Novel Drug Delivery System: Current and Future Scenario

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Abstract
Abstract: In present review we are presenting that the drug delivery system have revolutionized and rather than using conventional form we are using novel drug delivery system because it has site specific delivery, increased efficacy. By this method drug could be delivered efficiently with less side effects and more compliance. It helps to localize drug where it is needed without affecting other tissues. By novel drug delivery system frequency of doses are also decreased and it also decrease the fluctuation in circulating drug levels.

Keywords: Novel drug delivery system, drug delivery, efficacy, conventional, compliance

INTRODUCTION

Novel drug delivery systems (NDDS) 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 (1).

Novel Drug delivery is often approached via a drug’s chemical formulation, but it may also involve medical devices or drug-device combination products. Drug delivery is a concept heavily integrated with dosage form and route of administration. These systems can be characterised as controlled drug release systems and targeted drug delivery systems (1).

The therapeutic benefits of these new systems include:

- Increased efficacy of the drug
- Site specific delivery
- Decreased toxicity/side effects
- Increased convenience
- Viable treatments for previously incurable diseases
- Potential for prophylactic applications
- Better patient compliance.

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 delivery systems is deduced (2) as follows:

1. Carrier based Drug Delivery System:
   a) Liposomes
   b) Nanoparticles
   c) Microspheres
   d) Monoclonal antibodies
   e) Niosomes
2. Transdermal Drug Delivery Systems:
   a) Sonophoresis
   b) Osmotic pump
   c) Microencapsulation

1. Carrier based drug delivery system

A. Liposomes

Liposomes are a form of vesicles that consist either of many, few or just one phospholipid encapsulated. They are simply vesicles or ‘bags’ in which an aqueous volume is entirely enclosed by a membrane composed of lipid (fat) molecules, usually phospholipids. These vesicles can encapsulate water-soluble drugs in their aqueous spaces and lipid soluble drug within the membrane itself. The unique property of liposomes, namely their versatile, biodegradable, hypoallergenic nature, along with their similarity to biological membranes are the important factors in the continued efforts to develop liposomal drug delivery forms.

Phospholipids are amphipathic molecules (having affinity for both aqueous and polar moieties) as they have a hydrophobic tail is composed of two fatty acids containing 10-24 carbon atoms and 0-6 double bonds in each chain. In aqueous medium the phospholipid molecules are oriented in such a way that the polar portion of the molecule remains in contact with the polar environment and at the same shields the non-polar part. They align themselves closely in planer bilayer sheets to minimize the interaction between the bulky aqueous phase and long hydrocarbon fatty acyl chains. This alignment requires input of sufficient amount of energy (in the form of shaking, sonication, homogenization, heating, etc). Interactions are completely eliminated when these sheets fold over themselves to form closed, sealed and continuous bilayer vesicles.

Applications of liposomes

- Liposomes as drug / protein delivery vehicles,
- Liposomes are administrated orally, parenteral and topically as well as used in cosmetic and hair technologies.
- Liposomes in parasitic diseases and infections-conventional liposomes are digested by phagocytic cells in the body after intravenous administration, they are ideal vehicles for the targeting of drug molecules into these macrophages
- Liposomes in anticancer therapy- Many different liposome formulations of various anticancer agents were shown to be less toxic than the free drug
- Small liposomes composed of lipids with long and saturated hydrocarbon chains in mixtures with cholesterol were shown to accumulate at the sites of inflammations. They can also deliver anti-inflammatory drugs. Liposomes containing corticosteroids were injected also directly into the sites of inflammations, especially into arthritic joints where they acted as a sustained release system.

Advantages of liposome

- Increased efficacy and therapeutic index
- Increased stability via encapsulation
- Reduction in toxicity of the encapsulated agent,
- Improved pharmacokinetic effects
- Can be made into variety of sizes.

