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Physicochemical Properties and Methods to Determine the Permeability of Nanoparticles

Amanollah Zarei Ahmady[1,2], Nader Shakiba Maram[2*], Mira Jelvehgari[3], Neda Mohtasham[4] and Ali Yadollahpour[5]

[1]Department of Medicinal Chemistry, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Nanotechnology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3]Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Resident of Pediatrics, Abuzar Children`s Medical Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[5]Department of Medical Physics, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[*]Email: loveymi96@yahoo.com

ABSTRACT

Recently, the unique physical and chemical properties of nanoparticles were widely studied. Nanoparticles show special properties and advantages compared to their similar larger particles. Nanoparticles have wide applications in skin drug delivery, as carrier of peptide, protein, anti-inflammatory and respiratory tract drugs. Nanotechnology is used to reduce toxicity and side effects of drugs. Many techniques are available for measuring drugs permeability but none of them can be studied the effect of all factors simultaneously unless are used intact live animals or humans. In recent years, various models such as the location of perfusion (in situ) and cell culture studies have been given. Nanoparticles in properties such as heat transfer, solubility, surface to volume ratio and so on are different in compared to their similar coarse particles. Today, most cell culture models are prepared from immortalized cell lines that have originated from normal cells or colon cancer cells. Colon cancer cells are most used due to ability to differentiate and form an integrated single layer in polarized medium. Because of the special Characteristics, nanoparticles have many uses in the cosmetics industry, Preparation of sunscreens, paints, composites, coatings and even food products and increase of their medical and biological applications is Inevitable.

Keywords: Nanoparticles, Physicochemical, Permeability

INTRODUCTION

Nanoparticles, colloidal solid particles of macromolecular materials that their size has been formed 1-1000 nm (1). These medicinal particles tended to being dissolved, closured, and absorbed, and being connected to the nanoparticles matrix. Depending on the type of nanoparticles preparation method, nanocapsules and/or nanosefr with different characteristics and sustained release features may be prepared(2).In the late 60s of the twentieth

century, Speiser and Markleand formulated the first nanoparticles in pharmacy (1). The first article on review of nanoparticles in pharmacy was published by German JorgKreuter in 1978(3).Precise control of particle size as well as particle shape depends on the type of process formulation and the used devices. Unique physical and chemical properties of nanoparticles have caused to be widely studied during the last decade(4-6). Nanoparticles are materials that have one or more external dimensions or an internal structure at the Nano scale, and show new and superior properties compared to other materials of the same genus but on a larger scale. The nanoparticles contain a large range of materials including polymers, metal oxides, nanotubes, liposomes, micelles, etc, which have a diameter less than 100 nm(7). Three main factors which distinguish the properties of nanoparticles of a material compared to its normal form is increase of the ratio of surface to particles volume, nano-particles dimensions, and quantum effect. Today, because of these specific characteristics, the use of nanoparticles is increasing in industries such as cosmetic industries, sunscreens preparation, paints, composites, coatings, and even in food products, and many cases are also being developed and examined(8)and an increase in medical and biological use of nano-particles is unavoidable(9).Nanoparticles with multiple uses (Multifunctional) play an important role in the diagnosis and treatment of cancer. Displacement and distribution of nanoparticles in the body is independent of their size, therefore the side effects of nanoparticles cannot easily predict from the effects of the same material in larger dimensions. Today the use of nanotechnology in science of medicine more and specifically in drug delivery systems is increasing rapidly. Nanotechnology is used in medicinal systems to reduce toxicity and side effects of drugs.

During the recent years, a plenty research interest has focused on developing new drug delivery systems using Nanotechnology based techniques for medical theranostic applications (10-13).World of pharmacy requires appropriate carriers and formulations in order to deliver effective dose of drug to the place of effect and avoid side effects of drugs.

