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DEVELOPMENT AND CHRACTERIZATION OF SELF ASSEMBELED NANOPARTICLES: A REVIEW

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ABSTRACT

Various types of lipid based vesicular systems have been developed in controlled and targeted drug delivery. Self assembled nanoparticles (SAN) has advantages over traditional colloidal vesicular systems and also avoids some of their major disadvantages. SAN made of solid lipids are submicron colloidal carriers (50-1000nm). These consist of a solid hydrophobic core having a monolayer of phospholipid coating. The solid core contains drug dissolved or dispersed in the solid high melting fat matrix. The hydrophobic chains of phospholipids are embedded in the fat matrix. The outstanding characteristic of SAN is that they are nearly or wholly composed of ampiphillic prodrug. Serious drawbacks of the drugs could be effectively circumvented by covalent linkage of the drug to fatty acids. These lipidic prodrugs, if provided with some surface active property, tend to form supramolecular assemblages in aqueous media. They provide an efficient method for delivery of drugs directly to the targeted site, leading to reduction of drug toxicity with no adverse effects and also reduces the cost of therapy by imparting better biopharmaceutical properties to the drug, resulting in improved bioavailability, especially in case of poorly soluble drugs. This articles reflects the various types of drug carrier systems and various method of preparation of self assembeled nanoparticles and also characterized the SAN for different attributes.

INTRODUCTION: An ideal controlled drug delivery system should posses' two characteristics: the ability to reach the therapeutic index target and the ability to release the active pharmaceutical ingredient in a controlled manner [1]. Solid lipid nanoparticles (SLN), has advantages over the traditional colloidal systems and avoids some of their major disadvantages [2]. Drug targeting will ensure high therapeutic efficacy. But maybe even more important it will reduce side effects [3]. Various systems including liposomes, niosomes microspheres, virosomes, microemulsion, transfero-somes, monoclonal antibodies, erythrocytes have demonstrated their potential for application in effective drug delivery.

The vesicular system (liposomes, niosomes & Transferosomes) has more advantageous in controlled drug delivery [4]. These vesicles were first reported in 1965 by Bingham, and were given the name "Bingham bodies" which play a major role in modelling biological membranes, and in the transport and targeting of active agents [5].

Vesicular drug delivery system has some of the advantages like:

- Prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity if

selective uptake can be achieved due to the delivery of drug directly to the site of infection.

- Improves the bioavailability especially in the case of poorly soluble drugs.
- Both hydrophilic and lipophilic drugs can be incorporated.
- Delays elimination of rapidly metabolizable drugs and thus function as sustained release systems [6].

But these conventional vesicular system have some problems such as particulars (liposomes nanoparticles, microemulsions) and externally triggered (e.g. temperature, pH, or magnetic sensitive) carriers load drugs passively, which may lead to low drug loading efficiency and drug leakage in preparation, preservation and transport *in vivo* [7]. Some vesicular system associated problems are mentioned in table

Problems Associated With Conventional Vesicular System [8]:

Vesicular system	Problems
Liposomes	• Degradation by oxidation, sedimentation, leaching of drug • Lack of purity of the natural phospholipids • Expensive to prepare
Transferosomes	• Chemical instability because of their predisposition to oxidative degradation. • Lack of purity of the natural phospholipids. • Expensive to prepare
Niosomes	• Aqueous suspension may exhibit aggregation, fusion, leaching or hydrolysis of entrapped drugs, thus limiting the shelf life • Time consuming preparation • Requires specialized equipment. • Inefficient particularly if smaller quantities are required for a particular application or dose.

A potential solution for these problems is the use of self assembled nanoparticles (SAN) i.e., the pharmacosomes [9]. The outstanding characteristic of SAN over common nanoparticles or liposomes is that they are nearly wholly composed of amphiphilic prodrugs, so that high drug-loaded amount and very low drug leakage are archived easily. In addition, the amphiphilic monomers of SAN would like to permeate biomembranes of targets provided that SAN were decomposed on target surfaces. Pharmacosomes can be considered as one of SAN based on the various theories [10]. Pharmacosomes are like a panacea for most of the problems associated with liposomes, transferosomes, niosomes, and so forth. They are an efficient tool to achieve desired therapeutic goals such as drug targeting and controlled release [9].

