

Current Status and Future Prospects of New Drug Delivery System

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Quest for Novel Drug Delivery System (NDDS) has started since long back, but it has got momentum since last few decades. NDDS has several advantages over the conventional dosage form which includes better therapeutic outcome. NDDS is also preferred in the new patent regimen as this is one of the ways to introduce new products in the regulated market. Several types of NDDS have been developed during last few decades which are- Microparticles, Nanoparticles, Osmotically Modulated Drug Delivery Systems, Transdermal Therapeutic Systems (TTS), Aquasome, Dendrimers, Multiple Emulsions, Microemulsions, Liposomes, Niosomes, Pharmacosomes, Self-Regulating Drug Delivery System, Brain Targeted Delivery System etc. A recent study reveals that in 2000 the global market of NDDS was \$37.9 billion which shoots up to \$75B by 2005, whereas another study estimated that the U.S. sales of advanced drug delivery systems were over \$54.2 billion in 2004 which will reach \$153.5 billion by 2011. India is also showing similar trend and some Pharma companies have shifted their research focus to develop NDDS. Intensive researches are going on in India both in public and private sector and a number of such products are available in the Indian market.

Preamble:

From time immemorial it has been the endeavour of the physician and the Apothecary to provide patients with the best possible forms of medicines so that recovery from disease is faster and complete. The drugs are delivered in a suitable formulation keeping in view the safety, efficacy and acceptability among other factors, and the formulation is usually known as dosage form or drug delivery system. With the progress in all spheres of science and technology, the dosage forms have evolved from simple mixtures and pills to the highly sophisticated technology intensive drug delivery systems, which are known as Novel Drug Delivery Systems (NDDS).

Quest for New Drug Delivery System (NDDS) has got new impetus since early eighties to have improved therapeutic outcome from the same drug, because the NDDS have several advantages over the conventional dosage form¹⁻¹⁰. Since then several NDDS have been developed and it constitute a sizable portion of the global market. Indian researchers have shifted their interest towards NDDS since early eighties¹¹⁻²¹.

The driving force behind the development of NDDS has been two-fold. First, the obvious clinical advantages of these systems, and Second, their economic aspects. The NDDS have been and are being developed in order to attain greater control over a drug's pharmacokinetics and

pharmacodynamics after administration so that the dosage forms thus produced would be highly effective, safe and better than the conventional products. Often, reformulation of an old drug in a NDDS rejuvenates clinical interest in the drug, thus adding to its effective market life²²⁻²³. This brings us to the economic aspects of NDDS.

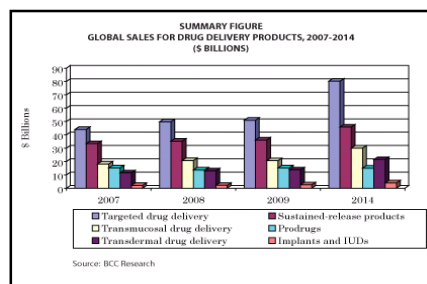
Besides the primary factors discussed above, the escalating interest in NDDS is also attributable to the Product Patent regime and the vast post-GATT generics market being eyed by the industries. With NDDS, relatively lesser investment of time and money could lead to higher margins of profit taking the advantages of patent cover. It is easier to develop a NDDS rather than a new molecule and a company can file an ANDA to US FDA more easily. Some of the Indian companies have already been succeeded in this arena.

According to a recent estimate, the development of a new drug for human use involves around \$800 million and 10-12 years of research inputs. However, 9 out of 10 drugs fail in their clinical study phase causing huge loss to the investigating organization. For NDDS development, an US estimate shows the development cost to be around \$40 million and a period between 3 months to 3 years. Thus the burden on company's exchequer is quite less with good chances of ensured returns. Usually, due to a small development cycle, multiple pipe-line NDDS products could be contemplated ensuring a bigger market-share in a particular segment.

A survey shows that the global market for advanced drug delivery systems was more than \$37.9 billion in 2000 and is estimated to reach \$75B by 2005 (i.e., controlled release \$19.8B, needle-less injection \$0.8B, injectable/ implantable polymer systems \$5.4B, transdermal \$9.6B, transnasal \$12.0B, pulmonary \$17.0B, transmucosal \$4.9B, rectal \$0.9B, liposomal drug delivery \$2.5B, cell/gene therapy \$3.8B, miscellaneous \$1.9B). This market is growing at a rapid pace, especially in the area of alternatives to injected macromolecules, as drug formulations seek to cash in on the \$6.2B worldwide market for genetically engineered protein and peptide drugs and other biological therapeutics²⁴.