Mechanism of liposome
TABLE 1: EXAMPLES OF PATENTS FOR LIPOSOMES

<table>
<thead>
<tr>
<th>Patent No</th>
<th>Assignee/Inventors</th>
<th>Filed On</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>US20070104777</td>
<td>Lau; John R; et al.</td>
<td>Dec. 21, 2006</td>
<td>Targeted Liposomal Drug Delivery System</td>
</tr>
<tr>
<td>US20070014845</td>
<td>Zhang; Yuanpeng; et al.</td>
<td>June 30, 2006</td>
<td>Liposomal Delivery Vehicle For Hydrophobic Drugs</td>
</tr>
<tr>
<td>US20020182248</td>
<td>Daiichi Pharma Co. Ltd.</td>
<td>Aug. 29, 2001</td>
<td>Liposomes And Liposomal Dispersions</td>
</tr>
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</table>

TABLE 2: SOME COMMERCIALLY AVAILABLE MARKETED LIPOSOMAL BASED PRODUCTS (12)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>AmBisome</td>
<td>Amphotericin B</td>
<td>NeXstar Pharmaceuticals</td>
<td>Systemic fungal infections</td>
</tr>
<tr>
<td>Abelcet</td>
<td>Amphotericin B</td>
<td>The Liposome Company</td>
<td>Systemic fungal infections</td>
</tr>
<tr>
<td>Amphotec</td>
<td>Amphotericin B</td>
<td>Sequus Pharmaceuticals</td>
<td>Systemic fungal infections</td>
</tr>
<tr>
<td>Doxil</td>
<td>Doxorubicin</td>
<td>Sequus Pharmaceuticals</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>DaunoXome</td>
<td>Daunorubicin</td>
<td>NeXstar Pharmaceuticals</td>
<td>Kaposi’s sarcoma</td>
</tr>
</tbody>
</table>

b. Nanoparticles

Nanoparticles (including nanospheres and nanocapsules of size 10-200nm) are in the solid state and are either amorphous or crystalline. They are able to adsorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the controlled release of drugs, in targeting particular organ/or tissue, as carriers of DNA in gene therapy, and in their abilities to deliver proteins peptides and genes through oral route (13). There are mainly 2 type of nanoparticles

i. **Nanospheres** are solid core spherical particulates, which contain drug embedded within the matrix or adsorbed onto the
surface (Matrix type). Nanocapsules are known to have two differentiated structures, a solid polymeric shell and a liquid—aqueous or non-core where the drug is deposited.

ii. **Nanocapsules** are vesicular system in which drug is essentially encapsulated within the central core surrounded by a polymeric sheath (Reservoir type). Nanospheres are compact solid polymeric matrixes where the drug is either placed in the center or dispersed over the surface.

### Advantages of nanosizing of drugs

- Increase surface area
- Enhances solubility, and
- Increase rate of dissolution
- Increase oral bioavailability
- Rapid onset of therapeutic action
- Decreased dose
- Decreased patient-to-patient variability
- Target specificity and limited side effects

### Mechanism of delivery

There are two ways through which nanostructures deliver drugs: passive and self-delivery. In the former, drugs are incorporated in the inner cavity of the structure mainly via the hydrophobic effect. When the nanostructure materials are targeted to particular sites, the intended amount of the drug is released because of the low content of the drugs which is encapsulated in a hydrophobic environment \(^{(16)}\). Conversely, in the latter; the drugs intended for release are directly conjugated to the carrier nanostructure material for easy delivery. In this approach, the timing of release is crucial as the drug will not reach the target site and it dissociates from the carrier very quickly, and conversely, its bioactivity and efficacy will be decreased if it is released from its Nano carrier system at the right time. \(^{(16)}\)

By using various types of nanoparticles for the delivery of the accurate amount of drug to the affected cells such as the cancer/tumour cells, without disturbing the physiology of the normal cells, the application of nanomedicine and nano-drug delivery system is certainly the trend that will remain to be the future arena of research and development for decades to come.

### Application of Nanoparticles \(^{(3)}\)

- The selection of nanoparticles for achieving efficient contrast for biological and cell imaging applications as well as for photo thermal therapeutic applications is based on the optical properties of nanoparticles.
- Polyethylene oxide (PEO) and polylactic acid (PLA) nanoparticles have been revealed as very promising system for the intravenous administration of drugs.
- Superparamagnetic iron oxide nanoparticles with appropriate surface chemistry can be used for numerous in vivo applications such as MRI contrast enhancement, tissue repair, and immunoassay, detoxification of biological fluids hyperthermia, drugs delivery and cell separation.
- Semiconductor and metallic NPs have immense potential for cancer diagnosis.
- Nanoparticles is also effectively employed to inhibit the tumor growth. The multihydroxylated nanoparticle showed antineoplastic activity with good efficiency and lower toxicity.

