EXECUTIVE SUMMARY

1. Any drug delivery system may be defined as a system comprising of:

   a) drug formulation
   b) medical device or dosage form/technology to carry the drug inside the body
   c) mechanism for the release

   Conventional drug delivery involves the formulation of the drug into a suitable form, such as a compressed tablet for oral administration or a solution for intravenous administration.

   These dosage forms have been found to have serious limitations in terms of higher dosage required, lower effectiveness, toxicity and adverse side effects.

   New drug delivery systems have been developed or are being developed to overcome the limitation of the conventional drug delivery systems to meet the need of the healthcare profession. These systems can be characterised as controlled drug release systems and targeted drug delivery systems.

   The therapeutic benefits of these new systems include :

   - Increased efficacy of the drug
   - Site specific delivery
   - Decreased toxicity/side effects
   - Increased convenience
   - Shorter hospitalizations
   - Viable treatments for previously incurable diseases
   - Potential for prophylactic applications
   - Lower healthcare costs - both short and long term
   - Better patient compliance.

2. There is no uniform and established definition of drug delivery systems. It is assumed to be based on two basic parameters :

   Route of entry (A) and Dosage form (B).

Any member of the cartesian product of (A X B) is defined as a drug delivery system.

Such a definition implies that there are a vast number of members in this group. Many of them may not even be feasible, while many others may not be relevant. So, the set of most relevant new drug delivery systems is deduced as follows :

a) Transdermal Delivery Systems

b) Carrier Based Delivery Systems

- Liposomes
- Monoclonal Antibodies
- Nanoparticles
- Microspheres

c) Variable Release Delivery Systems

- Osmotic Pump
- Microencapsulation
- Ion Exchange Resins
- Tablets in Capsules

d) Implantable Delivery Systen..

e) Nasal Delivery Systems

The purpose of these controlled drug delivery systems is at least one of the following :

- Sustain drug action at predetermined rates.

- Localise drug action by placing a rate controlled system near or at the desired tissue or organ.

- Target drug action by using carriers or chemical derivatisation to deliver drug to a particular site.

3. Several approaches to the design of controlled release systems have been developed. Major approaches include the following :

a) Approaches for Controlled Drug Delivery

- Reservoir Systems with a Rate Controlling Membrane
- Monolithic Systems
- Laminated Systems
- Chemical Systems

b) Approaches for Targeted Delivery

- Local Targeted Delivery
- Differential Metabolism Approach
- Biological Recognition
- Bio-physical Approach
- Prodrugs

Several factors affect the successful design of controlled release products. These require careful consideration in the developmental process.

- Physico-chemical drug properties
- Biological processes
- Routes of administration

In order to fulfill the two functions of controlled release technologies, viz., site specific targeted drug delivery and/or rate controlled drug delivery, the devices/products must meet two basic requirements :

(i) The device must hold the entire dosage of drug required for complete therapy; and

(ii) The device must be able to control the rate of drug release from the system.

Polymers play an important role in meeting both these requirements. They can be fabricated to act as reservoirs of the total amount of drug. Also their properties can be suitably modified to control the rate of release to the desired level.

For the regulatory approval of controlled release products, three critical issues in polymer formulation are involved.

a) Non toxicity
b) Bio-degradability; and
c) Controlled release of drug.

4. Although new delivery systems have a number of therapeutic benefits, but they do have certain limitations such as :

a) If systems fail, overdosing occurs due to doses dumping.
b) The large physical size of the dosage unit poses problems in usage.
c) Often sub optimum bio-availability is observed.
d) Variability in drug levels is also observed.

5. A few controlled release systems have already been commercialised abroad. Their technologies too are well established. These systems are :

Transdermal Patches
Implants
Nasal Systems
Microcapsules
Osmotic Systems
Ion exchange Resin Systems
Pellets in Capsules

6. Transdermal Drug Delivery Systems are laminated patches which adhere to the skin and permit absorption of drugs from the skin surface through its layers into the general blood circulation, at controlled rates, resulting in sustained blood levels. The benefits from transdermal drug delivery are :

a) it avoids the risk and inconvenience of intravenous therapy.
b) allows treatment to be discontinued if so desired.
c) the dosing regimen is simplified and the system is convenient to use, leading to excellent patient compliance.
d) lower dosages are sufficient, minimising side effects.
e) avoids the variable metabolism and absorption associated with oral drug administration.

7. Since, drug release from patches (Transdermal Drug Delivery System) is constant over very long periods, the homoastasis of the body is affected and the possibility of some undesirable effects on the abrupt removal of transdermal patches cannot be ruled out. It causes side-effects like dryness of the mouth or drowsiness. Anticholinergics like scopolamine can also interfere with orientation, cognition and memory and may cause delirium, particularly in geriatric patients. Therefore, it should be used with caution. A washout period could be allowed in such cases before the next patch is applied.

