomedicines because of its repairing and strengthening ability for physical systems (especially the immune system, which can then properly fight foreign invaders). Herbal medicine also aid to demolish offending pathogens without lethal side effects.[50] As per World Health Organization (WHO) almost 80% of world population are now applying medicinal plants to cure human disease.[51]

NANOPHYTOCHEMICALS

Nanophytochemicals are simply the preparation of active phytoconstituents which is the heart of the herbal drugs or standardized extracts using different solvents. Utilization of nanophytomedicine improves the usefulness and bioavailability of administered drugs. They also reduce the side effects and toxicity of administered drugs.

The combination of nanotechnology with traditional herbal medicine occur as a very constructive device in designing future i.e., herbal medicine with enhanced bioavailability profile and less toxicity.[52]

Aloe vera

The external layers contain a variety of pharmacologically active components include anthraquinones, chromones, poly-saccharides, and enzymes. Among them the anthraquinones and chromones are responsible for the anti-cancer activity, anti- inflammatory, and evacuating.[53] It has also been reported that some elements are also present like Al, B, Ba, Ca, Fe, Mg, Na, P, Si etc. in *Aloe vera* gel.[53-55]

Next the outer protective layer of the leaves consist of derivatives of hydroxyanthracene, anthraquinone and glycosides aloin A and B from 15% - 40% is reported by different investigations.[56-58] The other active principles of *Aloe* include hydroxyanthrone, aloe-emodin-anthrone 10-C-glucoside and chrones.

It has been already reported that middle layer of leaf consist of a yellow latex which contain anthraquinones and glycosides. The parenchymatous fleshy tissue contain proteins, lipids, amino acids, vitamins, enzymes, inorganic compounds and small organic compounds in addition to the different carbohydrates. There is some evidence of chemotaxonomic variation in the polysaccharide composition[59] 16-different polysaccharides and 12 major polypeptides (mol wt 15 - 77 kD), and various glycoproteins (29 kD in leaf gel).[60,61]

The innermost parenchymal layer of leaf gel contains almost 99% water, with glucomannans, lipids, sterols, amino acids and vitamins.[61,62] The other potentially active ingredients include vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids, and amino acids.[63-66] It also has several group of monosaccharide's and polysaccharides; numerous inorganic ingredients, vitamins B1, B2, B6, and C; niacinamide and choline, enzymes (acid and alkaline phosphatase, amylase, lactate dehydrogenase, lipase) and organic compounds (aloin, barbaloin, and emodin) as described by Hayes et al.[67] The most important functionally active component of *Aloe vera* is a long chain of acetylated mannose.[55,68,69]

Aloe vera juice help our body to heal itself from cancer and also from the damage tissues caused by chemotherapy and also radiotherapy because these destroys healthy immune cells which are essential for the recovery. *Aloe vera* emodin, an anthraquinone, has the capability to suppress or inhibit the expansion of malignant cancer cells making it to have antineoplastic properties.[70] Using a rat model, it can be suggested that the antimicrobial specially antibacterial effect of the *Aloe vera* gel *in vivo* could enhance the wound healing property by eliminating the bacteria that cause inflammation.[71]

Powdered *Aloe vera* gel is used to prevent progressive dermal ischemia results of any type injuries like burns, frostbite, electrical injury and intra arterial drug abuse. *In vivo* analysis of these injuries demonstrates that this gel acts as an inhibitor of thromboxane A2, a moderator of progressive tissue damage.[65]

GARLIC (Allium sativum)

Early investigation about garlic reported that \vegetable tissue of Allium sp are usually odour free and volatile odour principles in garlic oils were only generated during tissue damage and preparation that means the source of these volatile component was some non-volatile precursor compound. The first stable component of Allium is allin [(+)-*S*-allyl-L-cysteine sulfoxide (ACSO)] identified by Stroll et al 1948.[72] Allin is the key sulfur compound which is responsible for the majority of the odorous volatile compounds produced from any cut or crushed of garlic.[73] The sulfur compounds are responsible for not only garlic's pungent odor but also for its medicinal effects. The odor is formed from volatile compounds (allicin) by the action of the enzyme allinase on non-volatile compound (allin). The enzyme is heat sensitive, which is responsible for the drastic fall in odour intensity found in cooked garlic with similar physiological effects.[74]

Garlic has curative properties because of these organosulfur compounds, which are responsible for the typical odor and flavour of garlic.[75] The antibacterial activity of garlic is mainly attributed to thiosulfinates (e.g.,allicin).[75] Allicin mainly interrupts RNA synthesis and lipid production in bacterial system. If RNA production is not carry out properly or in less amount then protein synthesis will be severely affected. If proteins cannot be produced then growth and development of the organism will not occur as they are essential for all parts of cell structure. Besides this, synthesis of other biomolecules also partially inhibited e.g., DNA and protein, though RNA is the main target of allicin action.[76]