### TABLE 3: EXAMPLES OF PATENTS FOR NANOPARTICLES

<table>
<thead>
<tr>
<th>Patent No</th>
<th>Assignee/Inventors</th>
<th>Filed On</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>US20100278920 (^{18})</td>
<td>University of South Florida, Tampa, FL</td>
<td>April 26, 2010</td>
<td>Polyacrylate Nanoparticle Drug Delivery</td>
</tr>
<tr>
<td>US20090155374 (^{19})</td>
<td>Sung; Hsing-Wen; et al.</td>
<td>January 15, 2009</td>
<td>Nanoparticle For Protein Drug Delivery</td>
</tr>
</tbody>
</table>
Microspheres

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 μm. (22) Materials used for preparing Microspheres are polymers. Microsphere are spherical in shape so, therapeutic efficacy of microspheres containing drug depends upon their characteristics that can be altered in required terms by altering materials, methods, polymers or technique used. Microspheres have wide range of applications because of controlled and sustained release. (24)

Advantages of microspheres (56)

- Microspheres provide prolonged and constant therapeutic effect.
- Microspheres reduce the dosing frequency and therefore improve the patient compliance.
- They protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.
- Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
- Microspheres provide freedom from drug and recipients incompatibilities especially with buffer.

Mechanism of microsphere drug delivery

Engineered polymer microspheres made of biologically erodible polymers, which display strong adhesive interactions with gastrointestinal mucus and cellular linings, can traverse both the mucosal absorptive epithelium and the follicle-associated epithelium covering the lymphoid tissue of Peyer's patches. The polymers maintain contact with intestinal epithelium for extended periods of time and actually penetrate it, through and between cells. Thus, once loaded with compounds of pharmacological interest, the microspheres could be developed as delivery systems to transfer biologically active molecules to the circulation. We show that these microspheres increase the absorption of three model substances of widely different molecular size: dicumarol, insulin and plasmid DNA (23)

Applications of microspheres (56)

- Microspheres in vaccine delivery
- Targeting (i.e. site specific drug delivery) using micro particulate carrier.
- Monoclonal antibodies facilitated microspheres targeting
- Topical porous microspheres- These microspheres having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders.
- Imaging - Various cells, cell lines, tissues and organs can be imaged using radio labelled microspheres.
TABLE 4: EXAMPLES OF PATENTS FOR MICROSPHERES

<table>
<thead>
<tr>
<th>Patent No</th>
<th>Assignee/Inventors</th>
<th>Filed On</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>US20110151004</td>
<td>Wu; Daging; et al.</td>
<td>January 27, 2011</td>
<td>Injectable Microspheres</td>
</tr>
<tr>
<td>US20090318569</td>
<td>S K Chemicals Co. LTD. Gyeonggi-di, KR</td>
<td>August 31, 2007</td>
<td>Method For Producing Microspheres Loaded With Drugs &amp; Microspheres Produced Thereby</td>
</tr>
</tbody>
</table>

**d. Niosomes**

Niosomes (non-ionic surfactant vesicles) obtained on hydration are microscopic lamellar structures formed upon combining non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class with cholesterol.

The non-ionic surfactants form a closed bilayer vesicle in aqueous media based on its amphiphilic nature using some energy for instance heat, physical agitation to form this structure (27) In the bilayer structure, hydrophobic parts are oriented away from the aqueous solvent, whereas the hydrophilic heads remain in contact with the aqueous solvent. The properties of the vesicles can be changed by varying the composition of the vesicles, size, lamellarity, tapped volume, surface charge and concentration. Various forces act inside the vesicle, eg, van der Waals forces among surfactant molecules, repulsive forces emerging from the electrostatic interactions among charged groups of surfactant molecules, entropic repulsive forces of the head groups of surfactants, short-acting repulsive forces, etc. These forces are responsible for maintaining the vesicular structure of niosomes. But, the stability of niosomes are affected by type of surfactant, nature of encapsulated drug, storage temperature, detergents, use of membrane spanning lipids, the interfacial polymerisation of surfactant monomers in situ, inclusion of charged molecule (28).