8. Major Companies manufacturing transdermal patches are Ciba Geigy, Alza Corporation, Searle, Schwartz Pharma, Boehringer Ingelheim and Toaeiyo. The main products which have been commercialised include Transderm - Scop, Nitro-Dur, Nitrodisc and Deposit for delivering scopolamine, Transderm - Nitro for deliverying nitroglycerin as also Catarpress - TTS for delivering clonidine.

9 Implants are sterile polymeric devices of varied shapes containing one or more medicaments for introduction into body tissues for release in a controlled manner. The advantages of these devices are :

a) Implants can provide uninterrupted treatment for prolonged time periods e.g. several years or even a lifetime.
b) The treatment is often reversible since the device can be removed if any undesirable effects occur.
c) Implants provide the dual advantages of location and rate control.

10. Implantable drug delivery systems have following limitations.

a) Surgical intervention required either for implantation/subsequent removal.
b) Possibility of infection at implant sites.
c) The size of the device may pose acceptability problems.
d) In the case of hydrogel implants, because of the high water content, low molecular weight drugs are able to diffuse out quickly, making sustained delivery difficult.
e) The cross linking agents used may increase the frictional irritation of the implants.

11. The major areas of application of implants include diabetes, cancer, contraception, cardiovascular diseases and brain diseases. Major companies involved in the manufacture of these systems include Alza Corporation, Meditronic Inc, Becton Dickinson and Infusaid Inc. Variety of systems have so far been commercialised. Some of these are the Progestasert, Norplant, Today™, Vaginal ring, and Dual release ring for contraception, the lacrisert for artificial tear therapy, the Alzet osmotic pump for various drugs and the Ocusert for glaucoma management.

12. Conventional nasal formulations in the form of spray and drops have used delivery systems like the rhinyle catheters, single dose pipettes, metered dose spray pumps (non-pressurised) and metered dose aerosol valve devices.

Out of these, the spray pumps and the aerosol valve devices lend themselves to controlled delivery of nasal formulations. The spray pump operates on the mechanical energy provided by the depression of the actuator, while the aerosol valve device operates on the energy provided by the propellant in the system. Both systems are simple to use and provide multiple dosing facility.

The relevant criteria to assess which device is more suitable in a given case are :

- dose accuracy
- dose reproducibility for the same device, comparatively for different devices and from batch to batch for each device.
- tailing off or emptying characteristics.
- rapid priming of the dose especially for pump systems.
- absorption or adsorption of ingredients from the formulation into/ onto the device.
- leaching out of materials from the device into the formulation.

13. The advantages of Nasal Drug Delivery Systems are :

- Ease of administration.
- Rapid absorption and onset of action.
- Bypass of presystemic clearance.
- It is a non invasive route.
- Chronic self administration is possible.
- Simple formulations are sufficient.
- The nasal mucosa offers a large surface area for absorption and a favourable metabolic environment.
- Bio-availability appears to be satisfactory.
- Reduced hospital out patient care.
- Accurate consistent dosing.
- Greater efficiency with smaller doses leading to lower manufacturing costs.

14. The disadvantages associated with Nasal Drug Delivery Systems are :

- Untoward immunogenic reactions may occur.
- Inadequate availability of toxicity data for penetration enhancers.
- Nasal pathology may adversely affect product effectiveness.

15. A few nasal products have been commercialised. These include calitonin for metabolic bone disease, desmopressin acetate for primary mocturnal

enuresis. A few others are also developed for which approval is awaited e.g. Vitamin B_{12} for pernicious anemia, "Nasacort" for steroid delivery.

16. The oral route of administration for controlled release systems, has received a lot of attention. Most oral systems are either tablets or capsules, and the nature of the release mechanisms employed involve either diffusion or dissolution.

The system usually consist of two parts comprising of an immediately released dose and a sustaining portion that contains several times the therapeutic dose for maintaining drug levels at desired levels.

17. Microencapsulation is the process of applying relatively thin reproducible coatings to small particles of solids or droplets of liquids and dispersions to produce microcapsules. The various considerations in selecting a micro encapsulation process are :

- The route of administration of microcapsules primarily determines the procedure used for microencapsulation. For the oral route, a single coating could often suffice while the requirements for implantable microcapsules could be more stringent involving issues like the bio-degradability of the polymer implant and the antigenic and thrombogenic properties of the capsules.

- The physico-chemical properties of the drug would be another important consideration in choosing a microencapsulation process. It may not be possible to encapsulate solids by the same process as liquids. Also the acidity or alkalinity of the drug may preclude the use of certain wall materials.

- The physical and chemical properties of the wall materials need to be considered carefully before, during and after encapsulation. As an example, waxes or long chain fatty acids are soluble in many organic solvents. This property makes them good candidates for deposition about an aqueous drug core by spray drying. However, this very same property precludes their use in encapsulating organic liquids.

18. The advantages of microencapsulation are :

- Microencapsulation provides a means for converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and of controlling the release characteristics (or availability) of coated materials.

- Uniqueness of microencapsulation is the smallness of coated particles and their subsequent use and adaptation to a wide variety of dosage forms and product applications.