Pharmacosomes: They are the colloidal dispersions of drugs covalently bound to lipids. Depending upon the chemical structure of the drug–lipid complex they may exist as ultrafine vesicular, micellar, or hexagonal aggregates. As the system is formed by linking a drug (pharmakon) to a carrier (soma), they are termed as "pharmacosomes" [11]. They are an effective tool to achieve desired therapeutic goals such as drug targeting and controlled release. Any drug possessing an active hydrogen atom (-COOH, -OH, -NH2, etc.) can be esterified to the lipid, with or without spacer chain that strongly result in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer, in the organism.

The criterion for the development of the vesicular pharmacosome is dependent on surface and bulk interactions of lipids with drug [12]. These amphipathic prodrug mesogens may serve as building blocks by participating in supramolecular assemblages and thus acquire a colloidal state [13]. The prodrug conjoins hydrophilic and lipophilic properties (thereby acquiring amphiphilic characteristics), reduce interfacial tension, and, at higher concentrations, exhibit mesomorphic behavior [8]. Because of a decrease in interfacial tension, the contact area increases, therefore increasing bioavailability [14].

Advantages of Pharmacosomes [15]:

- Suitable for both hydrophilic and lipophilic drugs. The aqueous solution of these amphiphiles exhibits concentration dependant aggregation.
- High and predetermined entrapment efficiency as drug and carrier are covalently linked together.
- Volume of inclusion doesn't influence entrapment efficiency

- No need of removing the free un-entrapped drug from the formulation which is required in case of liposomes

- As drug is covalently bound membrane fluidity has no effect on release rate, but in turn depends upon the phase transition temperature of the drug lipid complex. No leakage of drug take place as the drug is covalently linked to the carrier

- Drug can be delivered directly to the site of infection.

- Drug release from pharmacosomes is by hydrolysis.

- Improves bioavailability especially in case of poorly soluble drugs.

- Reduction in adverse effects and toxicity.

- Reduced cost of therapy.

- Their degradation velocity into active drug molecule, after absorption depends very much on the size and functional groups of the drug molecule, the chain length of lipids and the spacer.

Advantages of Pharmacosomes over Liposomes [16]:

- In case of pharmacosome, volume of inclusion does not influence entrapment efficiency. On the other hand in case of liposomes, the volume of inclusion has great influence on entrapment efficiency.

- In pharmacosomes membrane fluidity depends upon the phase transition temperature of the drug lipid complex but it has no effect on release date because the drug is covalently bound. In liposomes, the lipid composition decides its membrane fluidity, which affects the rate of drug release and physical stability of the system.

- Drug release from pharmacosomes is by hydrolysis (including enzymatic) unlike liposomes the release of drug is by diffusion through bilayer, desorption from the surface or degradation of liposomes.

- Unlike liposomes in pharmacosomes there is no need of following the tedious, time consuming step for removing the free, un-entrapped drug from the formulation.

- In liposomes there are chances of sedimentation and leaching of drug but in pharmacosomes the leakage of drug does not take place because the drug is covalently linked to the carrier.

Introduction of Drug Carriers: Drug carriers are substances that serve as mechanisms to improve the delivery and the effectiveness of drugs. Drug carriers are used in various drug delivery systems such as:

- Controlled-release technology to prolong *in vivo* drug actions;
- Decrease drug metabolism, and
- Reduce drug toxicity.

Carriers are also used in designs to increase the effectiveness of drug delivery to the target sites of pharmacological actions [17]. The Therapeutic uses of a variety of drug carrier systems have significant impact on the treatment and potential cure of many chronic diseases, including cancer, diabetes mellitus, psoriasis, parkinsonism, Alzheimer, rheumatoid arthritis, HIV infection, infectious diseases, asthma, and drug addiction. Scientific efforts in these areas are multidisciplinary, involving the physical, biological, medical, pharmaceutical, biological materials, and engineering fields [18].

