Journal of
Chemistry & Applied Biochemistry

Open Science Publications

Volume 1, Issue 2 - 2014

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Transdermal Nanocarriers: New Challenges and Prospectives in the Treatment of Diabetes mellitus

Review Article

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Article Information: **Submission:** 17/10/2014; **Accepted:** 11/11/2014; **Published:** 12/11/2014

Abstract

In recent years nanotechnology in drug delivery systems has opened new areas for sustained release of therapeutic drugs to the site of action. The new generation of modern drug delivery systems has more advantages than their traditional systems. Infact wide spectrum applications of nanotechnology in pharmaceutical formulations are changing the scientific landscape of diagnosis, treatment and prevention of diseases. Various pharmaceutical nanotechnology based systems which can be termed as nanopharmaceuticals have brought about revolutionary changes in drug delivery as well as in the field of nanomedicine. Today 75% of drugs are taken through oral route and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. Administration of therapeutic agents topically offers many advantages over conventional, oral and invasive methods of drug delivery. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. The present review summarizes the most important applications of nanotechnology in drug delivery systems, the need for transdermal drug delivery systems, their advantages, limitations and the recent developments of such systems in the treatment of diabetes.

Keywords: Nanotechnology; Drug delivery; Diabetes; Transdermal nanocarriers

Introduction

Over the past few years nanotechnology is rapidly expanding, encircling the development of man-made materials in the range of 5-200 nanometer size range. Nanotechnology mainly deals with the design, synthesis and characterization on ultra small particles which is extended to broad area in pharmaceutical, medical, chemical and engineering application due to its unique properties [1,2]. The changes in properties of nanomaterials are mainly due to increase in surface area and dominance of quantum effects which is associated with very small sizes and large surface area to volume ratio. Nanoparticles demonstrate unique properties with potentially wide range of applications and thereby provides useful platform to explore various interdisciplinary fields. In medicine one of the important applications of nanotechnology is the use of nanomaterials in drug delivery systems to target tissue for the treatment of various diseases. Inspite of the limitations associated with the use of traditional medicine systems, there is also lack of target specificities, which further reduce the therapeutic efficacy of drug during its metabolism in the body and also the cellular toxicity of some of the drug molecules [3,4]. At present 95% of the all potential therapeutics have poor pharmacokinetics and biopharmaceutical properties. Therefore there is an effective need to develop suitable drug delivery systems that distribute the active drug molecule only to the site of target organ without affecting the healthy organs and tissues. In recent years, there has been tremendous growth in nanotechnology in the field of medicine especially in targeted drug delivery systems. In nanomedicine, the main goal is to diagnose and preserve health

ISSN: 2394-3106

Reviewed & Approved by Dr. Rangappa S. Keri, Assistant Professor, Centre for Nano and Material Sciences, Jain University, Bangalore – 562112, India

without side effects by using non invasive treatments [5]. The increase in surface area, versatility in target tissues, controlled drug release, solubility, and site-targeted drug delivery are some of the noteworthy characteristics that nanotechnology can contribute in drug-delivery systems. The strategy that the nanomedicine provides to the drugs and other materials in the nanometer scale (1-500 nm) can change the basic properties and improve the bioactivity of materials. With the development in nanotechnology it is now possible to generate drug nanoparticles that can increase drug efficiency and reduce side effects. Surface modifications of nanomaterials have strong effect on the interaction of these nanomaterials with cells in addition to this is also helps to covert toxic nanomaterial to less toxic form [6,7].

Recent advances in nanoparticulate systems for improved drug delivery exhibit a great potential for the successful administration of wide variety of active pharmaceuticals. The quantum effects at nanoscale determine a material's magnetic, thermal, optical and electrical properties [8]. It is generally expected that products at nanoscale will be cheaper and economically reliable because of less quantity of materials utilized during the process. Nature is considered as the ultimate source in nanotechnology which provides nanostructures that offer various functional proteins and many other biological compounds at cellular level which brings great significance to life on earth. Many biological systems in nature originated through a process of complex dynamic self-assembly comprising partition and separation of many substances into the desired pattern. Some biological systems contain nanosystems that are devoted to specific functions such as locomotion in protozoans, where actin moves along with myosin and kinesin moves along with microtubules. It is considered that one of the functions of proteins and compounds that exist at cellular level is that of nanotechnological separations. Thus a DNA molecule can be seen as a self-assembly machine which replicates itself and also produces complex organisms under the right conditions, subsequently, ribosomes construct protein molecules with accuracy following instructions from DNA. Further molecular motors that construct human muscles are recognized as sophisticated nanomachines that possess ability to convert chemical energy to mechanical energy with high efficiency [9].

Nanoparticles have been used to enhance the selectivity and efficiency of the drug delivery system because they act as mediators of drug release. Due to their extremely small size and large surface area there is possibility to further modify the surface with hydrophobic, hydrophilic, cationic, anionic or any neutral moieties to the surrounding environment which increases their targeting potential applications in biological sciences. The advancement of nanoparticle assisted drug delivery is widely expected to change the landscape of pharmaceutical industries in near future [10]. By virtue of their unique physico chemical properties, nanoparticles have shown promise in delivering a range of molecules to the defined target sites in the body. This special property of nanoparticles makes them a favourable material for biomedical applications. Nanotechnology induced advance approaches in the field of medicine regarding efficient drug delivery have been used especially in the treatment of diabetes. Nanotechnology is quite deliberate in developing modern drug delivery technologies which can expand drug markets. Nanotechnology can be used to reformulate already existing drugs thereby enhancing their overall performance, improve their stability, acceptability by increasing effectiveness, as well as safety and patient adherence, and eventually reduce health care costs [11,12]. Nanotechnology may also increase the performance of drugs that are unable to pass clinical trial phases.

