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A Review on Current Trends of Nanotechnology for Cancer Therapy

Bondar Ganesh H.[1], Nagoba S. N.[1]*, Pattewar Shraddha G.[1], Vijendra Swamy[1], Thonte S. S.[1].

[1]*Channabasweshwar Pharmacy College, Latur, Maharashtra, India.*

Corresponding Author: Nagoba S. N.

ABSTRACT: Targeted drug delivery is an advanced method of delivering drugs to the patients in such a targeted sequences that increases the concentration of delivered drug to the targeted body part of interest only (organs/tissues/ cells) which in turn improves efficacy of treatment by reducing side effects of drug administration. Basically, targeted drug delivery is to assist the drug molecule to reach preferably to the desired site. Thus, targeted delivery systems are urgently needed to achieve desire drug delivery efficiency, improve therapeutic efficacy in the targeted cells/tissues, and minimize toxic effects. Colloidal drug delivery vehicles have been studied in the laboratory for more than 30 years, but the few liposome based formulations already on the market are mainly concerned with reducing the side effects of the encapsulated drugs liposomes nanoparticles which show diminished phagocytosis have been developed and the range of sites which can be reached has been extended. In the past two decades there have been major advances in the development of niosomal drug delivery systems suitable for applications ranging from cancer chemotherapy to gene therapy. In general, an optimized system consists of niosomes with a range of 10-100 nm these formulation is more stable than liposomes.

Keywords: Nanotechnology; Targeting Methods, Niosomes.

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I. INTRODUCTION

Targeted drug delivery is a kind of smart drug delivery system which is less dose in delivering the drug to a patient. This conventional drug delivery system is done by the absorption of the drug across a biological membrane, whereas the targeted release system is that drug is released in a dosage form[1, 2]. Targeted drug delivery system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body; therefore avoiding any damage to the healthy tissue via the drug. The drug delivery system is highly integrated and requires various disciplines, such as chemists, biologist and engineers, to join forces to optimize this system.When implementing a targeted release system, the following design criteria for the system need to take into account: the drug properties, side effects of the drugs, the route taken for the delivery of the drug, the targeted site, and the disease [3, 4]. Drug Targeting is defined as the ability of a drug molecule to accumulate in the target organ or tissue selectively such that the concentration of the drug at the disease site is high, while its concentration in Non target organs and tissues is low, preferably, below certain minimal level so as to prevent any toxic effect. Thus, drug targeting can overcome the non-specific toxic effect of conventional drug delivery. This may also reduce the amount of drug required to dose. A drug can be targeted on the level of a whole organ, on the level of certain cells specific for a given organ, or even on the sub-cellular level of specific tissue[5]. The concept of drug targeting was first mentioned by Paul Ehrlich when he suggested the hypothetical "magic bullet" as an entity consisting of two componentsthe first one should recognize and bind the target, while the second should provide a therapeutic action in this target. Currently, the concept of 'magic bullet' includes a coordinated behavior of three components drug, targeting moiety and pharmaceutical carrier. [6]

Targeted drug delivery means accumulation of pharmacologically active moiety at desired target in therapeutic concentration at the same restricting its access to normal cellular lining, thus minimizing therapeutic

index. In site specific targeted drug delivery, active drug is delivered to very specific preselected compartments with maximum activity while reducing the concentration of drug to normal cells. The drug can be targeted to intracellular sites, virus cells, bacteria cell and parasites using different scientific strategies have proven highly effective. The minimum distribution of the parent drug to the non target cells with higher and effective concentration at the targeted site certainly maximize the benefits of targeted drug delivery.