Niosomes behave in vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability (29). As with liposomes, the properties of niosomes depend on the composition of the bilayer as well as method of their production. It is reported that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation, and thus entrapment efficiency (30).

**Advantages of Niosomes** (57)

- Targeted drug delivery can be achieved using niosomes the drug is delivered directly to the
body part where the therapeutic effect is required.

- Reduced dose is required to achieve the desired effect. Subsequent decrease in the side effects

- Niosomes are amphiphillic i.e. both hydrophilic and lipophilic in nature and can accommodate a large number of drugs with a wide range of solubilities.

- Improve the oral bioavailability of poorly soluble drugs

- The bilayers of the niosomes protect the enclosed Active pharmaceutical ingredient from the various factors present both inside and outside the body

**Mechanism of delivery**

Several mechanisms have been proposed, including: alteration of the barrier function of the stratum corneum, as a result of reversible perturbation of lipid organization; reduction of transepidermal water loss, which increases hydration of the stratum corneum and loosens its closely-packed cellular structure; and adsorption and/or fusion of niosomes on the surface of the skin, as revealed by freeze fracture electron microscopy and small angle X-ray scattering, leading to a high thermodynamic activity gradient of drug at the interface, which is the driving force for permeation of a drug. Adsorption of niosomes onto the cell surface occurs with little or no internalization of either aqueous or lipid components; it may take place either as a result of attracting physical forces or as a result of binding by specific receptors to ligands on the vesicle membrane and transfer of drug directly from vesicles to the skin. On the other hand, niosomes may fuse with the cell membrane, resulting in complete mixing of the niosomal contents with the cytoplasm. Finally, niosomes may be engulfed by the cell (endocytosis), with lysozymes present in the cytoplasm degrading or digesting the membranous structure of the niosome, thereby releasing the entrapped material into the medium. (58,59) As it is well known, the structure of niosomes is similar to liposome in structure; thus, the surface-functionalized liposome methods can be used to functionalize surface niosomes. Two types of active targeting strategies are widely used for drug targeting to the desired organ/tissue. One of the strategies was that ligands for active targeting have been attached directly to the cholesterol or that ligand was devoted to the distal end of PEG chains in PEGylated niosomes. The other one, the traditional niosomes formulation method, was incorporation of the cholesterol-PEG-ligand conjugate, into the niosomes formulation step. Preparation of PEGylated niosomes conjugated with each ligand (60,61)

**Applications of Niosomes**

- Protein and Peptide Delivery- Niosomes were applied to effectively keep the peptides from gastrointestinal collapse.

- Transdermal Delivery

- Vaccine and Antigen Delivery- Some surfactants have immunostimulatory possessions and have been applied as vaccine adjuvants. The adjuvanticity of niosomes primed from 1-monopalmitoyl glycerol: cholesterol: dicetyl phosphate (5:4:1) was established in mice that administered a subcutaneous vaccination of ovalbumin or a synthetic peptide comprising a known T-cell epitope and bovine serum albumin.

**TABLE 5: EXAMPLES OF PATENTS FOR NIOSOMAL DRUG DELIVERY**

<table>
<thead>
<tr>
<th>Patent No</th>
<th>Assignee/Inventors</th>
<th>Filed On</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>US20100068264</td>
<td>University of South Florida, Tampa, FL</td>
<td>November 20, 2009</td>
<td>Niosome Hydrogel Drug delivery Systems</td>
</tr>
</tbody>
</table>

**e. Resealed Erythrocytes as Drug Carriers**

Erythrocytes, the most abundant cells in the human body, have potential carrier capabilities for the delivery of drugs. Erythrocytes are biocompatible, biodegradable, possess very long circulation half-lives and can be loaded
with a variety of chemically and biologically active compounds using various chemical and physical methods Immature RBC are called “RETICULOCYTES.”

Erythrocyte (erythro = red and cytes = cell) is red cell. Erythrocyte is biconcave discs, anucleate Filled with hemoglobin (Hb), a protein that functions in gas transport.