Early studies reported that garlic extraction has shown the effectiveness especially slows down growth and development of both Gram positive and Gram negative bacteria, acid fast bacteria such as *Klabsiella*, *Staphylococcus*, *E. coli*, *Micrococcus*, *Pseudomonas*, *Salmonella*, *Enterobacter* and *Helicobacter pylori*.[77,78]

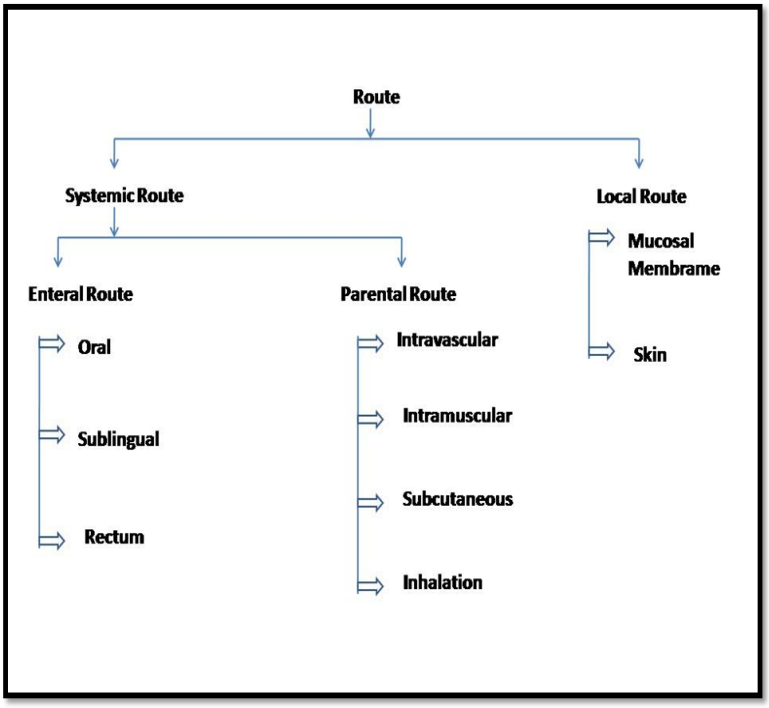
This antibacterial property is mainly due to the structural organization of organisms so, they are vulnerable to garlic constituents[79], particularly *Staphylococcus aureus*, contains only 2% lipid in their membrane[80] so that the permeability of allicin and other garlic components may

be effected by lipid content of the membranes. Therefore these phenomenons may support the cell wall destruction and damage of genetic materials of *Staphylococcus aureus* strongly.[82] Another example is about the inhibition property of garlic which showed that *E. coli* was inhibited more than 10 times greater than that seen in *Lactobacillus casei* for the same garlic dose.[84] This also may be the differing compositions of bacterial cell membranes and their permeability to allicin.[83]

Allicin itself is very unstable and decomposes rapidly [84] (Brodnitz et al. 1971). Also, upon reduction of allicin to diallyl disulfide, the antibacterial activity is greatly reduced.[85]

TYPES OF ADMINISTRATION ROUTES FOR DRUG

Route of administration is the way of drug delivery into the body to treat various diseases or disorders. Among different routes, selection of administration pathway is depend upon the drug and patient related factors like condition of the patient (unconscious, vomiting, diarrhoea), age of the patient, emergency /routine use or sometimes Patient's/doctor's choice. The various route of administration is given as follows-



In conventional release system the drug /medicine is administered in the above mentioned pathways where the drug is released at once in the human body most of the time these are not targeted also.

Oral route

The oral drugs are swelled after placing in mouth. Some advantages of oral route are mainly painless, cheap and can be self administered. Absorption of drug takes place along the whole length of the gastro intestinal tract.

The disadvantages are primarily the first pass effect means initially drugs absorbed in mouth then transported to liver passing through portal vain. Sometimes irritation to gastric mucosa results nausea and vomiting. In some cases only a part of the drug is absorbed and the acidic ph of gastrointestinal tract along with gastric juice cause the destruction of the drug.

Intravascular Route

In intravascular route system the absorption process is bypassed. Here the drug is injected directly into the blood.

Advantages of this route is quite pain free and show quick action. This system is very beneficial for specific, precise and almost immediate onset of any emergency condition. Besides this by this way unconscious patients will be treated.

Some disadvantages are having pain at the site of injection, greater risk of undesirable effects. There is a risk of embolism because of high concentration of drug attained quickly.[86]

TYPES OF DRUG RELEASE MECHANISM

- Conventional release
- Controlled release
- Sustained release

In modern era, the expansion of new drug delivery system creating more attention because the effective cost is very high to develop a new drug molecule instead. The principle objectives of sustained drug delivery over conventional delivery are to make sure about the safety and improvement of efficiency of drug with improved patient compliance. So the use of these dosage forms is increasing in treatment of acute and chronic diseases. Because they can keep up the concentration of drug in plasma above minimum effective concentration and below the minimum toxic level for extended period of time.[87]

SUSTAINED RELEASE DRUG DELIVERY

Generally in SR formulations, the first step is dissolution of drug into the matrix, which in turns swells into a gel, allowing the drug to exit through the gel's outer surface.