- Because of the smallness of the particles, drug moieties can be widely distributed throughout the gastro-intestinal tract, thus potentially improving drug absorption.

19. The disadvantages associated with microenapsulation are :

Though microencapsulation technology has made a fundamental impact on pharmaceutical applications, there are certain problem areas which cannot be ignored.

- The release characteristic of coated products are not always reproducible.
- The coating may often be discontinuous.
- No single technique can be adapted to all core materials.
- In the case of very sensitive pharmaceuticals the shelf life would be inadequate.
- Economic limitation too may be a stumbling block in its application.

20. Some Commercialised Products Using Microcapsules are :

- Leuprolide acetate for prostrate cancer
- Doxycycline
- Aspirin

21. The technology for osmotic pumps exploits the tendency of a fluid to equalise the concentration of substances on both sides of a semipermeable membrane. The osmotic pump system is a variable release system in that it can be designed to deliver different drugs at different rates. Osmotic devices can be employed for two purposes :

- To be used as research tools for animal pharmacology and chemical studies.
- To be used as dosage forms for drug delivery.

As drug delivery systems, for pharmaceutical applications they could be used as oral devices formulated as capsules or tablets as also in the form of implantable devices.

22. The unique proprietary technology of osmotic drug delivery offers several benefits.

- The delivery rates provided are higher than diffusion controlled systems.
- The biological environmental influences like pH, gastro-intestinal motility, etc., on the system are minimised.
- The system functions without being significantly affected by drug properties.
- The delivery rates are predictable and programmable.
- These systems are satisfactory in vitro and in vivo release profiles.
- The side effects of drugs administered are minimised.
- Patient compliance is improved since the frequency of dosing is reduced.
- The device is tamper resistant.

23. There appear to be no apparent disadvantages of these systems. These pumps are used widely in animal pharmacology studies to administer drugs locally to distant targets to study their effects. The study mainly involves optimisation of dosing frequency and rates as also the bio-availability of drugs. The versatility of these systems is evident from the fact that numerous drugs including peptides, neurotransmitters and nerve growth factors have been studied using these pumps.

24. Commercialised products employing this technology include Acuteim and Acusystem C to release drugs phenyl propanolamine and Vitamin C, respectively, both developed by Alza Corporation.

25. Ion Exchange Resin System involves preparation of drug charged resin and its drying to form beads. In the environment of the Gastro-intestinal tract the drug molecule is exchanged for an appropriately charged ion and so the drug is released at a controlled rate.

26. Some of the advantages of oral drug resinate preparations are :

- Reduction in the total drug dosage used.
- Fluctuations in blood levels are reduced.
- Frequency of dosing can be reduced making the treatment simpler for the patient.

Besides these, additional benefits from ion exchange delivery systems are:

- The release of drugs is governed by certain factors like pH and ion

strength and these conditions are fixed in the GI tract, making the formulation of such systems much more similar.

- A variety of ion exchange resins are available providing a wider choice to control resin characteristics like porosity and particle size.

27. The disadvantages associated with Ion Exchange Delivery System are :

- The possible risk of drug accumulation, should the balance between rate of release of drug and its excretion is not maintained.

- It is not possible to interrupt the treatment, once the drug is administered.

- Prolonged administration may disturb the ionic strength of the gastro-intestinal fluids.

The major ion exchange resin system commercialised todate is the Pennkinetic System, which has been used to deliver a variety of antitussives.

28. Pellets in Capsule System is a relatively simple technology and has been developed to deliver controlled amounts of the drug. The main systems commercialised so far include SODAS (Naproxen and Verpanil), ASTRIX (aspirin), DORRYX (doxycycline) SRYC (Erythromycin) and ELANTANLASO (Isosorbide mononitrate).

29. Liposomes are artificial microscopic bilayer vesicles or sacs made of phospholipids, enclosing an aqueous compartment. Liposomes resemble cell membranes in structure and composition.

In order that drugs be efficacious, they need to be administered in certain concentrations. However, dilution in blood, metabolism and uptake by healthy tissues can all occur, resulting in poor delivery at the diseased site in the body, on the one hand and toxicity effects on the other.

Liposomes provide the ideal means to tackle all these issues. Drugs incorporated in liposomes and administered to the body can be delivered at the desired site, in the needed concentrations without being toxic.

30. The advantages of the liposomes are :

- Liposomes can be metabolised in vivo since they are made of phospholipids.

- They are non toxic and non antigenic because they are made of phospholipids.
- Liposomes allow the sustained delivery of drugs with low therapeutic index by altering their pharmacokinetic pattern.
- They facilitate site specific drug uptake and delivery.
- Liposomes can protect encapsulated drugs from degradation.
- They can increase the convenience of therapy by reducing frequency of drug administration.
- They can alter tissue distribution of drugs in a therapeutically favourable way.
- Lioposomes show compatibility with both lipophilic and hydrophilic drugs.
- Liposomes surfaces can be modified to provide bioadhesion which can be used to enhance the residence time at a particular site.