**Healthy adult male=4.5millions/µml**

**Healthy adult female=4.8million/ µml**

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**Drug loaded Erythrocytes**

This is one of the growing and potential systems for delivery of drugs and enzymes. Erythrocytes are biocompatible, bio-degradable, possess long circulation half-life and can be loaded with variety of biologically active substances.

**Advantages of Resealed Erythrocytes as Drug Carriers**

- Their biocompatibility, particularly when autologous cells are used, hence no possibility of triggered immune response.
- Their biodegradability with no generation of toxic products.
- The considerably uniform size and shape of the carrier.
- Relatively inert intracellular environment.
- Prevention of degradation of the loaded drug from inactivation by endogenous chemicals.

**Mechanism of delivery**

Carrier erythrocytes are prepared by collecting blood sample from the organism of interest and separating erythrocytes from the plasma. By using various physical and chemical methods cells are broken and drug is entrapped into erythrocytes, finally they are resealed and resultant carriers are then called as “resealed erythrocytes”. Upon reinjection the drug loaded erythrocytes serve as slow circulation depots targets the drug to reticulo-endothelial system .Erythrocytes have been used as circulating depots for the sustained delivery of antineoplastic,antiparasitics, veterinary antiamoebics, vitamins, steroid, antibiotics, and cardiovascular drugs. The various mechanisms proposed for drug release include

- Passive diffusion
- Specialized membrane associated carrier transport phagocytosis of resealed cells by macrophages of RES, subsequent accumulation of drug into the macrophage interior, followed by slow release.
- Accumulation of erythrocytes in lymph nodes upon subcutaneous administration followed by haemolysis to release the drug

**Applications of Resealed Erythrocyte**

- Slow Drug Release- Erythrocytes have been used as circulating depots for the sustained delivery of antineoplastic, antiparasitics, veterinary, anti-amoebics, vitamins, steroids, antibiotics and cardiovascular drugs
- Drug Targeting- Surface-modified erythrocytes are used to target organs of mononuclear phagocytic system/ reticulo
endothelial system because the changes in the membrane are recognized by macrophages.

- Targeting Reticulo Endothelial System (RES) Organs- Damaged erythrocytes are rapidly cleared from circulation by phagocytic Kupffer cells in liver and spleen. Resealed erythrocytes, by modifying their membranes, can therefore be used to target the liver and spleen

### TABLE 6: EXAMPLES OF PATENTS FOR ERYTHROCYTE BASED DRUG DELIVERY

<table>
<thead>
<tr>
<th>Patent No</th>
<th>Assignee/Inventors</th>
<th>Filed On</th>
<th>Title</th>
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<tbody>
<tr>
<td>US20120141540</td>
<td>Magnani; Mauro et al.</td>
<td>June 7, 2010</td>
<td>Drug Delivery System</td>
</tr>
<tr>
<td>US20110262415</td>
<td>Grimald; Settimio et al.</td>
<td>December 18, 2009</td>
<td>Erythrocyte-based Delivery System method of preparation &amp; uses thereof</td>
</tr>
</tbody>
</table>

1. **Transdermal Drug Delivery System**

Transdermal drug delivery is defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe

The positive features of delivery drugs across the skin to achieve systemic effects are:

- Avoidance of first pass metabolism
- Avoidance of gastro intestinal incompatibility
- Predictable and extended duration of activity
- Improving physiological and pharmacological response
- Termination of therapy is easy at any point of time
- Greater patient compliance due to elimination of multiple dosing profile
- Provide suitability for self-administration
- Enhance therapeutic efficacy