In this regard, the use of colloidal carriers such as liposomes and nanoparticles are of appropriate methods in order to achieve the mentioned goal. It is known that drug delivery systems are designed based on nanoparticles will be followed by greater therapeutic efficacy, low toxicity, patient convenience and admission as well as the drug concentration at the place of effect (14-16).Today, nanoparticles have had wide uses that can point to following cases: skin drug delivery is used as carrier of antimicrobial and anti-cancer agents, carrier of peptides and protein drugs such as insulin, as well as carrier of anti-inflammatory drugs and breathing apparatus(17-20).It is reported that nanoparticles are effective in improving the physic-chemical properties of poorly water soluble drugs(17-19). As nanoparticles bioavailability of cyclosporine A has shown a 32% increase compared to the pure powder, that its reason has been reported increased speed of dissolution of drug from nanoparticles(21, 22). Endocytosis of nanoparticles from intestinal mucosa and other biological membranes can increase the bioavailability of less soluble drugs(23).

2. The advantages of nanoparticles as a drug delivery system

- Size and surface are the characteristics of particle that can be easily manipulated to reach particles to a specific target actively and passively.
- Nanoparticle control and slow the drug release during the transition and in the place of their effect. It also alters the location of drug distribution and resulting in drug clearance to increase efficacy of drug therapy and reduce the side effects.
- Controlled release and destruction can easily be adjusted by selecting matrix components. Drug loading is relatively high, and can be loaded without any chemical reaction and this is an important factor to preserve drug activity.
- Variations in drug prescription: particle size creates the possibility that the drug can be prescribed in the different systems of injection, inhalation, intranasal, intraocular and/or oral. Nanotechnology have also be helpful in the field of peptide drugs, that must mainly be prescribed in injection form to be preserved from the metabolism, and can provide conditions in order to prescribe them through other delivery methods.
- Reduce the amount of drug consumption: Considering the fact that major drugs are loaded in nanoparticles, must be released in a prolonged period and based on the body needs, therefore, excessive consumption of drugs or their metabolism in the liver will be prevented.
- Nanotechnology has also some uses in the field of simple diagnosis of diseases, imaging and rapid assessment of drug efficacy in individual. In general this technology has some uses in the production of artificial limbs, planting drugs, the use of individual diagnoses in the control in vivo and diagnostic experiments and new drug delivery.

- Gene therapy is another use of nanotechnology in the field of drug delivery of genes. Existing Vectors which are in terms of modified viruses, have effects on the body immune system , therefore conducting researches on making nanoparticles that have the capability of carry genes are required(5, 24, 25).
- Targeting a specific location is obtained through targeting ligands to the particle surface or the use of surface magnetic lead.

On the other hand, the main advantage of nanoparticles is their ability to cross membrane barriers, especially in the central nervous system and gastrointestinal tract. The success of nanoparticle systems may be due to high capacity of drug-loading in order to reduce the carrying amount required to prescribe drugs. Drug loading in nanoparticles is carried out in two ways: One is by combining and mixing the drug at the time of production of nanoparticles and the second one is the absorption of the drug after nanoparticles formed by placing them in a drug solution.

The more drugs can be loaded using the mixing method compared to the absorption method. Despite these advantages, nanoparticles have limitations, for example, their small size and large surface can lead to the accumulation of particles and physical manipulation of nanoparticles in forms of liquid and hard dry. In addition, the small size and large surface of nanoparticles cause another limitation in loading of the particles and immediate release of drug.

Couvreur et al. reported the absorption of two dactinomycin anti-neoplastic drugs and methotrexate on the nanoparticles poly-methyl-cyanoacrylate and poly-ethyl-cyanoacrylate(26). Drug absorption capacity is related to the hydrophobicity of polymer and special area of nanoparticles. In the case of mixing method, the increase in monomer concentration increases the efficiency of loading. But the process is reversed with increasing drug primary concentration in the solution(27). In addition to the absorption and mixing, other alternative methods were proposed by Yoo and colleagues(28).