31. The disadvantages of liposomes are :

- Their liquid crystal structure hinders a true membrane transfer and causes physical instability.
- Their loading capacity is quite weak.
- Allergic reactions are possible.
- Poor encapsulation of drugs could be a limitation.

32. Liposomes are basically stable structures since they represent the favourable thermodynamic state of phospholipids in water. However there are many circumstances in which liposome instability can occur.

Liposomal stability during storage influences their stability and performance in vivo. Stability problems with liposomes arise on two accounts, viz.,

- Increase/decrease in vesicle size as a result of spontaneous fusion or disintegration of vesicles on standing.

  Leakage and loss of low molecular weight drug load.

Both problems have been resolved to a large extent.

The stability problems during processing arise mainly on account of the phospholipids used. These get degraded mainly by peroxidation and hydrolysis reactions. Stability relating to the drug need to be handled on a case to case basis. Since, the drug is generally less stable than the lipids, conditions which ensure drug integrity will also ensure lipid stability.

33. Disease categories for Liposomal Drug Delivery

a) Infectious Diseases

- Leishmaniasis (Including Kalaazar)
- Brucellosis
- Tuberculosis
- Listeria infections
- Leprosy (bacterial)
- Malaria (protozoal)
- Hepatitis
- Yellow fever
- Cytomegalovirus infection (viral disease of liver)
- Fungal infections.

b) Immune System

Use as Adjuvants

- Metabolic Deficiencies in chronic granu-lomatous disease
- Vaccines delivery

c) Metal Detoxification

d) Cancer Chemotherapy

e) Arthritis

f) Heamophilia

g) Diabetes

Major companies developing liposomal products include the Liposome Company, Liposome Technology Inc., Squibb, Vestar Inc and Bristol Myers.

Several products undergoing clinical trials are doxorubicin, amphoterin B, gentamicin and daunorobicin.

Other formulations, besides the above, include :

- Vincristine

- Vaccine for AIDS

- Products for dry eye syndrome, glaucoma and allergies

- Albuterol for bronchodilation

- Products for preventing post surgical adhesions

- Immunomodulators including mirramyl tripeptide - phosphatidyl ethanolamine for cancer and viral infections.

34. Monoclonal antibodies are artificially produced proteins which exhibit specificity for one single antigen. The inherent specificity of the monoclonal antibodies for antigens provides the rationale for their use in drug targeting for therapeutic applications. The purpose is to destroy diseased tissues while leaving healthy tissues unharmed, thereby also reducing side effects of drugs.

Two aspects of monoclonal antibodies need to be understood for successful development of therapeutic products. One is the possible susceptibility of their binding properties to even minor modifications in the environment. The second involves the kinetics of antibody binding. It may be necessary, for example, that the antigenic determinant recognised by a given antibody is in a particular conformation before binding can take place.

35. The major application for which monoclonals are being studied for therapeutic use is cancer. Much of the work relates to the conjugation of different chemotherapeutic agents with antibodies and studying their effects in various tumor models. Clinical trials are being carried out for various products catering to different diseases like melanoma, sepsis, graft-vs-heart disease ovarian and colorectal cancer as also breast and lung cancer.

36. Nanoparticles are colloidal particulate systems in the sub-micron size range acting as carriers of drug molecules. These carriers are solid spheres and their surface is amorphous and lipophilic with a negative charge. Depending on the manufacturing procedure the size varies between 10 nm to 1000 nm. The porosity varies between 3 nm and 6 nm and the wall thickness in the case of nano capsules could be between 15 nm and 60 nm.

The drug is dissolved, entrapped and/or adsorbed to the macromolecular material. The preferred mode of administration is parenteral. However, it is possible to alter the distribution of nanoparticles in the body either by coating them with serum components or by attaching antibodies to their surfaces. Alternatively, magnetic nanoparticles could be used to enhance site specificity.

37. Nanoparticulate systems provide a number of benefits which are :

- They control both the site and rate of drug delivery
- Adverse effects and toxic reactions are minimised
- They enhance the therapeutic efficacy of the drug
- The particles are non toxic and bio-degradable
- Reproducibility is quite easily achieved
- They are quite stable and less costly than other colloidal systems.

Nanoparticulate delivery systems suffer from their targetability is limited to the liver, the spleen and to a small extent, the bone marrow.

38. Medical applications using nanoparticles are :

- Treatment of infections of the Reticulo Endothelial system.
- Enzyme replacement therapy in the liver.
- Treatment of Cancer.
- Vaccination.

39. Microspheres are small solid particulate carriers containing dispersed drug particles either in solution or crystalline form. The importance of Microspheres has been growing because of their use as carriers for drugs or other therapeutic agents. Microspheres are made from natural and synthetic polymers. Different materials have been used for microsphere systems like albumin, gelatin, starch, ethylcellulose and synthetic polymers such as polylactic acid polycyano acrylates and polyhydroxybutyrate.