A Targeted drug delivery system is preferred in the following situations:

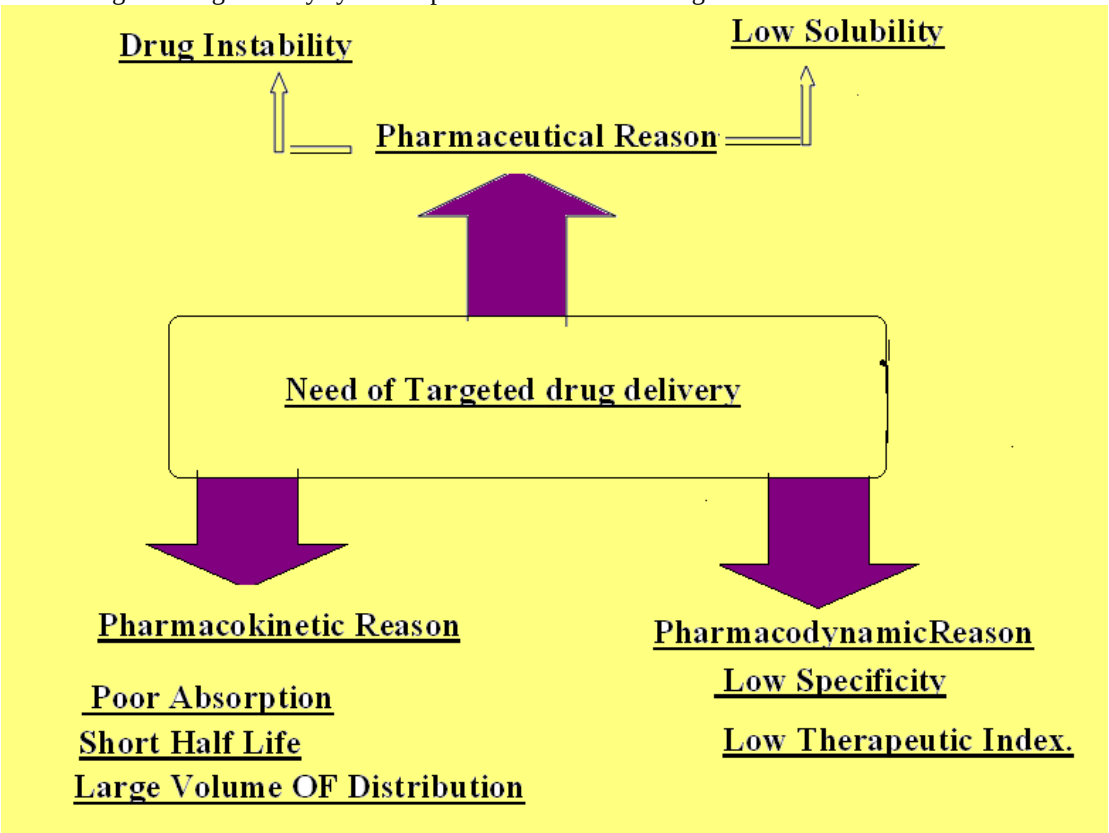


Figure : Need of Targeted drug delivery

II. TARGETING METHODS

Drug targeting to an area of interest within the body increases the therapeutic effectiveness as well as it reduces the toxicity that may arise otherwise. Two methods are widely used for drug targeting to the desired organ/tissue. [7]

Passive targeting

This is based on the accumulation of drug at areas around the site of interest, such as in case of tumor tissues. This is called Enhanced Permeability Retention (EPR) effect. Such a types of targeting occurs with almost all types of drug delivery carriers. Passive targeting is actually a misnomer because it cannot really be described as a form of selective targeting. Although the EPR effect applies for nanoparticle administered, the majority (>95%) of these nanoparticles tend to accumulate in organs other thanthose of interest such as liver, lungs and spleen. Thus, it is the distribution of drug by blood circulation. Examples include the use of anti-malarial drugs being targeted for the treatment of microbial infections such as leishmaniosis, candidiasis and brucellosis [7,8]

Active targeting

Through the use of ligand-receptor interactions, active targeting describes the drug targeting interactions. However, interactions between a ligand and a receptor are possible only when the two are in close propinquity, (i.e. less than about 0.5mm). [8] The currently available drug delivery systems are able to reach the target by the virtue of blood circulation and extravasations. Therefore, we can conclude that active receptor targeting actually means ligand-receptor interaction but that takes place only after blood circulation and extravasation [8]. Active targeting can further be divided into three different targeting levels.