1.2 Thermodynamic properties of nanoparticles

1.1.2. Heat transfer

One important and valid issue in thermodynamics is when the number of atoms is immense in a particular system. Coordination number in Nano systems at the in some cases has deviation. The main problem is how surface temperatures in a small system can be defined compared to large systems that easily can be seen. There may not been sudden changes in degrees between two consecutive rows of atoms, similar to what is seen in large systems(29).

Currently we have seen that the atoms and molecules that are excited by collectively (phonons) can play an important role in the optical properties of nano-particles and these vibrations act as a mechanism for heat transfer in Nano systems. Phonons are swing in a particular length scale. If different regions show different local temperatures, the distribution of phonons are also different. Phonons can disperse their energy, and as a result local temperature difference is created(30).

2.1.2. Melting point of Nanoparticles

Melting point of Nanoparticles is different from similar large substances, and this is similar to the glass transition temperature (Tg). Some examples can be found that the melting point is as a function of particle size(31, 32). Melting point has a linear relationship with the inverse of size of the crystal (29). The melting temperature of nanoparticles is calculated from this relation:

$$T_m = T_{mb}(1-\frac{C}{D})$$

That Tm is the melting temperature of nanoparticles, Tmb is melting temperature of coarse particles, C is the fixed-size of material, and D is crystalline size of nanoparticles.

3.1.2. Solubility

Solubility of solid material is the fundamental properties of materials. Many of the models used to predict materials solubility, are based on the amount of energy cohesion(33). The melting point and distribution coefficient of oil in

water(34) and molecular surface area of materials is different(35). The new model believes that the solubility of nanoparticles is much greater than that have been predicted by the relation of Oswald-Freundlich.

Two general description of solubility should be considered that molecular description of the bulk properties of soluble materials and particle properties that describes the interferometry between solutes and solvents. In coarse particles, surface to volume ratio is significantly smaller and particle description dominates the solubility, and this ratio increases in fine particles and considerably in nanoparticles. In small systems, particle description affects the solubility(36). One of the oldest dependency of solubility was brought by Kelvin(37, 38) that vapor pressure for the liquid droplets are in equilibrium with vapor pressure of that liquid.

$$In\frac{S}{S0}=\frac{2\gamma slM}{rRT\rho}$$

In relation of Asvald- Freundlich, S is solubility of small particles and S0 is solubility in equilibrium. M is the molecular weight. ρ is the density of pharmaceuticals and γSL interfacial tension between the solid and liquid phase around the particles. Surface tension is not constant for small particles and interferes with predictions of Asvald-Freundlich relation. Corrections have been suggested for the surface charge and opposite surface tension effects (pressure inside the particles) as well as electric traction (push out)(36). Kelvin equation limitation is that is for coarse particles and as we know is not considered for the surface tension and the radius in the Nano systems. An important feature of the pharmaceutical materials is solubility. The smaller particle size due to higher surface free energy and thus higher solubility causes greater curve in the diagram of solubility. It is concluded by Asvald-Freundlich equation that there is an inverse relationship between particles' size and solubility, and solubility increases with decreasing radius of spherical particles. This equation was amended in 1922 by Knapp that considered the effect of surface load on solubility.

Knapp found that particle size reduction increases solubility to a certain extent and when the particles' radius reaches less than this certain extent, solubility is decreased again(36). Also, by increasing the surface free energy (in smaller particles) particles tend to accumulation and growth (Oswald growth), which in turn can reduce particulate levels.

$$\frac{RT}{V_{\mathrm{m}}}\ln\frac{S}{S_0}=\frac{2\gamma}{r}=\frac{q^2}{8\pi Kr^4}$$

In this equation, S is small particle solubility and S0 is solubility in the balance. q is electrical load and k is the permeability of the dispersion medium particles, other parameters have been previously described. Asvald-Freundlich equation shows that there is a limited exponential increase in solubility.