India, the world's second most populous country, now has more people with type 2 diabetes than any other nation. Diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. With the spread of fast-food outlets and more sedentary lifestyles, the prevalence of diabetes throughout the world is rising alarmingly [13]. Despite many advances in the development of oral hypoglycaemic agents, an ideal drug for treating Type 2 diabetes is still a distant reality [14]. Today, physicians can prefer from among a variety of medications targeting various stages of disease, but each drug class associated with some side effects. The age-old molecules such as biguanides and sulfonylureas are still considered drugs of choice because of their well-studied mechanism of action, better tolerability, safety and ideal pharmacodynamic effects. The prevalence of type 2 diabetes has reached epidemic proportions and is continuously increasing all over the world [15].

As per global estimates predict that the total number of cases of diabetes were about 250 million in the year 2013, which represents a 60% increase in the prevalence compared to the year 2002, and prediction is that there will be about 380 million cases in the year 2030. This scenario clearly makes understanding of the pathogenesis of type 2 diabetes crucial in order to implement rational treatment strategies. Type 2 diabetes results from an insufficient compensatory insulin secretion to insulin resistance. Mostly insulin resistance is an early event due to environmental factors, obesity and β-cell function decline a gradual but generally late event. Major goals of management of diabetes in patients are to lower the incidence of degenerative complications and the risk of fatal or non-fatal health events, to improve quality of life, and to increase life expectancy. Some high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhoea, may occur during the treatment [16-18].

Recent advances in nanoparticulate systems for improved drug delivery display a great potential for the administration of wide variety of active pharmaceuticals. Many approaches have been used to enhance the penetration of drugs through skin. The role of these systems in the long-term treatment of diabetes, however, remains debatable. Especially questionable are those methods involving physical or chemical disruption of the skin, which might cause chronic pathological changes. Until we find an ideal drug for the treatment of type 2 diabetes, there is much possibility and interest for leading pharmaceutical companies to modify the pharmacokinetics of old drug molecules in order to better suit for larger sections of patients [19-22]. This review is an attempt to compile and describe various advances in drug delivery systems for the management of diabetes, particularly the extended and sustained release formulations of metformin and glipizide both of which have great potential in treatment of Type 2 diabetes mellitus.

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Role of nanocarriers in drug delivery

In the area of drug delivery various efforts have been undertaken by scientists from all over the world for the development of effective targeted delivery system in which the drug is only active in the target area of the body and sustained release formulations in which the drug is released over a period of time in a controlled manner from a formulation. Several therapeutic nanocarriers for different drug delivery systems have been approved and most of them are in clinical use [23]. These drug delivery systems are broadly categorized into four principle routes namely oral, transdermal, inhalation and parenteral. The primary route for the delivery of any drug therapy is through oral administration with once or twice daily dosing. However, there is large number of therapies particularly vaccine-based, protein-based, gene-based that cannot be delivered by this route. Pulmonary delivery is another non-invasive substitute method that is appropriate for small molecules and proteins. Some of the challenges of most drug delivery systems currently facing include *in-vivo* stability, solubility, intestinal absorption, poor bioavailability, sustained and targeted delivery to site of action, therapeutic effectiveness, side effects, and plasma fluctuations of drugs which either fall below the minimum effective concentrations or exceed the safe therapeutic concentrations. However, nanodrug delivery is an efficient approach primarily focussed to overcome these challenges due to fabrication and development of nanostructures at submicron scale and nanoscale with multiple advantages [24-25].

Generally, nanostructures have the capability to protect drugs encapsulated within themselves from enzymatic and hydrolytic degradation in the gastrointestinal tract, target the delivery of a wide range of drugs to different parts of the body for sustained release. They deliver drugs that are highly water insoluble and in addition to this it can also bypass the liver, thereby preventing the first pass metabolism of the incorporated drug. These nanocarriers increase oral bioavailability of drugs due to their specific uptake mechanisms such as absorptive endocytosis and are able to stay in the blood circulation for a longer period, releasing the incorporated drug in a sustained and controlled manner leading to less plasma fluctuations thereby minimizing side-effects and toxicity caused by drugs. Due to the small size of nanostructures, they possess the ability to penetrate deep inside the tissues and are effectively taken up by cells, allowing efficient delivery of drugs to site of action. The uptake of nanostructures was found to be 15-200 times faster than that of microparticles in the 1-10μm range. For targeted delivery, nanostructures can be conjugated with various drug molecules so that the linkage between the polymer and the lead substance can be manipulated to control the site and duration of action at which the drug is released. The linkage may be achieved by incorporation of lipids, amino acids, peptides or small chains as spacer molecules [26].