### TABLE 7: SOME COMMERCIALLY AVAILABLE MARKETED TRANSDERMAL SYSTEMS- [10]

<table>
<thead>
<tr>
<th>Product name</th>
<th>Chemical</th>
<th>Developer/Marketer</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alora</td>
<td>Estradiol</td>
<td>TheraTech/Proctor and Gamble</td>
<td>Postmenopausal syndrome</td>
</tr>
<tr>
<td>Catapres-TTS</td>
<td>Clonidine</td>
<td>Alza/Boehinger Ingelheim</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Deponit</td>
<td>Nitroglycerin</td>
<td>Schwarz-Pharma</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Minitran</td>
<td>Nitroglycerin</td>
<td>3M Pharmaceuticals</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Transderm-Scop</td>
<td>Scopolamine</td>
<td>Alza/Novartis</td>
<td>Motion sickness</td>
</tr>
</tbody>
</table>
Motion sickness | Estradiol | Noven Pharmaceuticals, Inc./Novartis | Postmenopausal syndrome

a. Sonophoresis

It is a process that exponentially increases the absorption of topical compounds (transdermal delivery) into the epidermis, dermis and skin appendages by ultrasonic energy. Sonophoresis is a localized, non-invasive, convenient and rapid method of delivering low molecular weight drugs as well as macromolecules into the skin.

Advantages of Sonophoresis

- Improved therapeutic efficacy by bypassing hepatic first-pass metabolism
- Help to avoid the inconvenience associated with parenteral drug delivery.
- It reduces the chance of dosing variation by providing programmed delivery of the drug.
- Sonophoresis also provides a therapeutic regimen that improves patient compliance
- It permits the use of a drug with a short biological half-life, since the drug is delivered to the target area without the need to recirculate in the blood.

Mechanism of drug delivery

Sonophoresis is considered to enhance drug delivery through a combination of thermal, chemical and mechanical alterations within the skin tissue. Sonophoresis uses ultrasound as a physical enhancer for systemic transdermal drug delivery (TDD). Low-frequency sonophoresis in the range of 20–100 kHz has been demonstrated to enhance the transdermal delivery of various low-molecular weight drugs and high-molecular weight proteins across the human skin. The bioeffects of ultrasound in tissues are mediated by thermal and nonthermal effects. Ultrasound-induced skin heating causes fluidization of stratum corneum (SC) lipids, facilitating transdermal permeation of molecules. Cavitation is the nonthermal effect of ultrasound and is believed to be the main mechanism of enhanced transdermal delivery in sonophoresis, by creating shock waves and acoustic micro-jets on the SC surface. Among the three different percutaneous penetration pathways including the intercellular, transcellular, and follicular penetration routes, both intercellular and transcellular pathways are primarily created and facilitated during ultrasound exposure for TDD. Sonophoresis may act synergistically with various other physical and chemical penetration enhancement methods in promoting transdermal drug delivery.
delivery. The ratio of frequency and peak rarefractional pressure, the distance between the surface of transducer and the skin surface, and the properties of the coupling medium such as the viscosity, density, acoustic impedance and the composition of the gas and liquid phases are factors affecting the efficacy of TDD using ultrasound\(^{(65)}\). Ultrasound mediated transdermal delivery of key compounds was first reported in 1954 by Fellinger and Schmid through successful treatment of digital polyarthritis using hydrocortisone ointment in combination with ultrasound. Sonophoresis is widely used in hospitals to deliver drugs through the skin. Pharmacists compound the drugs by mixing them with a coupling agent (gel, cream, ointment) that transfers ultrasonic energy from the ultrasound transducer to the skin. Thus, Application of ultrasound to the skin increases its permeability (sonophoresis) and enables the delivery of various substances into and through the the skin. Sonophoresis is also used in Physical Therapy. Reverse ultrasound technology may also be used for the extraction of interstitial fluid samples for analysis. So, In addition to its effects in delivering compounds into the skin, sonophoresis is being investigated as a way of drawing compounds such as glucose out of the skin.\(^{(43,44)}\)

**Applications of Sonophoresis**

- Transdermal heparin delivery
- Transdermal glucose monitoring
- Delivery of acetyl cholinesterase inhibitors for the treatment of Alzheimer's disease
- Treatment of bone diseases and Peyronie's
- Dermal exposure assessment

**b. Osmotically Controlled Drug Delivery Systems**

Osmotic pressure is used as driving force for these systems to release the drug in controlled manner. Osmotic drug delivery technique is the most interesting and widely acceptable among all other technologies used for the same. Intensive research has been carried out on osmotic systems and several patents are also published. Development of osmotic drug delivery systems was pioneered by Alza and it holds major number of the patents analysed and also markets several products based on osmotic principle. These systems can be used for both route of administration i.e. oral and parenterals. Oral osmotic systems are known as gastro-intestinal therapeutic systems (GITS). Parenteral osmotic drug delivery includes implantable pumps\(^{(45)}\).