Another study reveals that the U.S. market of advanced drug delivery systems were over \$54.2 billion in 2004. In 2005 they reached \$64.1 billion. It was predicted that over 5 years, this market will continue to grow at an average annual growth rate (AAGR) of 15.6% to reach \$153.5 billion by 2011. In 2005, the largest sector of the market consists of sustained release/ implants/transdermal drug delivery systems, with more than 50% of the total U.S. market. Through the forecast period this sector will gradually give way to targeted drug delivery systems, which may control almost 48% of the market in 2011. It has been predicted that the Targeted drug delivery has the highest growth rate, with a 23.3% AAGR through 2011. The next highest are transmucosal drug delivery systems, with

15.3%. The global market for advanced drug delivery systems amounted to \$134.3 billion in 2008, and was projected to increase to \$139 billion in 2009. The estimate for 2014 is \$196.4 billion, for a compound annual growth rate (CAGR) of 7.2% in the 5-year period. The largest segment of the market is targeted drug delivery, which reached \$50.9 billion in 2009 and is expected to increase to \$80.2 billion in 2014, for a CAGR of 9.5%. Sustained-release products have the second-largest market share, with estimated sales of \$36.1 billion in 2009 and \$45.8 billion in 2014, for a CAGR of 4.9%²⁵.



In India, the pharma market is about Rs 20,000 crore of which around five percent is the NDDS market, which amounts to the tune of Rs. 1000 crores. This gap between the Indian and global markets indicates that there is a tremendous scope of developing the NDDS market in India.

Several types of NDDS have been developed, which are as follows:

Types of Novel Drug Delivery Systems:

There are multiple schemes of classification of types and techniques of NDDS - based on therapeutic group of drugs loaded, physical form, intended application route, mechanism of delivery or action, etc. and none would be complete. Mention may, therefore, be made of a few popular and most promising NDDS in the following paragraphs.

1. Microparticulate Drug Delivery Systems

- Drugs encapsulated within polymeric beads in order to control the release, mask taste, prevent degradation from atmospheric moisture or oxygen, and to ensure proper delivery as desired has been a commercial success for quite a few decades. These multi-unit dosage forms are mainly intended for oral delivery, though parenteral and other routes of administration have also found commercial and clinical success. Various GRAS (Generally Regarded as Safe) excipients and polymer systems (both synthetic and natural) have been used extensively to form these dosage forms. Different systems implement various rate controlling mechanism including non-erodible mechanical barrier for diffusion controlled release, microporous membrane systems, water swellable and hydrogel systems, ion-exchange resin with polymer coating, differentially coated

multiparticulates, pH sensitive polymer coated systems, gastric floatation systems, mucoadhesive systems, colon-specific delivery systems, etc. a large spectrum of drug have been modulated for release and other properties, for e.g., theophylline, vitamin C, cardiovascular drugs, antipsychotics, antibacterials and chemotherapeutic agents, to name a few therapeutic classes of drugs. Some microparticles are made site-specific by incorporating magnetite and localizing them to specific tissue through application of external magnetic field. The selection of polymer for a particular multiparticulate system is crucial and a wide variety of polymers such as cellulose derivatives (methyl, ethyl, hydroxypropyl, hydroxypropyl methyl cellulose), acrylic polymers (Eudragits of various grades and other brands), biodegradable polymers (Polylactide coglycolic acid, poly lactic acid, polyglycolic acid, poly-epsilon caprolactone, alkyl polycyanoacrylate, etc.) and natural polymers (sodium alginate, albumin, other proteins, chitosan, etc.) are used depending on the requirement of the particular system to be developed²⁶.

2. Nanoparticles

- These are colloidal drug delivery systems in the nanometer size range having wide application potential at present. They have got all characteristics of the liposomes minus the stability problems. They have been utilized to deliver and control the release of drug molecules from suitable polymeric nanoparticles/nanospheres. Usually FDA approved biocompatible polymers such as poly (L-lactide - D-glycolic acid) [PLGA] have been used, though other polymers such as poly - epsilon-caprolactone, chitosan and polyalkyl cyanoacrylates have been also used. Their most promising area of application is tumor-targeting capability. They may also be engineered to be stealth (when coated with suitable agents such as PEG) to enhance circulation time in blood by fooling the physiological recognition mechanism during phagocytic uptake. Not only are the nanoparticles suitable for parenteral administration, but also they have been exploited as advanced systems for drug delivery through cornea, skin, bronchioles and of course oral routes. A few drugs have been marketed as nanoparticulate systems such as Amphotericin B, some antineoplastics and others including proteins, peptides and macromolecules have been investigated in animal and clinical models. The promises of nanoparticles as drug delivery system are only limited by the choice of suitable biocompatible polymers.