Routes of administration are by injection. i.e. intravenous, intramascular and intraarticular or by the nasal route. They reach the target site by some suitable passive mechanism or by direct administration into the relevant body compartment. The size of the microspheres can range from tens of nanometers to one hundred microns or more smaller particles below 500 nm are often termed nanoparticles or nanospheres.

The physical characteristics of these systems differ and depend on their applications. The feasibility of a microsphere system of drug delivery is determined largely by :

- the physico-chemical characteristics and dose of the drug used; and
- the required release pattern of the drug.

These aspects need to be considered carefully early in the development of an application.

40. Microspheres offer considerable advantage over conventional systems and are likely to play a crucial role for many theraples. Especially, they may be more useful than liposomes, in many respects. Microspheres possess some advantages over liposomes, which include :

a) a larger drug loading capacity than liposomes,

b) greater stability, than liposomes in vitro and in vivo especially with respect to drug leakage and control of release over longer time period, and

c) an easier sterilisation procedure during manufacture.

Microspheres suffer from a number of disadvantages in their use as carrier systems. Some of these are :

- They are cleared and taken up from the circulation by the reticulo-endothelial cells.

- 'Burst Effect' i.e. premature drug release is seen.

- The target site specificity of microspheres could be improved.

- Poor entrapment of drugs (payload characteristics) is seen.

41. Many microsphere systems are being studied for a variety of applications. Some of the type of systems and the drugs under investigation are :

Mitromycin C	Albumin system
5 fluorouracil	Fibrinogen system
Progesteone	Polybutyl cyanoacrylate system
Adriamycin	Collagem system
Proteins	Polyacryl starch system
Cisplatin	Ethylcellulose system
Enzymes	Acrylic system

A new development is the magnetic microspheres which appear to have great potential in the localised tumer treatment. They are infused intraartilly and a magnet of sufficient field strength as applied externally over the target area to localise the microspheres. These provide the dual benefit of increased site specificity and a minimised reticulo-endothelial clearance.

42. A Research and Development work will continue to be an integral part of developing novel drug delivery systems for ultimate commercial exploitation in the coming years. The reasons for these are mainly the following :

- Many of these systems, involving complex strategies especially in the targeted release area, pose a number of problems for basic research which need to be resolved at the molecular and cellular levels. Problems like reticulo-endothetial clearance and drug release into the target cells are examples.

- Even for fairly well established technologies like Transdermal Systems or certain implantable devices, developmental work in terms of formulation of different drugs for these technologies would be an ongoing effort.

- Polymer formulation to suit individual applications would involve work of a developmental nature.

In short two types of research are becoming evident in the area of controlled release technologies, the world over. Firstly, to validate the basic concepts of new controlled release technologies being developed whose commercial realisation cannot be done in the immediate future, and secondly to work on conceptually validated technologies and generate the required data to make them commercially viable.

43. Research and Development - World

Major thrust areas for research & development in the world, the various drug delivery systems are :

a) Liposomes

— Drug liposome formulations have been investigated for a variety of applications, including the treatment of cancer and infectious diseases, vaccines for influenza and AIDS, peptide delivery, ophthalmic, cardiovascular, and nonsteroidal anti-inflammatory drugs. Doxorubicin, Amphotericin B and Gentamicin are the most widely studied drugs. Ampicillin, eisomycin, Streptomycin and Penicillin have also been studied and increased therapeutic index obtained.

— In order to broaden the range of potential applications and to increase the duration of liposomal formulations in the

bloodstream, a technology is being developed to coat liposomes with carbohydrate moieties and target them.

— Varying liposome structure to obtain optimal drug release rates and targeting liposomes to migratory cell populations is also being explored.

— Studies to assess the potential of neosomes and virosomes as drug carriers are under way.

b) Transdermal Systems

— Research efforts are on to increase the permeability of drugs by this route, using several techniques.

— Electrically induced transport or iontophoresis is being tried in dental and physical therapy applications. One project involves the use of square, triangular or sinusoidal waveforms of a periodic DC current.

— Electro osmosis is another technique which uses less current than iontophoresis. This is being tried for drug with almost no ionic strength and with low viscosity.

— For better permeation of high molecular weight drugs, an ultra-sound technique is being investigated.

c) Osmotic Pumps/Implants/Infusion Pumps

— Multichannel devices e.g. the omniflow (Abbott Laboratories), a four channel pump is being developed to take care of independent and simultaneous delivery of several infusions.

— Efforts to provide versatility in programmable devices. e.g. Open loop systems in which drug delivery will be based on precise biological or pharmaco-kinetic parameters. An external source could be the doctor himself or a computer programme and an element is provided which would calculate the dose required.

— Closed loop systems are being developed for automatic drug dosing upon feedback from biosensors. The biosensors have not yet been developed adequately. An area for closed loop systems applications being studied is control of sodium nitro

prusside infusion rates to lower blood pressure after heart surgery. The IVAC 560 is one such device which is not yet available.