So should keep in mind that by a higher degree of density and accumulation and growth, surface also companies in the process of dissolution and dissolution can be greatly estimated(39). Unlike the well-known theory that smaller particles have a higher dissolution rate(40), is observed that there is an unusual dissolution behavior for small crystals near the critical value. Larger crystals of synthetic apatite (500-600 nm) have a higher dissolution rate than smaller crystals (150-250 nm), and found that the dissolution may be a self-inhibitory action. This behavior was attributed to the phenomenon of kinetics and dissolution model. In another study (41) found that more functionality of nanoparticles (above a nanometer) can be justified by Young's equation for their high interfacial tension interfaces. This may be an example to describe macroscopic systems of nano-scale systems, and thus it became clear that drug loading, as well as loading efficiency for micro-particles is higher than nanoparticles.

4.1.2. Surface to volume ratio of nanoparticles

Surface to volume ratio of nanomaterial are significantly larger than their large counterparts. If a particle be considered as a sphere, its surface is associated with the radius, but its volume is associated with r3. The number of atoms are scattered on the surface (F) and this dispersion ratio has a relation with surface to volume ratio, and thus associated with reverse radius.

$$F=\frac{6n^2-12n+8}{n^3}=\frac{6}{N^{1/3}}\left(1-\frac{2}{N^{1/3}}+\frac{8}{6N^{2/3}}\right)\approx\frac{6}{N^{1/3}}$$

The result of this equation is that all properties depend on the group dispersion on surface, and thus associated with reverse radius of particles and the number of atoms(42).

5.1.2. Optical properties of nanoparticles

Researchers have studied a lot on the optical properties of gold nanoparticles during several years, and have been interested in specific optical behavior of nanoparticles. The difference in color of particles is a direct result of the interaction of phonons and photons, which results in colored radiation dependent on particles' size. Raman Effect that arise from this interaction is one of the phenomenon has been known widely.

By reducing the particles' size, frequency energy emitted by photons and thus their color will change. Color change created in gold nanoparticles and/or other metal due to interaction with target biological molecules that alter their size was followed many applications. A functional sample is detection of vibrio cholera toxin that if this toxin is agglomerated with gold particles causes a color change of gold nanoparticles from red to purple.

Gold nanoparticles that are bind to DNA and become complex, because of the size of the gold-DNA complex shows this complex in blue color. In the presence of lead, this analyzed complex and free red nanoparticles release gold. Obviously, these examples show the measurability of these nanoparticles(29, 43, 44).

6.1.2. Rheological properties of nanoparticles

According to Mark-Houwink equation that is $[\eta] = KM^{\alpha}$ where α is indicative of the particles' shape and)η(is intrinsic viscosity. K is Huggins constant that indicates the polymer interaction with solvent. In 1988, Marriott provided this relation $\frac{\eta_s}{C} = k_1 + k_2C + k_3C^2$ where K2 is solvent interaction constant. These equations show the effect of particles' concentration on viscosity. However, the effect of particle size on rheology of dispersion medium is very complex. It has been proven that the particles' distribution in micron size compared to particles about 100 nm in higher shear stress, tend to be thickened(45, 46).

7.1.2.Induction of oxidative stress

Studies have shown that nanoparticles that enter the liver can locally induce oxidative stress. The intravenous prescription of nanoparticles of isobutyl cyanoacrylate that are biodegradable particle and/or polystyrene which are not biodegradable leads to the evacuation and reduction of glutathione and oxidized glutathione (GSSG) in the liver as well as act as an inhibitor of superoxide dismutase (SOD) activity. They also increase catalase enzyme activity slightly. Nano particles are not distributed in hepatocytes, and it shows the involvement of oxidative species that are likely to be produced by macrophages of the liver activated after phagocytosis of nanoparticles.

Absorption of polymeric nanoparticles by Kupffer cells in the liver causes changes in antioxidant systems of hepatocytes cells, possibly because of radical oxygen species production. It is observed that the nanoparticles in the lungs can induce oxidative stress through the pulmonary inflammatory response as well as through spontaneous reactions are dependent on the surface.