Transdermal nano drug delivery systems

The utilization of transdermal nanocarriers have significantly increased in the last few decades. These systems are designed around the two special features that are required in the modern pharmacy which includes temporal delivery and spatial location. Transdermal delivery has variety of advantages compared to the oral route [27-34]. Perhaps the greatest challenge for transdermal drug delivery is that only a limited number of drugs are amenable to administration by this route. It is very difficult to say which the ideal nanocarrier is, because every day new advantages and disadvantages of each carrier are being discovered (Figure 1). An important point highlighted by Panariti et al. [35] is that the interaction with various biological systems and nanocarrier cell internalization is determined by physicochemical properties of nanocarrier systems.

The main physicochemical properties that affect and influence cellular uptake are size, shape, rigidity, and charge in the surface of nanoparticles (Table 1). Nanoparticulated systems can be administered into organisms by almost all routes including transdermal which offers several advantages over other delivery systems (Figure 2) but with its own limitations (Table 2). Transdermal route of drug administration have unique advantages, the drug can easily bypass the first pass metabolism and reaches the systemic circulation. Painless, non invasive and patient-friendly application of patches offers good patient compliance and patches are also easy to remove in the event of hyperinsulinemia [36-39]. An overview of various transdermal nanocarriers has been depicted in Figure 3.

Different nanocarriers for TDDS

Liposomes

Liposomes are spherical, self-closed structures formed by one or several concentric lipid bilayers with an aqueous phase inside and between the lipid bilayers. Liposomes are biocompatible which can entrap water-soluble pharmaceutical agents in their internal water compartment and water-insoluble pharmaceuticals into the membrane. Liposomes usually provide a unique opportunity to deliver pharmaceuticals into cells or even inside individual cellular compartments. Size, charge and surface properties of liposomes can be easily changed simply by adding new ingredients to the lipid

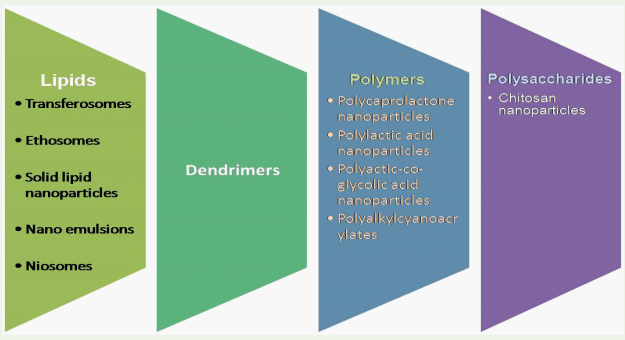

Figure 1: Functional materials used to design commonly used transdermal nanocarriers.

Table 1: Influence of physiochemical characteristics of nanocarriers on cellular uptake.

Favour the uptake	Decrease the cellular uptake
Small size	Large size
Rigidity	Negative surface charge
Spherical shape	
Positive surface charge	

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Table 2: Advantages and disadvantages of transdermal drug delivery systems.

Advantages	Disadvantages
Avoids gastrointestinal tract difficulties	Unsuitable for drugs that irritates or sensitize skin
More uniform plasma levels and reduction in the frequency of dosing Prolonged duration of action	Relatively only potent drugs are suitable because of low permeability of skin Possibility of local irritation at the site of action
Reduction of adverse effects	
Flexibility of quick termination of drug administration Suitable in instances like vomiting and diarrhoea Ease of rapid identification of medications in emergencies	

mixture before liposome preparation by variation of preparation methods [40]. Liposomes have become one of the pharmaceutical nanocarriers of choice for many purposes. In recent years, many liposome-based drugs and biomedical products have been approved for use as medicines. The transdermal penetration of liposomes are usually affected by many factors eg, formulation and particle size, as well as the presence of penetration enhancers but there are other important variables like lamellarity, lipid composition, charge on the liposomal surface, mode of application, and total lipid concentrations [41]. Liposomes can be designed to adhere to cellular membranes to deliver a drug payload or simply transfer drugs following endocytosis [42].

Liposomes have been used successfully to transport drugs across the skin. Biologically active materials encapsulated within liposomes are protected to varying extent from immediate degradation or dilution, suggesting drug delivery systems for the transport of drugs and other bioactive capsules to disease infected organs. The unique ability of liposomes to entrap drugs both in an aqueous and a lipid phase make such delivery systems attractive for hydrophilic and hydrophobic drugs. Hashimoto et al, have demonstrated the effect of orally administered insulin liposomes on alloxan diabetic rats. When the liposomes were administered orally to rats in the 3rd phase of acute alloxan diabetes, a reduction of the blood glucose level was observed in seven out of ten animals and the reduction persisted for several hours and was ranging from 30 to 75% [43]. Singh et al have reported antidiabetic efficacy of Glibenclamide loaded liposomes in alloxan induced diabetic rats. Initially multi-lamellar liposomes were prepared by employing thin film hydration technique. A lipid phase was prepared by dissolving weighed quantity of drug accurately. The antihyperglycemic effects of various Glibenclamide loaded liposomes were evaluated on fasting blood glucose levels in diabetic rats at different time levels. The level of blood glucose started to decrease from 2nd hour when Glibenclamide solution (standard) was given and reaches to normal level in 4th and 8th hour but after that it started to rise again. In case of formulated Glibenclamide the level of blood glucose started to decrease from 6th hour and it was maintained up to 16th hour [44]. Dinesh et al have reported formulation characterization and *in-vitro* evaluation of acarbose loaded ultra-deformable liposome gel for effective transdermal drug delivery. Spherical discrete, free flowing ultra deformable liposomes were prepared. The acorbose loaded ultra-deformable formulations one, two and three showed a percentage drug entrapment of 33.33 ± 2.2 %, 42.6 ± 1.8 %, and 46.66 ± 1.2 % respectively. The percentage cumulative *in vitro* drug release for these formulations were found to be 70.62 ± 0.24 %,73.35 ± 0.28 %, 84.70 ± 0.92 % respectively [45].