In recent years, the interest in micron and submicron systems (i.e. nanosystems) in pharmacy has surged. This is in part due to the advantages these systems may provide over existing systems. Designing drug delivery system is challenging in terms of targeting the drug to specific sites. Certain chemicals or therapeutic agents that show success in vitro fails to produce the same effect in the human body because of the limitation to target the designated area, as a result, high concentration are given to patients resulting in more intense side effects. While asking for a better and more targeted drug system in therapy, a

pharmaceutical scientist come across some time very often i.e. vesicular, colloidal, niosomal, microparticulate, nanoparticulate and lipid based submicron system. Depending on certain dosage form the above term could be coined alone or in conjugation with other terms to a particular system.

Dosage forms which confirm themselves as surfactant spherical vesicles are often known as vesicular system. Micron system comes range of um and submicron in nm. Typically a colloid is an intermediates size between molecular range and coarse range. Colloidal carriers are small particles of 100-400 nm in diameter, suspended in aqueous solution. These micro, nano, vesicular, colloidal, and lipid based carriers have the advantages of easy administration and efficiency over their long residence time, better targeting etc [19].

Need of Vesicular, Colloidal, Micro and Nanocarriers: Development of these carriers is a novel area of science that provides, with a new hope, the tools and technology to work at atomic, molecular and supramolecular levels leading to creation of devices and delivery systems with fundamentally new properties and functions. The carrier offers a number of advantages making it an ideal drug delivery vehicle.

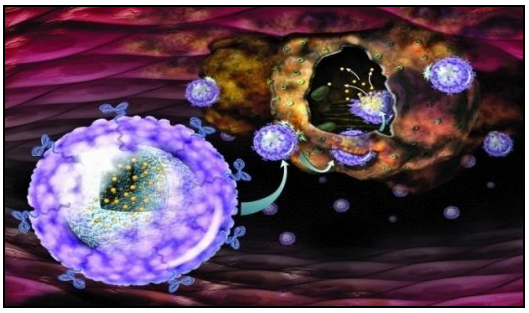
- Better drug delivery to certain impermeable sites of body.
- Owing to their small size, chemistry and distribution these carriers have better bridged the gaps between the structure and function of bio molecules.
- Reaching the micron or nano range with these particles enables them to be highly potential carriers in many biological as proteins, DNA, viruses and xenobiotics.
- Owing to size, nature and chemistry, these systems give better drug permeability from biological membranes and helps in solublization of some practically insoluble drugs and hence solve bioavailability problems of many drugs.
- It involves overlap of biotech, nanotech, and information technology, might result in many important application in life sciences including areas gene therapy, drug delivery, imaging, biomarkers, biosensors and novel drug discovery techniques [20-22].
- It also offers an attractive solution for transformation of biosystems, and provides a broad platform in several areas of bioscience [23-24].
- The surface properties of carriers can be modified for targeted drug delivery for e.g., small molecules, proteins, peptides, and nucleic acids loaded nanoparticles are not recognized by immune system and efficiently targeted to a particular type [25].
- Targeted drug carriers reduce drug toxicity and provide more efficient drug distribution.
- Drug carriers holds promise to deliver biotech drugs over various anatomic extremities of body such as blood brain barrier, branching pathways of the pulmonary system, and the tight epithelial junction of the skin etc.
- Drug carriers better penetrate tumours due to their leaky constitution, containing pores ranging from 100-1000 nm in diameter [26].

Some types of carrier based dosage forms:

1. **Nanoparticles:** Nanoparticles are particles of less than 100nm in diameter that exhibit new or enhanced size-dependent properties compared with larger particles of the same material [27]. Nanoparticles can be formed by a variety of methods with different methods also being used to form the same type of nanoparticles. For example, metal. Nanoparticles can be synthesized by various vapours, thermal decomposition, and wet chemical reduction of the corresponding metal salts [28].