Some considerations of formulations of sustained release formulations:

- The active chemical compound will sustain on its own if this has a long half life (over 6 hours).
- The pharmacological activity of this compound should be related to blood level otherwise time releasing has no purpose.
- If active transport is needed to absorb the active compound then the development of a time release product may be difficult.

If the pharmaceutically active compound has a short half life, huge amount of drug will be needed to sustain a long-lasting effective dose. So, a broad therapeutic window is essential to avoid toxicity, otherwise the risk is unwarranted and recommendation of another mode of administration would be required.[88]

WHY SUSTAINED RELESE OVER CONVENTIONAL RELEASE?

There are many more limitations of oral conventional dosage formulations[89]

1. Patient compliance is poor. Have a chance of missing the dose of a drug with short half life. So, here frequent administration is required.

2. In case of narrow therapeutic index drug the necessary drug concentration may lead to under medication or over medication.

3. A typical peak-valley plasma concentration time profile is obtained which make attainment of steady-state condition impossible.[90]

There are some advantages of sustained release drug delivery system over the conventional dosage form:

1. Reduction of dosing frequency

2. Dose reduction

3. Improved patient compliance.

5. Maintain constant level of drug concentration in blood plasma.

6. Toxicity level reduction due to overdose. Reduced fluctuations of peak valley concentration.

7. Night time dosing can be avoided.[91]

From the above discussion it is clear that drug administration through nanocarrier in general is much superior than the conventional routes of drug delivery in combating the diseases.

As an example,mesoporos silica material can draw the attention as a matrix or carrier of any drug because silica gel is very appropriate nanomaterial. In particular case for example oral drug delivery, silica is really an perfect material because of its suitable characters for working properly in the gastrointestinal tract at very low pH condition (pH 1-3) and consequently silica is able to protect the loaded drug molecules from the changes in pH as well as degradative enzymes and bile salts.[92,93]

DRUG RELEASE/DELIVERY FROM NANOCONJUGATE

Drug release or drug delivery from any matrices is implicated with many processes including erosion, diffusion, and leaching or dissolution.[94-95] In some cases more than one mechanisms are jointly responsible for release of drug; this may be attributed to the involvement of both diffusion and dissolution controlled processes.[96] In Modified drug delivery system (for example sustained or controlled release system) the diffusion process predominates because the encapsulated drug is distributed in a homogenous way in the polymeric matrix (capsules/tablets).

Zero-order kinetics, first order kinetics, Higuchi model and Hixson-Crowell models are widely used to describe the dissolution kinetics of drug from any solid matrices. Weibull model, Baker-Lonsdale model, Korsmeyer-Peppas and Ritger-Peppas model and Hopfenberg model are involved to interpret the drug release mechanism.[94-96]

SUSTAINED RELEASE OF DRUGS FROM NANO STRUCTURED MATERIALS LIKE SILICA AND CLAY

In this review paper it is shown that a lot of work has been carried out on different nano structured material and entrapment of herbal drugs inside those materials. In present time the sustained release are adopted over conventional release for curing of different diseases. So, various studies have been carried out to get the sustained release mechanism for entrapped chemical / herbal drugs from nanostructured material in body fluids.

Chakrabarty et al. (2011) studied on the release kinetics of Nanocarrier entrapped herbal values. Amdrographis paniculata has its antimicrobial, anti fungal etc. property. Its remain active in its antimicrobial state when it entrapped in Nanocarrier like silica gel. They have

shown the MIC values of the herbal extract Escherichia coli and Staphylococcus aureus successfully.[97]

In their paper Chakrabarty et al. (2011) examined spcially the antimicrobial activity of the released herbal extract from silica gel nanomaterial. The herbs Ocimum sanctum and Terminalia chebula were absorbed and adsorbed into the nano pore of silica gel matrix to make nanomaterial entrapped herbs. MIC values clearly signify that herbal properties remain unchanced in the entrapped condition.[98] The drug release kinetics was also observed in different pH (SBF-7.4 & HCL-1.2) in liquid liquid kinetics model.[99]

Xue et al (2015) fruitfully synthesised drug loaded nanoclay material by using electrospinning membranes technique. This technique is now very much used in polymer like clay fiber processing in the field of tissue engineering with drug release applications, in vitro antimicrobial applications and to study the sustained release mechanism of loaded drug.[100]

At the present time, the polymeric systems specially polymer clay nanocomposite are significantly used as drug carriers. Actually for sustained or controlled drug deliver these systems are suitable kit very much.[101]

CONCLUSION

From this review paper one can get an idea about different types of nanomaterial which are important in biotechnology to be used as drug delivery system. The importance of herbal drugs and the possibility of entrapment of those drugs inside the nanopores of different nano structured materials have been discussed. The study of release kinetics to get the sustained release of those entrapped drug molecules into the body fluids are being elaborated.

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