Transfersomes

Transferosome are a form of elastic or deformable vesicle which was first introduced in the early 1990's. Transferosomes possess good advantages as phospholipid drug vesicles for transdermal drug delivery. The driving force is nothing more than osmotic pressure; these liposomes are called transfersomes. Depending upon the choice of administration or application their self optimized and ultra flexible membrane properties are capable of delivering drugs reproducibly through the skin. The need to reach the narrow tubes that make up the skin (hair follicles and intercellular spaces between lipids) to deliver drugs, led to the invention of transfersomes. The original idea to use liposomes as drug delivery systems was very smart, as they are made of lipids similar to biological membranes, but they have rigid structure. The incorporation of elements in the lipid bilayer to make it flexible has made these carriers successful. Transferosomes deform and pass through narrow constriction (10 times smaller than their own diameter) without measurable loss. This deformation gives better penetration of intact vesicles. Traditional transformable

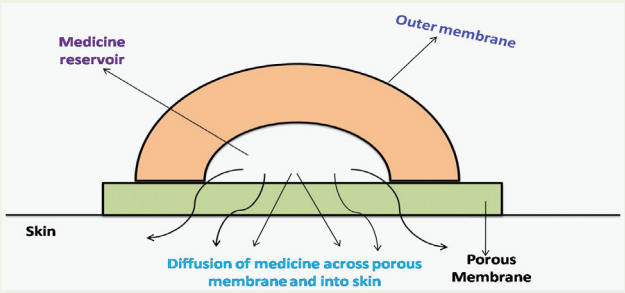

Figure 2: Transdermal patch showing diffusion of medicine in to the skin.

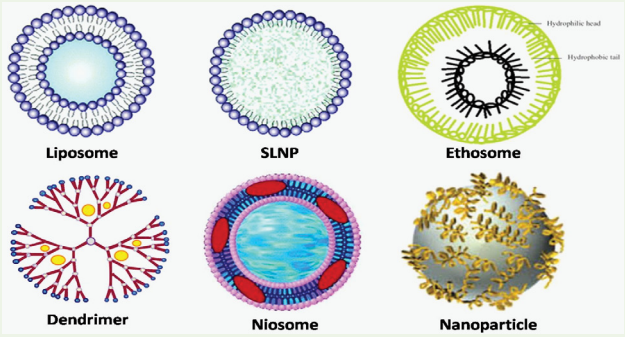

Figure 3: An overview of different drug carriers used in transdermal drug delivery systems.

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liposomes are made using surfactants in the lipid bilayer. The use of flexible transferosomes is an invaluable strategy to reach the objective of drug delivery via the transdermal route. The use of these kinds of nanocarriers seems to be more effective than liposomes, and their flexibility allows the possibility of using them as transdermal vaccine vectors [46]. Malakar et al have evaluated, formulated and optimized the ability of transferosome gel for transdermal drug delivery. The effect of independent process variables like ratio of lipids (soya lecithin: cholesterol), ratio of lipids and surfactants, and ratio of surfactants (Tween 80: sodium deoxycholate) on the *in-vitro* permeation flux (lg/cm^2/h) of formulated transferosomal gels containing insulin through porcine ear skin was optimized using 2^3 factorial design. The optimal permeation flux was achieved as 13.50 ± 0.22 lg/cm^2/h with drug entrapment efficiency of 56.55 ±0.37 % and average vesicle diameter range was found to be 625-815 nm [47].

Ethosomes

Ethosomes are lipid vesicles containing phospholipids, alcohol (in relatively high concentrations) and water. Ethosomes, contain alcohol in the lipid bilayer to make them more flexible and be able to be deformed when more pressure is applied. These carriers allow drugs to reach deeper skin layers and thereby reach systemic circulation. Ethosomes are easy to prepare, and they are recognized as safe and efficient. For these reasons, they could have wide variety of future applications. Their main characteristics are malleability and softness because of this they are considered as good drug-delivery systems. Ethosomes are able to contain and deliver a lot of molecules because they can transport highly lipophilic drugs. Ethosomes can entrap drug molecule with various physicochemical properties and in the future these systems offer a huge opportunity to make better therapies, besides which they can transport molecules through the skin and biological membranes [48-50].

Niosomes

Niosomes are generally made up of lipids and non-ionic surfactants, which are biodegradable and minimally toxic. Niosomes (non-ionic surfactant vesicles) obtained on hydration are microscopic lamellar structures which forms a closed bilayer vesicle in aqueous media depending upon its amphiphilic nature utilizing some energy for physical agitation and instant heat to create this structure. Niosomes were created with the same goal as transferosomes and ethosomes in order to make liposomes less rigid and let these bilayer systems go where liposomes cannot go. In addition, the incorporation of non-ionic surfactants gives better stability to the liposomes. In the bilayer structure, hydrophobic parts are usually oriented away from the aqueous solvent, whereas the hydrophilic heads remain in close 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 such as repulsive forces emerging from the electrostatic interactions among charged groups of surfactant molecules, vanderwaal forces among surfactant molecules, entropic repulsive forces of the head groups of surfactants, short-acting repulsive forces, etc. These forces play a key role in maintaining the vesicular structure of niosomes.