First order targeting

This is the distribution of drug to capillary beds of target sites-organ or tissue, for example, in case of lymphatic

tissue, peritoneal cavity, pleural cavity, cerebral ventricles, eyes, joints, etc [7, 9]

Second order targeting

This is the targeting of drugs to specific sites such as the tumor cells, for example, to kupffer cells in liver.[7]

Third order targeting

It is the type of drug targeting wherein the drug is intracellularly localized at the target site via endocytosis or through receptor-based ligand mediated entry. [9]

III. COMPONENTS OF TARGETED DRUG DELIVERY

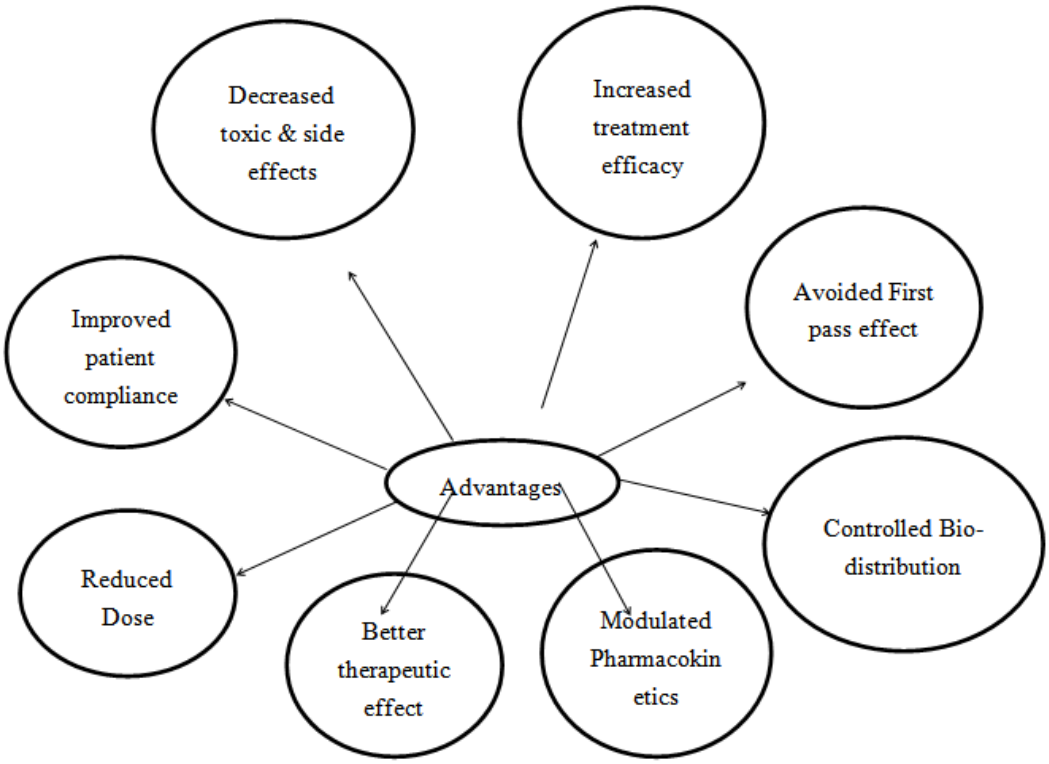
A drug delivery system primarily constitutes a target and drug carriers or markers. Target means specific organ or a cell or group of cells, which in chronic or acute condition need treatment. Route of administration involves drug carrier as a important targeting moiety and after its leakage from its carrier/markers to reach the drug to the specific or targeted site via biological metabolism with its clearance as well as not to reach at non targeted site to make this delivery system more site specific with reduced side effects of drugs and its quantity too.Carrier is one of the special molecule or system essentially required for effective transportation of loaded drug up to the pre-selected sites. These are engineered vectors which retain drug inside or onto them either via encapsulation and/ or via spacer moiety and transport or deliver it into vicinity of target cell [10,11, 12]. Drug delivery Vehicles These transport the drug either within or in the vicinity of target. An ideal drug delivery vehicle is supposed to cross even stubborn sites such as a blood brain barrier. It should be easily recognized by the target cells and the drug-ligand complex hence formed should be stable. These need to be non-toxic, biodegradable as well. The biodegradable nature of drug carrier enables them to be easily cleared away by the body and physiological mechanism, and thus avoids any chance of their accumulation within cells that may lead to cytotoxicity [13, 14.] Nanotechnology-based delivery systems Nanomaterials were initially studied for their properties and then they came into use in different applications. However, the recent observations have been diverted towards the field of drug delivery. This came into being due to complications involved in the use of large-sized materials for drug delivery, such as poor solubility, poor bioavailability, therapeutic inefficacy, side effects and need for targeted delivery of drugs. Recently, nanomedicine has emerged as the medical application of nanotechnology. Therefore, drug delivery at nanoscale has become possible due to the development and fabrication of nanostructures. These nanostructures are assumed to possess the potential of protecting drugs from their disintegration by the various enzymes of the gastrointestinal tract. Since nanoparticles are very small in size, Nanodrug delivery can allow for the delivery of drugs with poor solubility in water and also aid in avoiding the first pass metabolism of liver. Nanotechnology derived drug delivery can cause the drug to remain in blood circulation for a long time, thereby leading to lesser fluctuations in plasma levels and therefore, minimal side effects. These particles or structures can easily penetrate tissues and are readily taken up by cells. This allows for effective targeted delivery. The uptake of Nano-sized particles is reported to be about 15-250 times higher in comparison to microparticles[15].