Nanoparticles – Categories and Applications [29]:

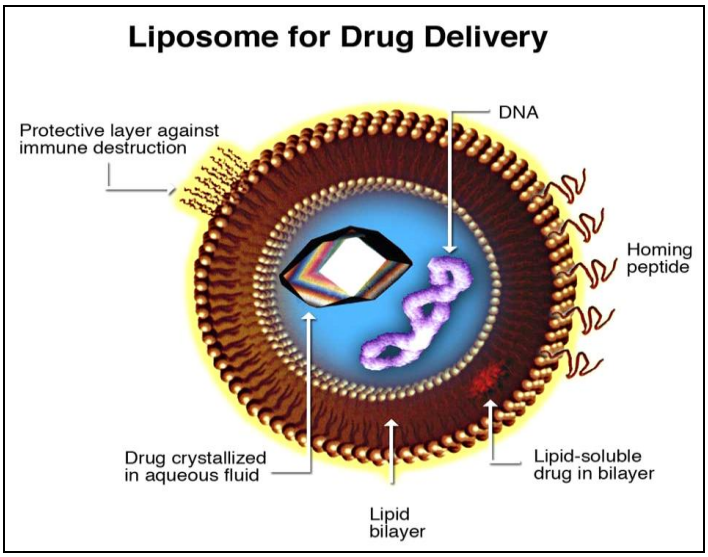
Nanostructure	Example Material or Application
Nanotubes	Carbon, (fullerenes)
Nanowires	Metals, Semiconductors, Oxides, Sulfides, Nitrides
Nanocrystals	Insulators, Semiconductors, Metals, magnetic materials
Other nanoparticles	ceramic oxides, metals



TARGETED NANOPARTICLES

2. **Liposomes**: Liposomes are composite structures made of phospholipids and may contain small amounts of other molecules. Though liposomes can vary in size from low micrometer range to tens of micrometers, unilamellar liposomes are typically in the lower size range with various targeting ligands attached to their surface allowing for their surface-attachment and accumulation in pathological areas for treatment of disease [30].

   According to their size, liposomes are known as small unilamellar vesicles (SUV) (10-100 nm) of Large Unilamellar vesicles (LUV) (100-300 nm). If more than one bilayers are present, then they are referred to as Multilamellar Vesicles (MUV). Liposomes are formed when thin lipid films or lipid cakes are hydrated and stacks of liquid crystalline bilayers become fluid and swell. During agitation hydrated lipid sheets detach and self associate to form vesicles, which prevent interaction of water with the hydrocarbon core of the bilayer at the edges [31].

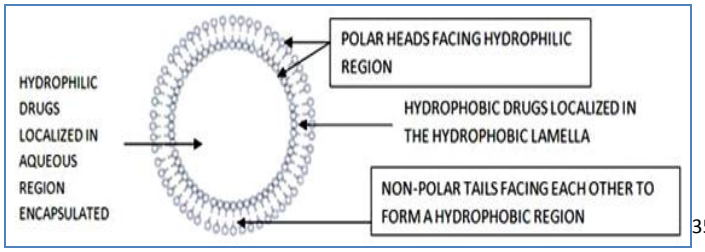


LIPOSOMES FOR DRUG DELIVERY

3. **Ethosomes**: Ethosomes are non-invasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. Although ethosomal systems are conceptually sophisticated, they are characterized by simplicity in their preparation, safety, and efficacy-- a combination that can highly expand their application. Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents. This article reviews work carried out *in vitro, in vivo*, in animal models, and in humans with various ethosomal systems incorporating a wide range of drugs. Because of their unique structure, ethosomes are able to encapsulate and deliver through the skin highly lipophilic molecules such as cannabinoids, testosterone, and minoxidil, as well as cationic drugs such as propranolol and trihexyphenidil [32].

4. **Aquasomes:** Aquasomes are nanoparticulate carrier system but instead of being simple nanoparticles these are three layered self assembled structures, comprised of a solid phase nanocrystalline core coated with oligomeric film to which biochemically active molecules are adsorbed with or without modification. Aquasomes are called as “bodies of water" their water like properties protect and preserve fragile biological molecules, and this property of maintaining conformational integrity as well as high degree of surface exposure are exploited in targeting of bio-active molecules like peptide and protein hormones, antigens and genes to specific sites [33].

5. **Niosomes**: Niosomes are unilamellar or multilamellar vesicles which are very similar to liposomes in structure, prepared primarily from non-ionic surfactant vesicles. They are one of the most studied alternatives to liposomes. Niosomes can be changed or modified by the incorporation of other excipients like cholesterol, into the membrane and they can possess one or more lipid bilayers encapsulating an aquous core. A diverse range of materials have been used to form niosomes such as sucrose ester surfactants and poluoxtethylene alkyl ether surfactants [34].