The niosomes were originally used in the cosmetics industry, and the versatility of these systems has allowed their use to spread to other areas. For example, in pharmaceutical products, they are formulated for drug delivery. They are used for many routes of administration: oral, parenteral, ocular, and vaginal, including transdermal. The application of niosomes in transdermal drug delivery has been very important, because they can carry anti-aging agents and antifungal molecules, among other drugs. Due to presence of hydrophilic, amphiphilic and lipophilic moieties in the structure, these can accommodate drug molecules with a wide range of solubility [51,52]. Pardakhty et al. have studied pharmacokinetic properties of niosome-loaded insulin in diabetic rats. They entrapped recombinant human insulin in multilamellar niosomes composed of polyoxyethylene alkyl ether surfactants (Brij 52 and Brij 92) or sorbitan monostearate (Span 60) and cholesterol. The amount of insulin released in simulated intestinal fluid (SIF) and simulated gastric fluid (SGF) were measured at 37 °C. The results obtained showed that animals treated with oral niosome-encapsulated insulin (100 IU/kg) showed decreased levels of blood glucose and elevated serum insulin, which in the case of Brij 92 niosomes, hypoglycemic effect was significant ($P<0.05$) [53].

Raja et al have reported formulation and evaluation of maltodextrin based proniosomal drug delivery system possessing antidiabetic glipizide drug. Glipizide loaded maltodextrin based proniosome were prepared (Figure 4) by slurry method with different surfactant to cholesterol ratio. The corresponding proniosome formulations were evaluated for entrapment efficiency. The results showed higher entrapment efficiency of 84.25 ± 1.25 and *in-vitro* release of 99.23% at the end of 24h [54].

Azza et al have reported formulation and evaluation of metformin hydrochloride (MH)-loaded niosomes as controlled release drug delivery system. Reverse phase evapouration technique with slight modification was adopted for the preparation of MH-loaded niosomes by using span 40 and cholesterol (Figure 5). To obtain negative and positive charged vesicles diacetyl phosphate (DCP) and 1, 2-dioleoyl-3-trimethylammonium propane chloride salt (DOTAP) was used. The mean particle size ranged from 223.5 to 384.6 nm and the MH-loaded niosomes effectively sustain the release of drugs particularly with the positively charged niosomes. By measuring the serum values of glucose and metformin the bioavailability of MH- loaded niosomes were determined. Results showed that the MH-loaded niosomal preparation significantly prolonged the intensity of hypoglycemic effect more than that of free MH solution [55].

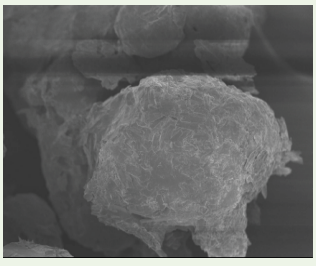

Figure 4: Maltodextrin based proniosome loaded with antidiabetic drug Glipizide.

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Dendrimers

Dendrimers are polymer-based macromolecules designed from monomeric or oligomeric units, such that each layer of branching units doubles or triples the number of peripheral groups. The void area within a dendrimer, the degree of its branching, its simplicity of modification and preparation, and size control offer great potential for drug delivery. The term "dendrimer" is Greek: "dendra" means tree and "meros" means part. This name was coined in the late 1970s by a research group formed by Vogtle, Denkewalter, Tomalia, and Newkome. Dendrimers are nonpeptidic fractal 3-D structures made of numerous small molecules. Modification of the degree of branching may allow for encapsulation of a molecule within this structure. For example, a dendrimer may become water-soluble when end-groups of dendrimers are functionalized with hydrophilic groups, such as carboxylic acids. Thus, water-soluble dendrimers may be designed with internal hydrophobicity, suitable for the encapsulation of a hydrophobic drug. The use of dendrimers to encapsulate hydrophobic and labile molecules has been a successful road. The permeability of dendrimers through the skin depends on physicochemical characteristics like generation size, molecular weight, surface charge, composition, and concentration [56-59].

Nanoparticles

The main property of drug delivery systems is to reach the organ of interest and often to go through it. The use of different carriers like those mentioned previously in this text, in addition to this nanoparticle also contributes significant role to accomplishing the core objective of drug delivery [60]. From the past few years, scientists have designed lots of nanocarriers for helping to improve transport of therapeutic drugs into the skin and through biological membranes. Skin is considered as an important route for various drug delivery systems, and moreover because of its larger contact area it can be very valuable to administer drugs both locally and systemically. Nanotechnology in the pharmaceutical industry opens a new avenue of therapies for the treatment of many diseases and represents hope that people may be benefited to lead a better life. Nowadays, it is quite easier to encapsulate a wide variety of pharmacologically active molecules into nanoparticles like drugs, proteins, peptides, DNA, etc. To enable percutaneous delivery gold nanoparticles, has been used to encapsulate protein drugs to trigger, the interaction between the skin barrier and gold nanoparticles so that the increase in skin permeability effectively initiates percutaneous absorption of the coadministered proteins. Gold nanoparticles have major applications in drug delivery systems and especially used in cosmetic products such as facial gold masks [61,62]. Silver nanodrugs are related to solid-drug nanoparticles in that the active agent appears to be the breakdown product of the particle. Silver nanoparticles display nominal penetration into skin and are subsequently considered safe. Studies of long-term occupational exposure to silver ions and silver nanoparticles have concluded that they are relatively nontoxic. Based on colloidal liquid form and their size, nanoparticles are categorized as nanospheres and nanocapsules. Nanospheres are solid-core structures where as nanocapsules are hollow-core structures. They can also be classified based on the material (polymers, polysaccharides, lipids and proteins) from which they were designed. Polysaccharide nanoparticles and polymeric nanoparticles are very good options for transdermal delivery since they can be tailor-made in various sizes and it are quite easier to modify their surface polarity in order to improve skin penetration [63,64].