Development Technique of Drug Targeting Strategies

There is a growing need for multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas to control the pharmacokinetics, Pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs must be taken into consideration. To develop a dosage forms formulation scientist apply knowledge of polymer science, pharmaceutics biopharmaceutics bio-conjugate chemistry, and molecular biology, microbiology.

Figure : Strategies of drug targeting

ADVANTAGES OF TARGETED DRUG DELIVERY SYSTEM[16,17,18]



Niosomes

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with Nontarget tissue[19]. Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media[20] . In Niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate[21] . Niosomes are one of the best among these

carriers.Structurally, niosomes are similar to liposomes and also areequiactive in drug delivery potential but high chemicalstability and economy makes niosomes superior thanliposomes. Both consist of bilayer, which is made up ofnon-ionic surfactant in the case of niosomes and phospholipids in case of liposomes. Niosomes aremicroscopic lamellar structures of size range between 10 to100 nm and consists of biodegradable, non-immunogenicand biocompatible surfactsnts[22].
Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery.

Advantages of Niosomes

- Osmotically active
- Increase the stability of the entrapped drug
- Handling and storage of surfactants do not require any special conditions.
- Can increase the oral bioavailability of drugs
- Can enhance the skin penetration of of drugs
- The surfactants are biodegradable, biocompatible and non- immunogenic.
- Improve the therapeutic performance of drug by protecting it form the biological environment and restricting effects to target cells.
- At times the maintenance of the constant drug concentration whithin the biophase is not desired.
- Useful to dignose various disease.
- Extremely versatile as a drug carrier, niosomes can entrap drugs a wide range of drugs.
- In niosomes preparation drugs are entrapped like as hydrophilic, amphiphilic and liphophillic moieties.
- Manufacturing of niosomes can be easily done and requirements are easily available for the formulation of niosomes.
- They improve oral bioavailability of poorly absorbed drugs.