**Advantages of Osmotic Systems**

- They typically give a zero-order release profile after an initial lag.
- Drug release is independent of gastric pH and hydrodynamic condition.
- Higher release rates are possible with osmotic systems compared with conventional diffusion controlled drug delivery systems.
- The Rationale for this approach is that the presence of water in git is relatively constant, at least in terms of the amount required for
activation and controlling osmotically base technologies.

- The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.

**Mechanism of delivery**

Osmotically controlled drug delivery systems utilize the principles of osmotic pressure for the controlled delivery of active agents. Osmotic pressure is a colligative property, which is dependent on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solvent and solute system show an osmotic pressure proportionate to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic drug delivery system. This results a constant zero order release rate of drug. The rate of drug release from osmotic pump depends on the osmotic pressure of the core and the drug solubility; hence, these systems are suitable for delivery of drugs with moderate water solubility (67). The release rate of drugs from these systems is independent of the physiological factors of the gastrointestinal (GI) tract to a large extent (47).

**Applications of Osmotically controlled drug delivery system**

- Theophylline, aspirin, carbamazepine and nifedipine - The core consists of an active ingredient that is sparingly soluble in water, a hydrophilic polymeric swelling agent composed of a mixture of a vinylpyrrolidone–vinyl acetate copolymer with an ethylene oxide homopolymer, and a water-soluble substance for inducing osmosis. This mixture has the surprising advantage that pressure produced during swelling does not cause the system to rupture and that the swelling speed is uniform, which allows almost constant amounts of active ingredient to be released from the system.
- Nicotine delivery by an oral osmotic device.
- Osmotic device that deliver drug below saturation are useful for dispensing drugs that are irritants to mucosal and GIT tissue such as potassium chloride, aspirin, and indomethacin.

**TABLE 8: Some Commercially Available Marketed Oral Osmotic Systems**-[46]

<table>
<thead>
<tr>
<th>Product name</th>
<th>Chemical</th>
<th>Developer/Marketer</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpress LP</td>
<td>Prazosin</td>
<td>Alsa/Pfizer (France)</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Calan SR</td>
<td>Verapamil</td>
<td>Alza/GD Searle &amp; Co.</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Covera HS</td>
<td>Verapamil</td>
<td>Alza/G.D. Searle</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Efidar/24</td>
<td>Pseudoephedrine</td>
<td>Alza/Novartis</td>
<td>Cold medication.</td>
</tr>
<tr>
<td>Glucotrol XL</td>
<td>Glipizide</td>
<td>Alza/Pfizer</td>
<td>Anti-diabetic</td>
</tr>
<tr>
<td>Minipress XL</td>
<td>Prazosin</td>
<td>Alza/Pfizer</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Volmax</td>
<td>Albuterol</td>
<td>Alza/Muro Pharmaceuticals</td>
<td>Bronchospasm</td>
</tr>
</tbody>
</table>

c. **Microencapsulation**

Microencapsulation is the process in which small droplets or particles of liquid or solid material are surrounded or coated by a continuous film of polymeric materials. Microencapsulation process helps for converting the liquids to solids, changing the colloidal and surface properties, providing environmental protection and controlling the release characteristics of different coated materials. Some of these properties can be achieved by macropackaging techniques but in microencapsulation the small coated particles are used to make a wide variety of dosage forms and has not been feasible (49).
Advantages of microencapsulation

- An effective protection of the encapsulated active agent against (e.g. enzymatic) degradation
- The possibility to accurately control the release rate of the incorporated drug over periods of hours to months
- An easy administration (compared to alternative parenteral controlled release dosage forms, such as macro-sized implants)
- Desired, pre-programmed drug release profiles can be provided which match the therapeutic needs of the patient.

Mechanism of drug delivery

Major mechanisms of drug release from microcapsules include diffusion, dissolution, osmosis and erosion.