Vandana et al have reported rosiglitazone loaded gelatin nanoparticles by using two step desolvation method (Figure 6). The results showed that rosiglitazone loaded gelatin nanoparticles of size 22 to 76 nm showed drug encapsulation efficiency in between 82-90 %. *In vitro* study release across spectrapore membrane showed sustained drug release of prolonged duration (80 % drug release at the end of 32 h). In addition to this gelatin nanoparticles also exhibited excellent redispersibility with a minimal increase in particle size. Finally they concluded that two step dissolution methods are well suited to prepare rosiglitazone loaded gelatin nanoparticles which can be considered as promising agents for rational drug delivery in diabetes [65]. Amolkumar et al have reported formulation and evaluation of glipizide loaded nanoparticles (Figure 7). To develop nanoparticles with 3^2 full factorial design emulsification solvent evaporation technique was used. Initially the drug and the polymer were dissolved in dichloromethane/methanol mixed solvents. Inorder to reduce the particle size in nano scale high pressure homogenizer was used. Dissolution study of the selected formulation showed 209.6 nm size and 95.66 ± 1.70 percent encapsulation efficiency. From the *in-vitro* studies it was found that glipizide loaded nanoparticles showed a sustained release up to seven days (64.79 ± 2.68) and follows first order kinetics. The blood glucose level was decreased to 132.66 ± 9.83 mg/dL over seven days time interval. Finally it was concluded that sustained release of glipizide loaded nanoparticles could be able to manage type II diabetes with reduced dose frequency, minimal side effects and enhanced patient compliance [66].

Chander et al. have reported development and characterization of

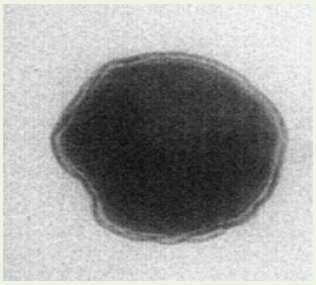

Figure 5: TEM image showing Metformin Hydrochloride loaded niosomes.

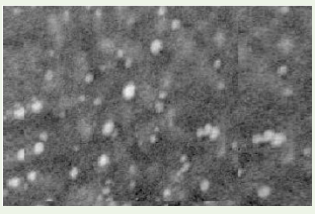

Figure 6: Rosiglitazone loaded gelatin nanoparticles.

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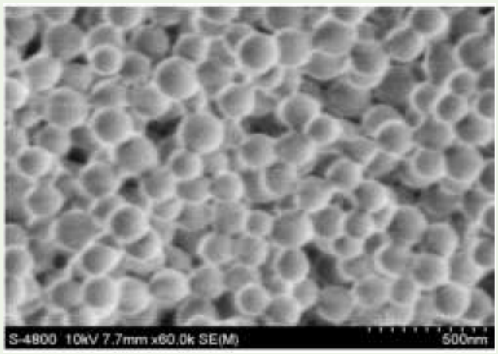

Figure 7: FE-SEM image of glipizide loaded nanoparticles.

nanoparticles of Glibenclamide (GB) by solvent displacement method (Figure 8). GB enriched nanoparticles Drug: Polymer ratio was found to be an important factor in determining the size of the nanoparticles besides other factors but smallest particle size was observed at drug : polymer (1:1) which is mainly attributed to the amount of surfactant enough to maintain the stability of nanoparticles at an equimolar ratio of drug and polymer and moreover coalescence of droplets did not occur at this ratio. Further with the increase in drug concentration with respect to polymer the encapsulation efficiency as well as drug loading capacity was found to be increased. The formulated nanoparticles showed a significant change in saturation solubility in comparison to pure drug and decreased t_{min} with improved bioavailability. Over all the developed GB nanoparticles showed superior activity when compared to plain GB in alloxan induced diabetic model with reduced dose frequency, decreased side effects and improved patient compliance [67].

Nanoemulsions

Emulsions with droplet size in the nanometric scale (typically in the range 20-200 nm) are often referred in the literature as miniemulsions, nano-emulsions, ultrafine emulsions, submicron emulsions. Nanoemulsions are isotropic dispersed systems of two nonmiscible liquids, generally consisting of an oily system dispersed in an aqueous system, or an aqueous system dispersed in an oily system but forming droplets or other oily phases of nanometric sizes. Nanoemulsions are thermodynamically considered as unstable systems, in contrast to microemulsions, because nanoemulsions require high energy to generate them. Due to their small droplet size nano-emulsions possess extra stability against sedimentation or creaming with Ostwald ripening forming the main mechanism of nano-emulsion breakdown. The main application of nanoemulsions is the preparation of nanoparticles using a polymerizable monomer as the disperse phase where nano-emulsion droplets act as nanoreactors. Despite this, they can be stable for long periods due to their extremely small size and the use of adequate surfactants. Hydrophobic and hydrophilic drugs can be formulated in nanoemulsions because it is possible to make water/oil or oil/water nanoemulsions. They are nontoxic and non-irritant systems, and they can be used for skin or mucous membranes and parenteral and nonparenteral administration in general, and they have been utilized in the cosmetic field [68,69].