Disadvantages of Niosomes

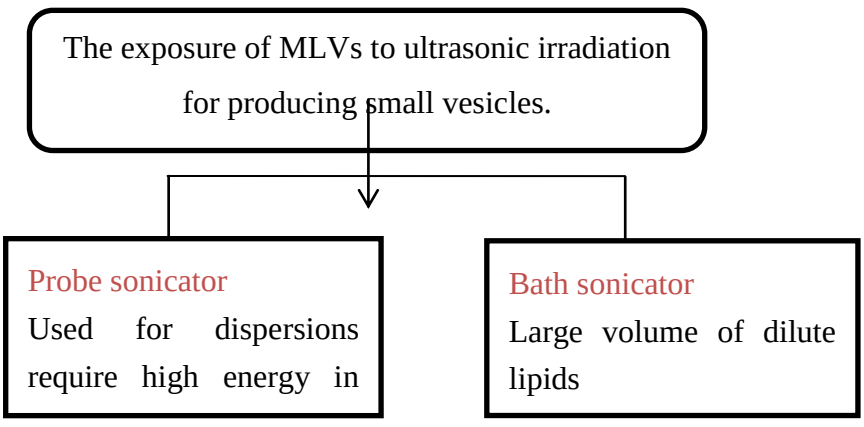
- Aqueous suspension of niosome may exhibit fusion, aggregation leaching or hydrolysis of entrapped drug, thus limiting the shelf life of niosome dispersion.
- Required specialized equipment
- Insufficient drug loading
- Niosomes are physically unstable
- In niosomes preparation chanses of entrapped drug leaking

TYPES OF NIOSOMES

Niosomes can be divided into three groups depends on their vesicles size:
(i) Small Unilamellar Vesicles (SUV, Size=0.025-0.05 µm)
(ii) Multilamellar Vesicles (MLV, Size=>0.05 µm)
(iii) Large Unilamellar Vesicles (LUV, Size=>0.10 µm).

IV. METHODS OF PREAPRATION OF NIOSOMES

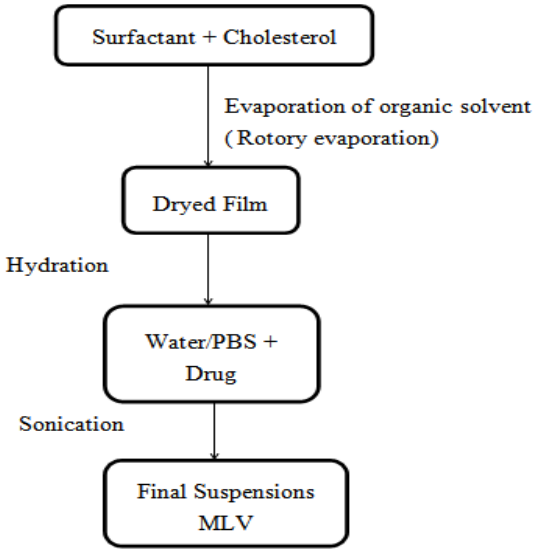
1. Sonication Method



Sonication
MLVs ⟶ Hazy transpareter… solution

5-10 min
Centrifugation 30 min
Clear SUV Dispersion

2. Thin- film hydration method



3. Ether injection method[23,24]

This method provides a means of makingNiosomes by slowly introducing a solution ofsurfactant dissolved in diethyl ether into warmwater maintained at 60°C. The surfactant mixturein ether is injected through 14-gauge needle into anaqueous solution of material. Evaporation of ether leads to formation of single layered vesicles.Depending upon the conditions used the diameterof the vesicle range from 50 to 1000 nm.

4. Micro fluidization[25]:

Micro fluidization is a recent technique to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed.

5. The Bubble Method[26]

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

6. Reverse Phase Evaporation Technique (Rev) [27]

Cholesterol and surfactant (1:1) are dissolved in amixture of ether and chloroform. An aqueous phase containing drug is added to this and the resultingtwo phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of asmall amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous68niosome suspension is diluted with PBS and heated on a water bath at60°C for 10 min to yield Niosomes.It was reported that the preparation of DiclofenacSodium Niosomes using Tween 85 by this method.

7. Preparation Of Niosomes From Proniosomes:

To produce niosomes the final step is to coat the carrier which is soluble in water for example glucitol with surface acting agents. The dry formulation is obtained by this technique. Where each paticle which is soluble in water is coated with a surfactant which is thin film and dry. This formulation is called as "Proniosomes".[28] Eg :Nateglinidemaltodextrin complex[29]