- Diffusion- Diffusion is the most commonly involved mechanism wherein the dissolution fluid penetrates the shell, dissolves the core and leak out through the interstitial channels or pores. Thus, the overall release depends on, (a) the rate at which dissolution fluid penetrates the wall of microcapsules, (b) the rate at which drug dissolves in the dissolution fluid, and (c) the rate at which the dissolved drug leak out and disperse from the surface.\(^{(50)}\)

- Dissolution- Dissolution rate of polymer coat determines the release rate of drug from the microcapsule when the coat is soluble in the dissolution fluid. Thickness of coat and its solubility in the dissolution fluid influence the release rate.\(^{(51)}\)

- Osmosis- The polymer coat of microcapsule acts as semi permeable membrane and allows the creation of an osmotic pressure difference between the inside and the outside of the microcapsule and drives drug solution out of the microcapsule through small pores in the coat.\(^{(52)}\)

- Erosion- Erosion of coat due to pH and/or enzymatic hydrolysis causes drug release with certain coat materials like glyceryl monostearate, bee’s wax and stearyl alcohol.\(^{(53)}\)

Applications of microencapsulation\(^{(68)}\)

- Prolonged release dosage forms. The microencapsulated drug can be administered, as microencapsulation is perhaps most useful for the preparation of tablets, capsules or parenteral dosage forms.

- Microencapsulation can be used to prepare enteric-coated dosage forms, so that the medicament will be selectively absorbed in the intestine rather than the stomach.

- It can be used to mask the taste of bitter drugs.

- From the mechanical point of view, microencapsulation has been used to aid in the addition of oily medicines to tableted dosage forms. This has been used to overcome problems inherent in producing tablets from otherwise tacky granulations and in direct compression to tablets.

- It has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat. Microencapsulation does not yet provide a perfect barrier for materials, which degrade in the presence of oxygen, moisture or heat, however a great degree of protection against these elements can be provided.

Recent advances in NDDS

- By using various types of nanoparticles for the delivery of the accurate amount of drug to the affected cells such as the cancer/tumour cells, without disturbing the physiology of the normal cells, the application of nanomedicine and nano-drug delivery system is certainly the trend that will remain to be the future arena of research and development for decades to come.
• An injectable slow-release partial opioid agonist or opioid antagonist in a poly (D, L-lactide) microspheres with a small amount of residual ethyl acetate was provided by Tice et al. and Markland et al.\(^{(69)}\) where an o/w emulsion is first prepared from an organic phase made of ethyl acetate and an aqueous phase comprised an aqueous ethyl acetate containing solution of polyvinyl alcohol.

• Once-daily formulations based on osmotic principles are playing an increasingly important role in improving patient compliance. Therefore, most of the currently marketed products are based on drugs used in long-term therapies for diabetes, hypertension, attention-deficit disorder, and other chronic disease states.

• Evolution of niosomes is represented by proniosomes or “dry niosomes”, which have been proposed as niosomal formulations; these need to be hydrated before use, and hydration results in formation of an aqueous niosomal dispersion. Proniosomes decrease the aggregation, leakage, and fusion problems associated with traditional niosomes and offer a versatile transdermal drug delivery system.

• Currently used ligands for liposome targeting include antibodies and their fragments, folate, transferrin and certain peptides. Liposomes can be made stimuli-sensitive — that is, capable of releasing their contents at abnormal pH values and temperatures characteristic of pathological sites, such as cancers, in the body.

CONCLUSION

Novel Drug delivery System (NDDS) NDDS is a combination of advance technique and new dosage forms which are far better than conventional dosage forms. Advantages of Novel Drug Delivery System are: Optimum dose at the right time and right location, Efficient use of expensive drugs, excipients and reduction in production cost. Beneficial to patients, better therapy, improved comfort and standard of living. Novel drug delivery system not only reduces the repeated administration to overcome non-compliance, but also helps to increase the therapeutice value by reducing toxicity and increasing the bioavailability, and so on basic modes of novel drug delivery systems are: Targeted Drug Delivery System, Controlled Drug Delivery System etc. Novel Drug delivery & drug targeting is new techniques which is used in pharmaceutical science. Like targeting drug delivery, vaccine delivery, Gene therapy, commercial development of novel carries (liposomes)

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