Nanoemulsions can be prepared by three methods mainly: high-pressure homogenization, microfluidization and phase-inversion temperature. Transdermal delivery using nanoemulsions has decreased due to the stability problems inherent to this dosage form. Li et al have reported the efficacy of nano emulsions coated with alginate /chitosin act as effective oral insulin delivery systems. The relative pharmacological bioavailability of the coated nanoemulsion with 25 and 50 IU/kg insulin were found to be 8.42% and 5.72% in normal rats and 8.19% and 7.84% in diabetic rats respectively. Moreover, there were significant prolonged hypoglycaemic effects were observed after oral administration of the coated nanoemulsions compared with subcutaneous insulin. They finally concluded that, the nanoemulsion coated with alginate/chitosan was a potential delivery system for oral delivery of polypeptides and proteins [70]. Mohammed et al have reported investigation of nanoemulsion system for transdermal drug delivery of Glibenclamide (Figure 9). The nanoemulsion formulation mainly consists of labrafac and triacetin (1:1) as an internal oil phase in external aqueous phase. Tween 80 was used as surfactant and diethylglycol as a cosurfactant. The nanoemulsion formulation had small droplet size of nearly 117 nm, with uniform size distribution (PI < 0.247) and low viscosity (< 73.0 mP). From the results it concluded that size and region of nanoemulsion existence was strongly influenced by the presence of surfactant and cosurfactant. The nanoemulsion formulation in the form of dermal gel can be prepared effectively for both *in vivo* and *ex vivo* studies and a novel transdermal system for Glibenclamide could be introduced successfully.

Enkhzaya et al. have reported the formulation parameters influencing the physicochemical characteristics of rosiglitazone-loaded cationic lipid emulsion. By using cationic lipid DOTAP, DOPE, castor oil, tween 20, and tween 80 rosiglitazone loaded cationic lipid emulsions were prepared. They optimized various parameters in terms of droplet size on the effect of cationic lipid emulsion composition ratio on drug encapsulation efficiency, *in-vitro* drug release and cellular uptake of rosiglitazone loaded emulsion. The results showed that the rosiglitazone loaded cationic emulsion improves *in-vitro* drug release in comparison to rosiglitazone alone. The cellular uptake of rosiglitazone in insulin resistant HepG2 cells was more than the normal HepG2 cells. In conclusion these cationic lipid emulsions can be used as excellent drug delivery systems for rosiglitazone and could enhance its cellular uptake efficiency in target cells [71].

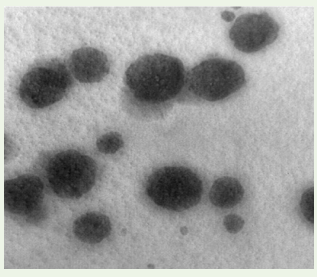

Figure 8: TEM image of Glibenclamide nanoparticles.

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Solid-lipid-nanoparticles

Solid lipid nanoparticles (SLPs) are lipid-based submicron colloidal carriers. In the early 1990s SLNPs treated as a pharmaceutical alternative to liposomes and emulsions. Presence of relatively rigid core comprising of hydrophobic lipids that are solid at room and body temperatures, surrounded by a monolayer of phospholipids makes them more stable than liposomes in biological systems. These aggregates are further stabilized by the inclusion of high levels of surfactants further stabilizes the aggregates of SLNPs. Because of their ease of biodegradation, they are less toxic when compared to polymer or ceramic nanoparticles. They have controllable pharmacokinetic parameters and can be engineered with three types of hydrophobic core designs: a homogenous matrix, a drug-enriched shell, or a drug-enriched core. Two primary production methods exist for SLNPs which includes a high-pressure homogenization technique devised by Muller and Lucks and a microemulsion technique pioneered by Gasco. It has been confirmed that the compound payload exits the hydrophobic core at warmer temperatures conversely, the compound payload enters the hydrophobic core at cooler temperatures. These properties are used to load and unload SLNP's for the delivery of therapeutic drugs, taking advantage of recent techniques to selectively produce hypo and hyperthermia.

Additionally, the quantity of surfactant used during the process of synthesis contributes to the release profile of the drug payload. SLNPs can be used to deliver drugs orally, topically, or via inhalation. Rakesh et al have reported the ability of SLNPs as a carrier for antidiabetic drug metformin for transdermal drug delivery. Metformin-SLNPs were prepared by solvent diffusion technique using propylene glycol (solvent), polymethacrylic acid (polymer) and soya lecithin (lipid base). After doing the evaluation of the above mentioned pharmaceutical parameters, Metformin-SLNP'S were loaded in Methocel K100M transdermal patches. *Ex-vivo* permeation studies indicate that the high cumulative amount of drug was permeated from Metformin-SLNPs [72] (Figure 10).