[35]

6. **Proniosomes**: A Novel approach to delivery of hydrolysable, poorly soluble drugs is described. This method is based on a liposomes production method using “proniosomes”. These proniosomes consists of maltodextrin powder coated with surfactant or a surfactant/drug mixture to yield dry powder. Upon addition of hot water and brief agitation, the maltodextrin dissolves and the surfactant forms a suspension of multilamellar vesicles (niosomes) containing the poorly soluble drug.

   Niosomes slowly release drug into solution. The proniosome powder can also be mixed with hydrogel powder. Adding hot water to the mixed powder allows formation of a hydrogel powder. Adding hot water to the mixed powders allows formation of a hydrogel in which niosomes spontaneously form. The niosomes-containing hydrogel can be formulated as a gel that will degrade and release intact niosomes or as a stable gel, which slowly releases the drug from niosomes that remain inside the gel matrix [36].

7. **Transferosomes:** Transferosomes are composed of phospholipid, surfactant, and water for enhanced transdermal delivery. The transfersomal system was much more efficient at delivering a low and high molecular weight drug to the skin in terms of quantity and depth. In the present study transferosomes and liposomes were prepared by using dexamethasone as a model drug. The system was evaluated in vitro for vesicle shape and size, entrapment efficiency, degree of deformability, number of vesicles per cubic mm, and drug diffusion across the artificial membrane and rat skin. The effects of surfactant type, composition, charge, and concentration of surfactant were studied. The in vivo performance of selected formulation was evaluated by using a carrageenan-induced rat paw edema model [37].

8. **Dendrimers:** Dendrimers are repetitively branched molecules [38, 39]. The name comes from the Greek word "δένδρον" (pronounced dendron), which translates to "tree". Synonymous terms for dendrimer include arborols and cascade molecules. However, dendrimer is currently the internationally accepted term. A dendrimer is typically symmetric around the core, and often adopts a spherical three-dimensional morphology.

   The word Dendron is also encountered frequently. A dendron usually contains a single chemically addressable group called the focal point [40].

9. **Pharmacosomes:** Pharmacosomes are the colloidal dispersions of drugs covalently bound to lipids. Depending upon the chemical structure of the drug–lipid complex they may exist as ultrafine vesicular, micellar, or hexagonal aggregates. As the system is formed by linking a drug (pharmakon) to a carrier (soma), they are termed as “pharmacosomes” [11]. They are an effective tool to achieve desired therapeutic goals such as drug targeting and controlled release. Any drug possessing an active hydrogen atom (- COOH, -OH, -NH2, etc.) can be esterified to the lipid, with or without spacer chain that strongly result in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer, in the organism [12].

10. **Microemulsion**: Microemulsions are clear, thermo-dynamically stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a co-surfactant. The aqueous phase may contain salt(s) and/or other ingredients, and the "oil" may actually be a complex mixture of different hydrocarbons and olefins. In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions. The three basic types of microemulsions are direct (oil dispersed in water, o/w), reversed (water dispersed in oil, w/o) and bicontinuous. In ternary systems such as microemulsions, where two immiscible phases (water and ‘oil’) are present with a surfactant, the surfactant molecules may form a monolayer at the interface between the oil and water, with the

hydrophobic tails of the surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase [41, 42].

11. **Microspheres**: Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm (1 mm)). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are [43].

Preparation: Two methods are mainly employed to prepare pharmacosomes. They are:

- Hand-shaking method.
- Ether-injection method.

Hand-shaking method: In the hand-shaking method, the dried film of the drug–lipid complex is deposited in a round-bottom flask and upon hydration with aqueous medium, readily gives a vesicular suspension.

Ether-injection method: In the ether-injection method, an organic solution of the drug–lipid complex is injected slowly into the hot aqueous medium, wherein the vesicles are readily formed. At low concentration the amphiphiles exists in the monomer state. Further increase in monomers may lead to variety of structures i.e., micelles of spherical or rod like or disc shaped type or cubic or hexagonal shape.