3. Osmotically Modulated Drug Delivery Systems

- A very successful form of NDDS is the osmotic systems, usually, tablets coated with semi-permeable barrier polymers that has a laser-drilled precision hole as drug delivery orifice. In the

gastrointestinal fluid the osmotic materials inside the tablets cause increase in osmotic pressure inside the barrier which forces drug to rush out of the orifice at a predetermined rate. Various modifications of the basic systems are available such as the Push-Pull System (with a movable partition inside the tablet), SCOT (Single Component Osmotic Tablet), PorTab (with an osmotic core), etc., which have been developed to deliver a multitude of drugs such as Phenylpropranolamine, Prazosin, Verapamil, Enalapril, Diltiazem, Salbutamol, Chlorpheniramine, Glipizide, etc. and have been a great commercial success.

4. Transdermal Therapeutic Systems (TTS)

- Skin as a port of non-invasive painless drug delivery has become reality with introduction of Transdermal Therapeutic Systems. Commercially, nitroglycerine, scopolamine, nicotine and a few female hormones are available as TTS. However, they did not have had such expected success with other drugs. But immense potential lies in TTS as future smart drug delivery devices. Various polymer layered systems, reservoir systems, microsealed systems, and self-adhesive systems of TTS are available from different companies. The patented polymeric systems are the key to a successful TTS and the modulation of drug release is the key to efficacy in clinical set up.

5. Aquasome

- These are carbohydrate stabilized nanoparticles of ceramics / calcium phosphate having water-like properties that help to protect and preserve the fragile biological molecules. They are comprised of a solid nanocrystalline core coated with oligomeric film to which the drug moieties or biochemically active molecules are adsorbed with or without modification. These three layered structures are self-assembled by non-covalent and ionic bonds. Their intended route of administration is parenteral and with advancement of research in this field, other routes might be contemplated.

6. Dendrimers

- In search for novel biomaterials for controlled and targeted delivery of bioactives, Starburst Dendrimers are the latest stars that bear promising properties for the delivery of drugs, vaccine, metals or genes to the desired sites. In spite of being polymers they bear similarity with vesicular structures such as micelles, liposomes and globular proteins. The dendrimers are three-dimensional branched structures like trees and hence the name "Dendrimer" [dendron (GR.) = tree]. They possess a very large number of chain ends and synthesized chemically. Into the branches of dendrimers drugs and other biologically active molecules could be entrapped for controlled and/or targeted delivery initially via parenteral route and subsequently other routes could be tried.

7. Multiple Emulsions - These are emulsions of emulsions in which the internal phase consists of dispersed globules, which are made of a simple (two-phase) emulsion. There are two types - oil/water/oil or water/oil/water, i.e., two similar phases separated by an immiscible phase, which is sometimes called liquid membrane that acts as a semipermeable membrane for drug molecules to diffuse through it at a controlled rate. A promising use of multiple emulsions is drug targeting via antibody / ligand tagging to the carrier droplets. Also, because of their globular size drugs may be targeted to lungs and reticuloendothelial systems (RES). The techniques of multiple emulsions formulation has also been used to prepare micro- and nano-particles for controlled and targeted drug delivery.

8. Microemulsions - Microemulsions are transparent thermodynamically stable systems of colloidal nature that are formed from classical emulsions, but at specific phase-volume ratios. They afford solubilization of water-insoluble molecules, thereby improving their bioavailability as well as applicability and reduced ADME problems. Therefore, various hitherto problematic drugs such as the NSAIDs, antifungal antibiotics, etc. have been formulated as microemulsions. A widely used immunosuppressant, Cyclosporin, have been formulated commercially as a microemulsion for increased solubility and bioavailability (NEORAL®). Proteins and peptides may also be formulated as oral microemulsions, such as oral insulin systems, and also scope exists in developing oral vaccines through this system. However, problems of large-scale manufacture and more importantly, the selection of suitable emulsifier-oil-cosurfactant system to develop the workable microemulsions have still remained the hurdles in wide-spread commercial exploitation of this excellent system of drug carriers.