— Research on chrono-biological applications to determine whether circadian rhythms affect the metabolism of drugs, and whether diurnal variations exist in pain perception and narcotic analgesic requirements, are also being carried out.

— Developmental work by different manufacturers to provide several programmable options like optional alarms, drug dose tapering ability, different drugs delivery etc. are going on.

— Other areas of developmental work are remote controlled reprogramming of implants and treatment of implants with antimicrobial agents to provide prevention of post surgical infections.

d) Monoclonal Antibodies

— The main thrust lies in the development of bifunctional monoclonals which have one binding site for the antigen and the other for the drug.

e) Nasal drug delivery

— The basic research efforts are directed to attempt the delivery of peptides and proteins via this route.

f) Microspheres/Nanoparticles

— The developmental work for microspheres relates mainly to trying out different drug formulations especially for cancer therapy.

44. In India major thrust areas of research and development for each of these systems are :

a) Liposomes

— Investigation of suitability of liposomes as vehicles for homing of drug/enzymes to specific sites in the biophase.

— Evaluation of liposomes as models for study of membrane structure and function.

— Targeted drug delivery through liposomes for the treatment of tuberculosis.

— Studies to enhance effectiveness of liposomised sodium stibogluconate against L. donovani infection by giving the drug more than once.

— Use of plant glycosides for drug delivery systems.

— Drug development and selective targeting of anti leishmanial drug.

— Development of recombinant toxins for site specific targeted delivery for diagnosis of infectious diseases.

— Evaluation of virosomes as a potential tool for targeting of drugs.

— Receptor mediated Endocytosis of Macromolecular conjugates in Selective Drug Delivery.

b) Nanoparticles

— Study of nanoparticles as a drug delivery system for primaquine and metronidazole.

c) Transdermal drug delivery

— Development of primaquine transdermal tape. In vitro and in vivo animal studies completed, efficacy studies are in progress.

— Development of centhraquin transdermal tape. In vitro and in vivo animal studies are completed. Toxicity studies are in progress.

— Feasibility studies of transdermal drug delivery of tetracycline sulphate.

— Feasibility studies in developing transdermal films of anti-arthritic drug.

d) Implants

— Cefazoline sustained release bio-degradable microbeads (in vitro and in vivo animal studies).

— Sustained release tablet (SRT) formulation of rifampicin. (In vivo studies)

— Development of sustained release oral dosage from of pyrazinamide. (In vivo studies)

— Optimisation of an indigeneous spheronization technology to develop controlled release products.

— Prolonged Release Liquid Formulation using ion exchange resins.

f) Microencapsulation/microspheres

— Possibilities of controlled and targeted release of drugs are under examination. NCL can undertake work for specific industrial sponsors in microencapsulation technology for drugs and pharmaceuticals.

— In vitro release studies on microcapsules for controlled release of diphtheria toxoid.

g) Polymers in drug delivery

— Novel bases for rectal administration as suppositories. The work relates to improving the properties of bases.

— Study of controlled release of drug from radiation cured polymeric systems.

— A radiation cured transdermal system (852 EHA 15 MNA) has been studied on radiation polymerized beads.

45. Status of Indian Technology and Gaps

Technology levels abroad and in India have been compared with respect to the following aspects :

Raw materials
Machinery
Formulation
Manufacturing technology
Commercialisation

a) Transdermal Systems

World

Well established suppliers for polymers and plasticizers adhesives are available.

Master file applications giving details of polymer manufacture, their stability and toxicity data are filed and available for reference with the Bureau of Drugs or the Bureau of Foods. This information is available for a variety of polymers.

Capability to formulate polymer characteristics as per requirements of individual applications exists.

Machinery for manufacture of either individual product components or the final transdermal product is easily available.

The technological competence for large scale manufacture of the products is well established and available.

A number of products are available and many more being developed.

India

No reputed suppliers available of polymers for use in controlled release applications.

No suppliers are available for product component manufacture.

No data base on polymer characterisation available.

Several laboratories are working on initial formulation studies with different drugs.

Indigenous machinery is not available either for manufacturing individual product components or the final product, on a commercial scale.

The general opinion in industry and research institutes is that technical competence exists but is dormant in our country, because of resource constraints.

No product is yet in the market.

b) Liposomes

World

Raw materials required for liposome manufacture are available readily.

Techniques for making liposomes and incorporating drugs are standardised.

Machinery available for labscale, scale up as also manufacture of liposomal systems.

Several products are on the brink of commercialisation.

India

Raw materials are mostly imported. Indigenous materials being traced for study of neosomes.

Formulation studies are receiving high priority attention in a very few laboratories.

Machinery available for lab scale manufacture, for large scale need to be imported.

No products are as yet marketed.

c) Implants

World

Raw materials are available easily from well established polymer suppliers.

Highly sophisticated programmable systems are being devised.

Machinery and facilities are readily available for lab scale, pilot plant and manufacture.

Manufacturing technology is well developed with several companies manufacturing different types of products.

A lot of products are being marketed ranging from simple systems to highly sophisticated devices. Many more are on the brink of commercialisation.