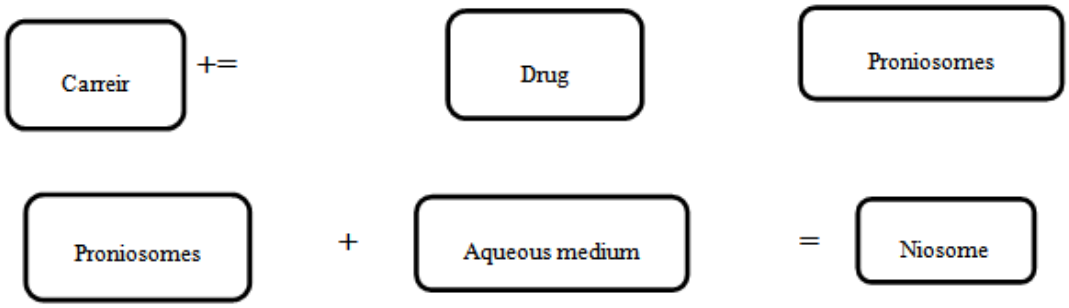


Fig: Formation of Niosomes from Proniosomes

7. TRANSMEMBRANE PH GRADIENT (INSIDE ACIDIC) DRUG UPTAKE PROCESS

This method is done by dissolving cholesterol and surfactant in chloroform. The organic solvent is reordered to obtain a thin film of surfactant cholesterol mixture on RBF wall the solvent in which the mixture is dissolved is evaporated under low pressure. The MLV's formed are freeze thawed for three times which are then subjected to sonication. The aqueous solution of the drug of concentration 10mg/ ml is added to suspension of niosomes and vortexed. Using disodium phosphate solution of 1M the products pH is made to somewhat neutral. To yield niosomes the obtained mixture is further heated at temperature of 600 C.[30]

Evaluation of Niosomes

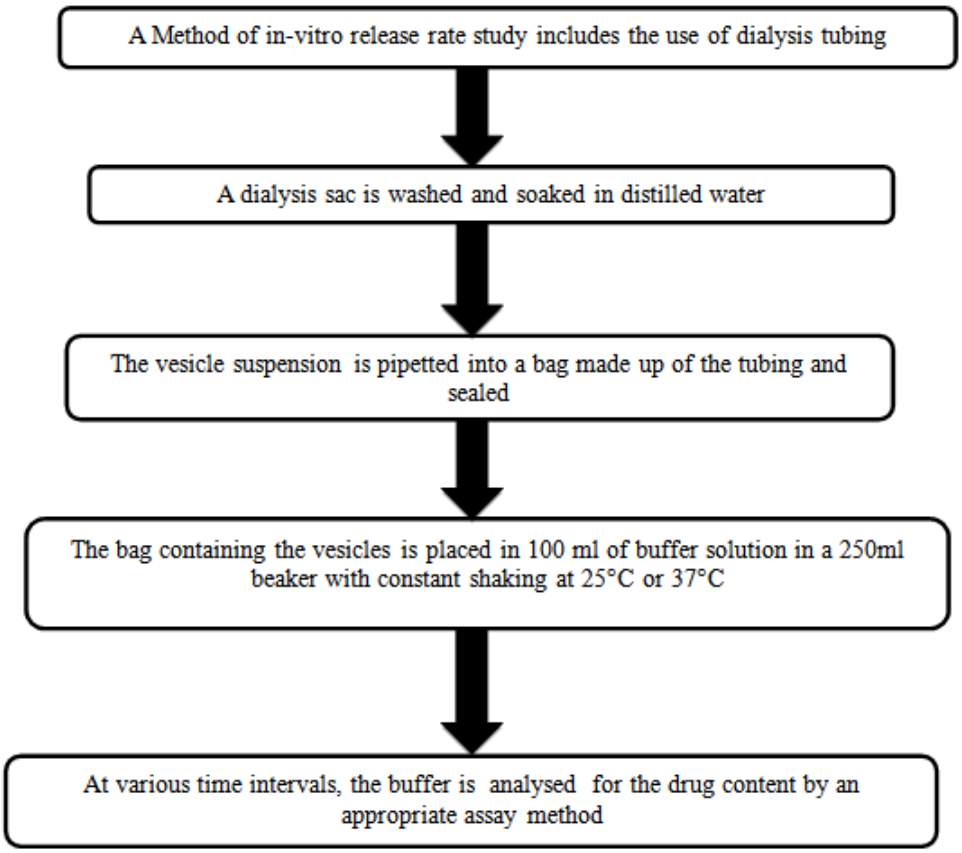
1. Vesicle diameter: Niosomes diameter can be determined usin[(25, 26, 27 31)]

- Light microscopy
- Photon correlation microscopy
- Freez fracture electron microscopy
- Freeze thawing

2. Drug content: The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method.

3. FTIR: The FTIR study is carried by using there is no interaction between the drug and the excipients used in the formulation.