Mantelli *et al*., compared the effect of diglyceride prodrug on interfacial tension, with the effect produced by a standard detergent dodecylamine hydrochloride, and found similar effect on lowering of surface tension. Above the critical micelle concentration (CMC), the prodrug exhibits mesomorphic lyotropic behavior, and assembles in supramolecular structures [44, 45].

Other Approaches: Another approach for producing pharmacosomes was recently developed in which a biodegradable micelle forming drug conjunct was synthesized from the hydrophobic drug adriamycin and a polymer composed of polyoxyethylene glycol and polyaspartic acid. This method has the benefit that although it may be possible to dilute out the micelle, the drug will probably not precipitate because of the water solubility of the monomeric drug conjunct [46]. There are various methods like emulsion precipitation, melt homogenization and thin layer ultrasonication technique are also used to prepare the pharmacosomes. Scientist prepared the pharmacogel of propranolol hydrochloride by constructing the three component phase diagram [47].

Approaches have been done to attach drugs to various glyceride-like groups, and the resulting amphiphilic molecules have been spontaneously dispersed. They were labelled pharmacosomes because of their tendencies to form unilamellar vesicles. It was suggested that these molecules should enhance lymph transport [48].

Characterisation: The prepared prodrugs are generally characterized for their structural confirmation (by IR, NMR spectrophotometery, thin layer chromatography (TLC), melting point determination), partition coefficient, surface tension, and prodrug hydrolysis [49, 50]. Yang *et al*., found that CDP-diacyl prodrug initially forms large vesicles, which diminish in size and finally form micelles. They shows that slow kinetics are essential requirement for phospholipid on biomembrane in order to confer stability to the lipid bilayer and prevent the rapid exchange of lipids between membranes of living cells, the phase transition temperature of pharmacosomes in the vesicular and Micellar state could have significant influence on their interaction with membranes.

Like other vesicular systems, pharmacosomes are characterized for different attributes such as size and size distribution, nuclear magnetic resonance (NMR) spectroscopy, entrapment efficiency, in vitro release rate, stability studies, etc. The approach has successfully improved the therapeutic performance of various drugs i.e. pindolol maleate, buprannolol hydrochloride, taxol, acyclovir, etc [51, 52]. Mantelli *et al*., compared the effect of diglyceride prodrug on

interfacial tension, with the effect produced by a standard detergent dodecylamine hydrochloride and observed same effect on lowering of surface tension. Above the critical micelle concentration (CMC), the prodrug exhibits mesotropic lyotropic behaviour, and assembles in supramolecular structures [53, 54].

CONCLUSION: Vesicular systems have been realized as extensively useful carrier systems in various scientific domains. In spite of certain drawbacks (fusion, aggregation), pharmacosomes still play an important role in the selective targeting, and the controlled delivery of various drugs. Pharmacosomes have immense potential, and further advantages of the vesicular system can be exploited by expanding this approach to additional drugs. The influence of spacer groups and linkage also should be observed more rigorously for further improvement in drug-fate and biological activity of the drug to achieve the therapeutic goal. The system yet requires greater efforts towards investigating the non-bilayer phases and exploring the mechanism of action. Current research trends are generally based on using different approaches like pegylation, biotinyzation etc. for cellular targeting.

REFERENCES:

1. Y. Jin *et al.,* "Self-Assembled Drug Delivery Systems-Properties and In Vitro –In Vivo Behaviour of Acyclovir Self-Assembled Nanoparticles (san)," Int. J. Pharm. **309** (1–2), 199–207 (2006).
2. R.H. Muller, K. Mader, S. Gohla," Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the art", Eur. J. Pharm. Biopharm. 50 (2000) 161–177.
3. Torchilin, V.P., 2000. "Drug targeting". Eur. J. Pharm. Sci. 11, S81–S91.
4. Gregoriadis, G., Florence, A.T., 1993 "Liposomes in drug delivery". Drugs 45, 15–28.
5. Baillie, A.J., Florence, A.T., Hume, L., Muirhead, G.T., Rogerson, A., 1985. "The preparation and properties of niosomes-non-ionic surfactant vesicles". J. Pharm. Pharmcol. 37, 863–868.
6. Pozansky.M.J and Juliano.R.L. Pharmacol.Rev, 1983, 36, 277.
7. Bangham.A.D, Standish.M.M and Watkins.J.G., J.Mol.Biol, 1965,13, 238.
8. Ogihara Umedai, Sasaki.T, Toyama.H, Odak, Sneha.M, Nishigori.H., Cancer Detect Prev, 1997, 21(6), 490.
9. S.S. Biju et al., "Vesicular Systems: An Overview," Ind. Jour. Pharm. Sci. 68 (2), 141–153 (2006).
10. M.O. Vaizoglu and P.P. Speiser, "Pharmacosomes—A Novel Drug Delivery System," Acta Pharm. Suec. **23,** 163–172 (1986).
11. Yiguang Jin, Li Tong, Ping Ai, Miao Li, and Xinpu Hou. "Self Assembeled Drug Delievery System" Int.Jour. Pharm. Sci, 309 (2006) 199-207
12. Vizoglu, O., Speiser, P., 1992. The pharmacosomes drug delivery approach. Eur. J. Pharm. Biopharm. 38, 1–6.
13. I.P. Kaur and M. Kanwar, "Ocular Preparations: The Formulation Approach," Drug Dev. Ind. Pharm. **28** (5), 473–493 (2002).
14. Goymann, C.M., Hamann, H.J., 1991. "Pharmacosomes-multilammelar vesicels consisting of a pure drug". Eur. J. Pharm. Biopharm. 37, 113–117.
15. Vyas S.P., Jaitely Vikas, Kanaujia P. "Int. Jour. Pharm. Sci., 186(1999) 177-189
16. F. Volkering et al., "Influence of Nonionic Surfactants on Bioavailability and Biodegradation of Polycyclic Aromatic Hydrocarbons," App. Environ. Micro. **61** (5), 1699–1705 (1995).
17. Vaizoglu.M.O and Speiser.P.P. "Pharmacosomes— A Novel Drug Delivery system," Acta Pharm. Suec,1986, 23, 163–172.
18. Jain.N.K., Advances In Controlled and Novel Drug Delivery, 2003, CBS Publishers, New Delhi, India, 276.
19. Volkering.F *et al.*, "Influence of Nonionic Surfactants on Bioavailability and Biodegradation of Polycyclic Aromatic Hydrocarbons," App. Environ. Micro, 1995, 61(5), 1699–1705.
20. Jain. N.K., Advances In Controlled and Novel Drug Delivery (CBS Publishers, New Delhi, India, 2003), p. 276.
21. Nagy ZK; Balogh A, Vajna B, Farkas A, Patyi G, Kramarics A, Marosi G (2011). "Comparison of Electrospun and Extruded Soluplus-Based Solid Dosage Forms of Improved Dissolution". Journal of Pharmaceutical Sciences. doi:10.1002 /jps.22731
22. http://www.begellhouse.com/journals/3667c4ae6e8fd136
23. http://www.pharmainfo.net/reviews/comparative-review-recently-developed-particulate-drug-carrier-systems
24. Roco M.C. "Nanotechnology; convergence with modern biology and medicine", Curr. Opin Biotechnol, 2003, 14, 337-343
25. Gupta R.B. and Kompella, "Nanoparticle Technology for drug delievery", Taylor & Francis Group, New York, U.B. Eds. 2006. 1-379.
26. Wilikinson J.M. "Nanotechnology applications in medicine". Med Device Technol, (2003), 14, 29-31
27. Roco M.C. Williams R.S. Alivisatos P (eds.), Biological, medical and health applications
28. "Nanotechnology Research Direction, "Chap. 8, Kluwer Academic Publishers. Boston, 2000.
29. Schimidt J., Montemagno C., "Using machines in cells Drug Discov." 2002, 7, 500-503
30. Cohen H., Levy R.J., Gao J., Fihbein I., Kousaev V., Sosnowski S. "Sustained delivery and expression of DNA encapsulated in polymeric nanoparticles Gene Ther"., 2000., 7, 1896-1905
31. Lobenberg R., Kreuter j., "Macrophage targeting of azidothymidine; a promising strategy for AIDS therapy". AIDS Res. Hum, Retroviruses, 1996, 12, 1709-1715
32. http://www.nanocompositech.com/glossary-nanocomposite-nanotechnology.htm
33. Johans C. (2003). " Novel Routes to Metal Nanoparticles: Electrodeposition and Reactions at
34. Liquid / Liquid Interfaces". Dissertation for the degree of Doctor of Science in Technology, Helsinki University of Technology. ISBN 951-22-6467-6.
35. Rao CNR (2004). "New developments of nanomaterials". Journal of Materials Chemistry. Volume 4.
36. Torchilin VP. (2006) Adv Drug Deliv Rev. 20
37. Bangham A. D., Standish M.M., Watkins J.C., J, Mol. Biol. 1965,13,238-252
38. http://www.ncbi.nlm.nih.gov/pubmed/12911264
39. http://www.ijptonline.com/wp-content/uploads/2009/10/446-457.pdf
40. Dubey Subodh, Jain Amit, Mehta S.C. , Gupta Pavan, Jain Sandeep, Sahu Jagdish . " Niosomes: The ultimate drug carrier" vol 2, No 1 (2010)