India

Some polymers are available indigenously for research. However, many polymers are being imported.

Only simple systems are being formulated.

Manufacturing facilities not available in India.

No products marketed on a large scale. A few are being tested on humans.

d) Nasal Delivery Systems

World

Raw materials available easily and so are a variety of formulations.

Well established facilities are available.

One product is marketed. Several others are expected to be launched soon.

e) Microspheres/Nanoparticles

World

A variety of polymers available from well established suppliers.

Many formulations are under study. A few unique formulations are ready to be commercialised.

Facilities for manufacture are not well established.

India

Many polymers need to be imported.

There is no evidence of formulation know-how.

Manufacturing facilities are not established, and no products are marketed.

f) Microencapsulation

World

Raw materials are easily available.

Formulation know-how available but closely guarded.

Well established manufacturing facilities for several techniques, both mechanical and chemical.

A large number of products are available.

India

Polymer availability not satisfactory.

Formulation know-how is present but to a limited extent.

Well established tehnology for mechanical techniques.

A few products are available.

g) Monoclonal Antibodies

World

Monoclonals and polymers are readily available.

The first product is expected to be marketed shortly. Several others are in the pipeline.

India

The hybridoma technology is still not very well established in India.

Facilities for scale up and large scale manufacture not available. No products are available.

h) Osmotic Pump

World

Raw materials are easily available and a few formulations are marketed.

Facilities for large scale production are established.

Technology is well established and several products are available.

India

Some polymers are available, though most medical grade polymers still need to be imported.

Formulations are not available.

Technology is not well established.

No products are available.

i) Ion Exchange Resins

World

Raw materials are available and several formulations have been marketed. Facilities and technology for manufacture also are available.

India

Raw materials, i.e., resins are available. Also a few formulations are available, technology for manufacture and facilities required are also available.

46. Markets

The estimated market for the novel drug delivery systems on a global basis and probable size of the Indian market is presented in Table E.1 to Table E.4.

TABLE : E.1

REGIONWISE MARKET FORECAST (WORLD)

(All Figures in US $ Million)
(at 1990 prices)

Sr. No.	Category	Region									
		World		USA		Western Europe		Japan		Rest of the World	
		1990	1996	1990	1996	1990	1996	1990	1996	1990	1996
1.	Total World Markets	1776	7065	760	2750	592	2050	308	1708	116	557
	(growth % p.a.)	-	26	-	24	-	23	-	32	-	30
2.	% share	100	100	43	39	33	29	17	24	7	8

TABLE : E.2

REGIONWISE SEGMENT WISE MARKET ESTIMATES (WORLD)

(All values in US $ Million)
(at 1990 prices)

Sr. No.		1990					1996				
		Total World	USA	Western Europe	Japan	Rest	Total World	USA	Western Europe	Japan	Rest
1.	Liposomes	Nil	-	-	-	-	860	356	268	184	52
2.	Monoclonal Antibodies	80	40	15	22	3	1150	495	287	276	92
3.	Nasal Drug Delivery Systems	150	15	130	-	5	450	78	207	133	32
4.	Implants	16	10	5	1	-	50	26	13.6	7.5	2.9
5.	Transdermal Systems	510	259	155	64	32	1160	495	302	277	86
6.	Variable Release Products	960	410	264	214	71	3305	1263	938	820	284
	Total	**1716**	**734**	**569**	**301**	**111**	**6975**	**2713**	**2015.6**	**1697.5**	**549.9**

TABLE : E.3

CONTROLLED DRUG DELIVERY MARKET (WORLD) SHARE DISTRIBUTION

(US $ Million)
(at 1990 prices)

	Amb	TD	Nasal	VR	CB	Total Market
1. Value (US $ Million)						
- 1990	16.0	510.0	150.0	960.0	80.0	1776
- 1996	50.0	1160.0	450.0	3305.0	2010.00	7065
2. Percentage share						
- 1990	4.5	27.6	8.2	52.0	4.5	100
- 1993	2.9	18.5	7.3	49.2	20.2	100
- 1996	2.5	16.2	6.2	45.8	28.0	100
3. Annualised average compounded growth rates	22.0	14.0	20.0	24.0	70.0	26

Amb : Ambulatory infusion devices (Implants)
TD : Transdermal Delivery Systems
Nasal : Nasal Delivery Systems
VR : Variable release delivery systems
CB : Carrier based delivery systems

TABLE : E.4

MARKET ESTIMATES FOR CONTROLLED DELIVERY SYSTEMS (INDIA)

Sr. No.	Item	Period (All values in Rs. million) 1990	1996
1.	Total indigenous drug market	33000	77000
2.	% of indigenous drug market to 'Rest' drug market	7.5	7.5
3.	Market for new delivery systems - 'Rest' region	1330	10000
4.	Indigenous market for new delivery systems	100-159 (0.45%)	750-1000 (0.9-1.3%)
5.	Individual systems		
	a) Carrier based Delivery System		
	- Liposomes	-	75-150
	- Mab	-	125-175
	b) Nasal System*	-	40
	c) Implants**	-	5
	d) Trans dermal Systems*	-	115
	e) Variable Release Products*		
	- Microencapsulation - Ion Exchange Resins - Osmotic Pumps - Erodible Implants	93-143	385-500

* Includes only relevant market segments in India.