4. In-vitro drug release:



APPLICATIONS OF NIOSOMES[32-35]

- It is used as Drug Targeting.
- It is used in Ophthalmic drug delivery
- Niosomes as Carriers for Hemoglobin
- It is used as Anti-neoplastic Treatment i.e. Cancer Disease.
- It is used act as Delivery of Peptide Drugs.
- Transdermal Drug Delivery Systems Utilizing Niosomes
- It is used as Leishmaniasis i.e. Dermal and Mucocutaneous infections e.g. Sodium stibogluconate.
- It is used in Studying Immune Response.
- It is used in gene delivery like enzyme, DNAs
- It is used in cosmetis

REFERENCES:

[1]. Vyas SP, Khar RK; Basis of targeted Drug Delivery. In Targeted and controlled Drug Delivery, CBS Publishers and Distributors Reprint, 2008: 42-46, 74.
[2]. Allen TM, Cullis PR; Drug Delivery Systems: Entering the Mainstream. Science, 2004;303 (5665): 1818-1822.
[3]. Muller RH, Keck CM; Challenges and solutions for the delivery of biotech drugs-a review of drug nanocrystal technology and lipid nanoparticles. Journal of Biotechnology, 2004; 113 (1–3): 151-170.
[4]. Mark SW, Torchilin, Vladimir P; Drug delivery systems. AccessScience, McGrawHill Companies, 2011.
[5]. Allen TM, Cullis PR; Drug Delivery Systems: Entering the Mainstream. Science, 2004;303 (5665): 1818-1822.
[6]. Vyas SP, Khar RK; Basis of targeted Drug Delivery. In Targeted and controlled Drug Delivery, CBS Publishers and Distributors Reprint, 2008: 42-46, 74.
[7]. V.P. Torchilin. Drug targeting. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 11 Suppl 2:S81-91 (2000).
[8]. D. Peer, J.M. Karp, S. Hong, O.C. Farokhzad, R. Margalit, and R. Langer. Nanocarriers as an emerging platform for cancer therapy. Nature nanotechnology. 2:751-760 (2007).