Cell penetration of nanodrug

There are several natural biological barriers to inhibit the body suffering from damage, such as blood brain barrier, blood-eye barrier, biomembrane barrier and so on, but the existence of these barriers also gives the difficulty to the treatment of morbidity spot. Nanoparticles are solid colloid particles mainly composed of macromolecule substance and the particle size is 1-1000nm. It can pass various biological barriers but utilization of its cell penetration ability in order to carry therapeutic molecules to the targeting cell is the major problem of drug playing curative effect. In order to solve this issue, researchers from all over the world are currently testing many sorts of nanomaterials. Ding et al. [73] have prepared monostearin solid lipid nanoparticles (MSIN), investigated the cellular uptake of MSIN and the influence on the cellular uptake by MSIN modified with PEG2000 in human-type 2 cell alveolar epithelial cell line (A549) and murine macrophages cell line (J774A1). Becker et al prepared DNA-wrapped single-walled cabon nanotubes and investigated length-dependent cellular uptake of these carbon nanotubes. Their studies showed that the cellular uptake of carbon nanotubes had a choice of lengths and the cut-off point was found to be 180 ± 17 nm. They speculated that different cell may have different selective range of length to uptake the corresponding carbon nanotubes [74].

Controllability of nano drugs

The interactions of nanodrug with nanocarrier are made to be the controlled-release formulations with suitable methods (Figure 11) When drug-carrier complex enter inside the body, the drug is slowly released out of nanoparticles at the steady speed automatically in the given programmed time through the process of leaching, infiltration and proliferation or dissolution and act on the specific target organ, tissue and cell.

In addition to this, the nanocarriers prevent drug from degradation by various biological enzymes and extends the effective time period of drugs. At the same time at this controlled-release nanodrug can decrease the peak phenomenon of blood concentration, reduce toxic effects and improve overall efficacy.

Conclusion

The interdisciplinary multifunctional nature of nanotechnology and nanodrugs enabled diversification and advancements to improve the quality of life. Because nanodrug is a new type of drug, the development of nano-drug will cause the revolution of the diagnosis and treatment however at present, the basic theory of nanotechnology applied in medicine and the preparation of nanodrugs are not fully

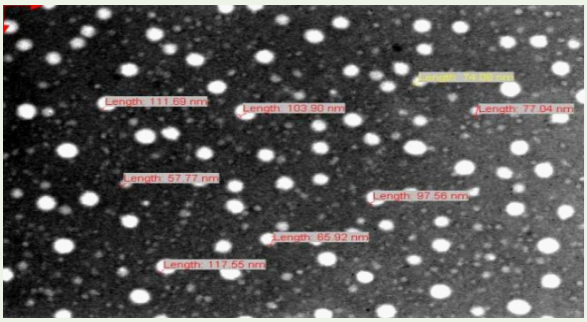

Figure 9: TEM positive image of Glibenclamide nanoemulsions.

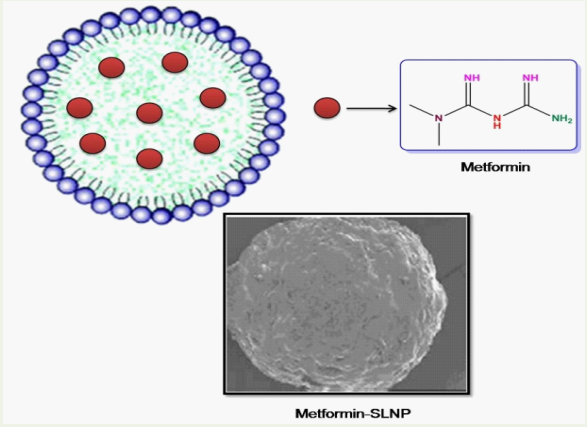

Figure 10: Metformin loaded solid lipid nanoparticles.

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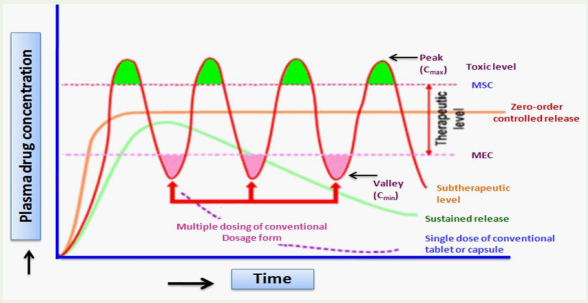

Figure 11: Different doses of drug molecules and their comparative graphs for conventional, sustained and controlled release with time.

explored. Therefore extensive research has to be carried out in the field of nanotechnology applied in medicine has a great deal of work needs to be done, but the superior capability that nanodrugs owns indicates a very wide range of applications in the clinical treatment of various diseases. Transdermal drug delivery offers an attractive alternative to the conventional drug delivery methods of oral administration and injection. However at present the clinical use of transdermal drug delivery is limited by the fact that very few drugs can be delivered transdermally at a viable rate. This difficulty is mainly because the stratum corneum of the skin acts as efficient barrier that limits the penetration of drugs through the skin. Inorder to increase the rate of drugs available for transdermal drug delivery the use of nanocarriers became an excellent alternative source for delivering both lipophilic and hydrophilic drugs throughout the stratum corneum with the possibility having local or systemic effect for treating various diseases.

Aknowledgements

The authors sincerely thank the management of VIT University for providing all the necessary facilities for writing this review in paper form.

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