** Includes only non-erodible implants. Erodable implants are included in Variable Release Products.

47. The evaluation of new systems is based on certain critical factors. These are identified as :

- Market Potential (National Health Programmes)
- Technology development/availability
- Expected development time for commercialisation
- Cost of development
- Opportunity cost
- Product performance reliability

48. Each delivery system is given an overall ranking based on the six criteria indicated above. To arrive at a realistic picture, the long term cost of not developing a particular technology has also been considered. The options are selected taking into account two requirements.

a) the need to avail of new delivery systems both for domestic consumption as also to widen the potential export market.

b) create the knowledge base in these technologies to provide for self sufficiency in the long run.

TABLE : E.5

TECHNOLOGY OPTIONS AND THRUST AREAS

	High Priority	**Medium Priority**	**Low Priority**
Basic Research	- Simple/ - Indigenous Technologies	- Ion exchange systems	
Developmental research for commercialisation including alternative indigenous technologies	- Microcapsules - Implantable vaccines for contraception	-	- Ion exchange systems - Liposomes for teishmaniasu, Leprosy, Malaria
Technology Acquisition	- Implants - Medical grade polymers	- Micro valves for nasal systems	

49. **Recommendations**

The recommendations relate to the following major areas :

- Basic Research
- Developmental research leading to commercialisation
- Scale up
- Technology Transfer
- General

a) Basic Research

The following are identified as thrust areas for basic research.

- Basic research on medical grade polymers.

- Development of indigenous technologies for drug delivery which are not too sophisticated or costly. Indigenous technologies can be developed for many celluloses having good bio-degradability.

b) Developmental Research for Commercialisation

- Drug incorporation and in vivo targeting of liposomes specifically for infectious diseases like leishmaniasis, leprosy, malaria, fungal diseases and vaccines with special emphasis on contraceptive vaccines.

- Government laboratories could be asked to take up the developmental work.

- Development of implantable vaccines for contraception.

- Feasibility studies need to be carried out for each drug identified for developmental work. Some drugs suggested for such work are insulin and oxytocin.

- Medical grade polymer formulation and fabrication.

- Development of alternative indigenous systems especially those which can be manufactured, using available machinery.

c) Scale Up

Laboratory scale production is achieved in our country for several technologies. It is absolutely necessary to set up or expand scaling up facilities as the need may be at various regional centres, to boost commercialisation. The following technologies in particular need attention in scale up :

Microencapsulation
Liposomes for specified applications

d) Technology Transfer

Advances made abroad could be gainfully utilised by importing technology(ies). This is especially true for technologies which have been successfully commercialized, which are easily available and for which indigenous development efforts would entail considerable time and money. The identified areas for transfer are :

Implants

- Progestasert for contraception
- Occusert for glaucoma
- Norplant for contraception
- Dual release vaginal contraceptive ring for contraception

Polymers

New polymers of medical grade which are avilable for sale could be acquired straight away.

Nasal Systems

Micro valves for metering accurate doses of drug for nasal systems could be imported for certain critical applications.

Technology for nanoparticles could be imported rather than developed in the indigenous laboratories.

Technology for 24 hour dosage forms would also be procured from abroad.

50. **General**

- The follow up of laboratory level research work to commercialisation was largely a matter of individual initiative. It is recommended that industry - academic interaction be formalised. Specific strategies are suggested for more fruitful academic - industry interaction. These are :

  - Project selection needs to be done with the involvement of industry.
  - There must be a focused approach to commercialisation.
  - Greater financial support should be enlisted from industry.

- Since the successful development of advanced drug delivery systems technologies is dependent on multi-disciplinary inputs, an evaluation of the type and number of skilled personnel required for the purpose needs to be undertaken.

- It is desirable to organise workshops periodically. Besides, a newsletter specifically for controlled release technologies could be published. This would create awareness among Indian research organisations and avoid duplication of work.

- Immediate attention must be paid to the regulatory mechanism relating to the new delivery technologies. Quite a few regulations have been enacted abroad for these new systems. These need to be analysed for their possible incorporation into the Indian legal code. It may not be appropriate to wait for the systems to develop in India before initiating efforts in this direction.

- Standards for medical grade polymer characteristics need to be laid out.

- New drug delivery systems should be introduced in India to ensure efficacy, safety and cost effectiveness.

51. **Review**

A yearly review to monitor the level of technology development is recommended. The review should aim to :

- identify new developments, if any,
- monitor achievements of research and developmental objectives,
- identify new thrust areas and
- identify scale up needs of fruitful basic research.

The purpose of the review would help to reset priorities in research and development in the light of new developments at different points in time.