[9]. K. Rani and S. Paliwal, "A review on targeted drug delivery: Its entire focus on advanced therapeutics and diagnostics," Scholars Journals of Applied Medical Sciences, 2014
[10]. Y.H. Bae and K. Park, "Targeted drug delivery to tumors: Myths,reality and possibility," Journal of Controlled Release, vol. 153, 2011.
[11]. .J. Agnihotri, S. Saraf, and A. Khale, "Targeting: new potential carriers for targeted drug delivery system," International Journal of Pharmaceutical Sciences Review and Research, vol. 8, 2011.
[12]. Florence AT; Drug delivery: Advances and Commercial opportunities, Connect Pharma, Oxford, 1994.
[13]. Gref R1, Minamitake Y, Peracchia MT, Trubetskoy V, Torchilin V, Langer R; Biodegradable long-circulating polymeric nanospheres. Science, 1994; 263(5153):1600– 1603.
[14]. Kannagi R, Izawa M, Koike T, Miyazaki K, Kimura N; Carbohydrate-mediated cell adhesion in cancer metastasis and angiogenesis. Cancer Science, 2004; 95: 377– 384
[15]. K. Rani and S. Paliwal, "A review on targeted drug delivery: Its entire focus on advanced therapeutics and diagnostics," Scholars Journals of Applied Medical Sciences, 2014.
[16]. N. Martinho, C. Damge, and C.P. Reis, "Recent advances in drug delivery systems,"Journal of Biomaterials and Nanobiotechnology, vol. 2, 2011.
[17]. C.J. Chapman Allison , A.C, Gregoriadis, g 1974. Liposomes as immunological adjuvant. Nature 252,252.
[18]. Malhotra M, Jain NK. Niosomes as Drug Carriers. Indian Drugs. 31(3):1994; 81-86.
[19]. Buckton G, Harwood. Interfacial phenomena in Drug Delivery and Targeting Academic Publishers, Switzerland. 1995; 154-155
[20]. Handjani-vila RM: Dispersion of lamellar phases of nonionic lipids in cosmetic products. Int J Cosmetic Sci, 1979; 1: 303
[21]. Rogerson A., Cummings J., Willmott N. and Florence A.T. The distribution of doxorubicin in mice following administration in niosomes. J Pharm Pharmacol. 1988; 40(5): 337–342
[22]. Baillie A.J., Coombs G.H. and Dolan T.F. Non-ionic surfactant vesicles, niosomes, as delivery system for the anti-leishmania drug, sodium stribogluconate J.Pharm.Pharmacol. 1986; 38: 502-505.
[23]. Khandare JN, Madhavi G and Tamhankar BM. Niosomes Novel Drug Delivery System. The Eastern Pharmacist. 1994;37:61-64.
[24]. Chauhan S, Luorence MJ, The preparation of polyoxyethylene containing non-ionic surfactant vesicles. J Pharm Pharmacol, 1989, (41), 6.
[25]. Raja Naresh R.A., Anti-inflammatory activity of Niosome encapsulated diclofenac sodium with Tween - 85 in Arthitic rats. Ind.J.Pharmacol. 1994;26: 46-48.
[26]. Khandare JN, Madhavi G, Tamhankar BM. Niosomes: Novel drug delivery system. The Eastern Pharmacist. 37:1994; 614
[27]. Das Krishnagopal and Ram Alpana. Niosome As A Novel Drug Delivery System: A Review. International Journal of Applied Pharmaceutics, 2013;6(1):1-7.
[28]. ChanduV. Pola,ArunachalamA,JeganathS, Yamini K, TharanginK,ChaitanyaG. Niosomes: A Novel Drug Delivery System. INTERNATIONAL JOURNAL OF NOVEL TRENDS IN PHARMACEUTICAL SCIENCES, FEB, 2012; 2(1): 25-31.
[29]. Uchegbu IF, Vyas SP. Nonionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharmaceutics. 1998 ;172(1):3370.
[30]. Sahoo RK, Biswas N, Guha A, Sahoo N, Kuotsu K. Development and in vitro/in vivo evaluation of controlled release provesicles of a nateglinide–maltodextrin complex. APSB.2014 ;4(5):40816.
[31]. Mayer LD, Bally MB, Hope MJ, Cullis PR. Uptake of antineoplastic agents into large unilamellar vesicles in response to a membrane potential. Biochimica et BiophysicaActa (BBA)Biomembranes. 1985 ;816(2):294302.
[32]. Arul Jothy M, Shanmuganathan S, Nagalakshmi. An Overview On Niosome As Carrier In Dermal Drug Delivery. Journal Of Pharmaceutical Sciences And Research,2015;7(11):923-927
[33]. Chandraprakash KS, Udupa N., Umadevi P., Pillai GK., Formulation and Evaluation of Methotrexate Niosomes. Ind J Pharm.Sci. 1992, 54(5): 197.
[34]. Agarwal S., VasudhaBakshi., Villa P., Raghuram AP., Pandey S., Udupa N., Effect of cholesterol content and surfactant HLB on vesicle properties of niosomes. IJPS, 2004, 66(1): 121-123.
[35]. Madhav. NVS and saini. A, niosomes: a novel drug delivery system. Int. J.rpc. 2011, 1(3): 498-511.
[36]. Mark chasin, Biodegradable polymers as drug delivery systems. 2008, 261-338.
[37]. A.D. Sezer, Recent Advance in Novel Drug Carrier System, Croatia, InTech Prepress.