41. http://pharmaxchange.info/press/2010/12/niosomes/
42. http://pubs.acs.org/doi/abs/10.1021/bk-2004-0879.ch003
43. http://www.ncbi.nlm.nih.gov/pubmed/14606665
44. D. Astruc, E. Boisselier, C. Ornelas (2010). "Dendrimers Designed for Functions: From Physical, Photophysical, and Supramolecular Properties to Applications in Sensing, Catalysis, Molecular Electronics, and Nanomedicine". Chem. Rev. 110: 1857 1959.
45. Vögtle, Fritz/Richardt, Gabriele/Werner, Nicole Dendrimer Chemistry Concepts, Syntheses, Properties, Applications 2009.
46. Nanjwade, Basavaraj K.; Hiren M. Bechraa, Ganesh K. Derkara, F.V. Manvia, Veerendra K. Nanjwade (2009). "Dendrimers: Emerging polymers for drug-delivery systems". European Journal of Pharmaceutical Sciences (Elsevier) 38 (3): 185–196.
47. S. R. Turner, D. B. Siano and J. Bock, "A Microemulsion Process for Producing Acrylamide-Alkyl Acrylamide Copolymers", U. S. Patent No. 4, 521,580, June 1985.
48. Ovando V.M. Polymer Bulletin 2005, 54, 129-140
49. Paint and Coatings Industry Magazine, January 1st, 2010: Opaque Polyethylene Microspheres for the coatings applications Steve. A. "Lipophilic Drug Derivatives for use in Liposomes," US Patent 5534499 (1996).
50. Taskintuna.I *et al*., "Evaluation of a Novel Lipid Prodrug for Intraocular Drug Delivery: Effect of Acyclovir Diphosphate Dimyristoylglycerol in a Rabbit Model with Herpes Simplex Virus- Retinitis, "Retin, 1997, 17(1), 57–64.
51. Lawrence.M.J. "Surfactant Systems: Their Use in Drug Delivery," Chem. Soc. Rev, 1994, 23, 417–424.
52. Jain N.K., Namedo Alok "Liquid crystalline pharmacogel based enhanced transdermal delivery of propranolol hydrochloride" Int Journal of Controlled Release 82 (2002) 223–236
53. Valentino. J.S and William. N.C., "Lymphatic Transport of Drugs", 1992, CRC Press, Boca Raton, FL, 205.
54. Mantelli, S., Speiser, P. and Hauser, H., Chem. Phys. Lipids, 1985, 37, 329
55. N.K. Jain. "Advance in novel controlled drug delivery system". 276.
56. Steve, A, U.S. patent US S, 534, 499, 1996, 9 July, p 11
57. Taskintuna, I., Banker, A.S., Flores-Aguilar, M., Lynn, B.G., Alden, K.A., Hostetler, K.Y. and Freeman, W.R., Retina, 1997, 17, 57.
58. Steve. A., U. S. patent US S, 534, 499 (C1 S14-25, A61K31/70), 1996, 9july, 11.
59. Mantelli. S, Speiser. P and Hauser. H., Chem. Phys. Lipids, 1985, 37, 329.

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