9. Liposomes - These are uni-/multi-lamellar phospholipid vesicles composed of concentric spherical layers of aqueous zones sandwiched between phospholipid membranes. Both water and oil soluble drugs can be encapsulated in the liposomes either in the aqueous zone or the lipid-bilayers according to their solubility. They are often referred to as "artificial cells" as they resemble one in almost all practical aspects. They showed immense potential in delivery of anti-tumor therapeutics as well as anti-fungals. Drugs such as Amphotericin B, Doxorubicin and Daunorubicin have been successfully launched in market as liposomes. However, drug leakage problems, poor stability and scale-up cost are some hurdles in full-scale exploitation of liposomes. As a way-out, the freeze-dried

liposomal particles known as Proliposomes have been formulated for delivery via transdermal, ophthalmic, mucocutaneous, pulmonary, oral and parenteral routes. PEGylated liposomes have application as stealth vehicles for prolonged and targeted drug delivery.

10. Niosomes - These are vesicles like liposomes, but made up of non-ionic surfactants and like liposomes. They can also entrap hydrophilic as well as lipophilic drugs. They have better stability than liposomes and hence have greater interest for industrial adoption. The non-ionic surfactant systems make niosomes inherently target-specific to tumor, liver and brain. They have been reported to be useful as targeting systems of drugs for treatment of cancer and in therapy of microbial diseases caused particularly by virus and parasites. Tumor targeting of Methotrexate in mice model have been highly successful. Other drugs such as sodium stibogluconate, doxorubicin, etoposide, used systemically and certain dermal therapeutic agents such as 5- α -dihydrotestosterone, triamcinolone acetonide, etc. have been found to be of improved efficacy when formulated as niosomes. Since no special handling / storage precautions are required for niosomes, their commercial exploitation would be easier. They are biodegradable and reduce systemic toxicity of various antitumor and antimicrobial agents by localizing the drug to specific sites of action. Also, being surfactant in composition, they have got an ability to fool body's phagocytic defense mechanism and act as stealth drug carriers making their effective circulation time longer than the drug given in conventional forms.

11. Pharmacosomes - The name is given recently to certain vesicular drug carrier systems where the drug is conjugated with the vesicle-forming agent, usually, palmitic / stearic acids or their derivatives. Thus, the problem of drug leakage and low entrapment efficiency, often associated with other vesicular system, is eliminated. Any drug with a certain cut-off molecular weight may be formulated as pharmacosomes provided it has active functional groups to integrate with the vesicle-forming amphiphilic molecule.

12. Brain Specific Chemical Delivery Systems- In order to achieve brain-specific drug delivery, the approach can be either circumventing the blood-brain-barrier through drug-latentiation or conversion of water soluble entities to lipid soluble ones. In general there are two types of systems for brain - specific sustained release of drugs (i) Dihydropyridine-pyridinium type redox delivery system, and (ii) chemical delivery system, based on the use of endocyclic nitrogen atom of nicotinamide²⁷⁻²⁸.

13. Self-Regulating Drug Delivery System - These are delivery systems which deliver drug at a time when needed by the body and at a variable rate determined by physiological need. These are intelligent self-regulatory or pulsatile drug delivery systems, which release drug in response to external stimuli like heat, light, ultrasound, magnetic fields, pH and/or chemicals. These usually utilize certain special polymers that may be pH-sensitive, or the drugs may be released in response to antibody interaction, enzyme-substrate reaction, competitive binding, or metal-concentration dependant hydrolysis. A classical example of a self-regulated drug delivery system is the Insulin Pump - a semi permeable polymer membrane coated depot system in which insulin is linked to a substrate matrix via a plant protein called Concavallin A. In response to high glucose level in blood, the insulin is liberated and glucose replaces it in the depot. When glucose level falls to normal, the insulin is taken up and bound to Concavallin A, thus self-regulating the drug release.

Conclusion:

Pharmaceutical innovations like the Novel Drug Delivery Systems presents health professionals with a broad range of arsenals to treat diseases with never before efficacy, safety and precision. Clinically the NDDS not only smoothens the saw-tooth pattern of drug levels in blood, but also affords targeting the drugs to their site of action and thus reduces dose-related side effects. Smaller quantity of drug and fewer numbers of dosing could be used to treat a disease with increased success. It is hoped that with more and more research endeavours being focused into this arena, in near future, a large portions of the conventional dosage forms would be replaced by these NDDS and an overall betterment of health care delivery is expected with that change over. Pharmaceutical companies are interested to conduct research on NDDS to get edge over the big pharmaceutical companies to capture the regulated market through ANDA in regulated market. Moreover development and implementation of new branches like Pharmacovigilance will ensure availability of safer medicines to our people. Pharmacoeconomics will provide cost effective health care, which may help to extend the health care to the underprivileged.

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