In addition to pulmonary studies, little studies were conducted on oxidative stress in the other tissues. However, Fernandez and colleagues reported that reduced glutathione is not enough for beginning of significant hepatocytes damages (without lipid peroxidation). It should be noted that many studies to prove safe use of nanoparticles is necessary because chronic depletion of antioxidant substances can cause serious health problems(47).

2.2. Evaluation of intestinal permeability:

1.2.2. In vitro methods:

Small intestine has two major tasks that seem contradictory. These two actions are effective absorption of electrolytes liquid foodstuff and drugs, and on the other hand simultaneous excretion of toxic pro-inflammatory substances and substances that are potentially antigen. The selective ability of the intestinal epithelium to prevent the absorption of these harmful compounds is often called as permeability.

Abnormal permeability is considered an important factor in the pathogenesis and pathophysiology of various diseases such as celiac, rheumatoid arthritis, enteritis caused by the use of non-steroidal anti-inflammatory drugs and

Crohn disease. In recent years, various models have been offered for in vitro studies on absorption of new drugs. However, systemic productivity is influenced by several factors. However, measuring the penetration of a combination from gastrointestinal tract can be an easy way to evaluate its absorption from the gastrointestinal tract wall. For this purpose, various methods can be done, but the effect of all factors cannot be studied simultaneously unless alive and intact human or animal be use. Many methods are available to measure the permeability of drugs(48). The advantage of these methods compared to computational methods is the combinations not only in terms of physicochemical properties but also in terms of absorption by carrier proteins are compared. The biological methods can be also used to investigate the effect of additives such as soluble-maker and moisturizing substances on intestinal permeability of drugs. Generally, the passage of two basic views would be examined that include: combination harvested by the system and other its passage through the system.

Therefore, selection of the type of system is important. The examined combination harvested by the system must be considered that at the low values of harvest, determining the amount of harvested drug will be accompanied with some problems. Although the use of labeled material can help to solve the problem, but these materials are rarely available in the early stage of making new drugs(49).

1.1.2.2. Intestinal Brush membrane vesicles:
In this method, cell homogenates sequestrated by calcium chloride are used after centrifugation (48). The resulting final mass contains proteins and phospholipids of intestinal wall, which contain most of enzymes in the Brush membrane as well as translational activity. Re-distribution of this mass in the buffer leads vesicles formation. These vesicles are mixed with the study material in buffer, and are filtered after a certain period. Then the amount of material picked up by the vesicles is determined. Since the sequestration-centrifugation process only leads separation of Brush membrane components, therefore only intracellular passing through the apical membrane can be studied by this method.A model changed by this method is separation of Brush membrane components and fixing them on a chromatography column which has been provided by Pidgeon and colleagues(50). In this method, which is called Immobilized Artificial Membrane (IAM), the study drug is estimated by an aqueous solvent and the capacity factors. Despite some limitations of this method, it is observed that the prediction of treatment productivity for a series of compounds is comparable with predictions of more sophisticated methods such as using Caco-2 cells.

2.1.2.2. Isolated intestinal cells:
Isolated cells of intestines of humans and animals can be used as systems of harvest type in measuring oral drugs' productivity. The epithelial cells separation process takes place essentially through two ways. The first method is in place (in situ), in which intestine is perfused by solutions containing intestinal enzyme, and thus become free cells. In the second method which is ex vivo, cells are made by chelation agents or enzymes(48, 51).

The cells are isolated and extracted by fast centrifugation or filtration. Due to the low volume of cells, determination often takes place by counting radioactive. Of course, this is considered a disadvantage in the early stage of making new drugs, due to the lack of easy access to radioactive materials.

3.1.2.2. Returned intestinal loops:
In this method, part of the intestine immediately after killing animals is isolated and washed by ice buffer to remove food debris. Then, from one end is closed by thread and carefully returned using a glass rod and then divided to loops of 2-4 cm (weighing 30-50 g). Each part of the intestine can be used for this purpose. However, jejunum, ileum and colon, have greater usage.

In the next step the cut pieces along with a solution containing the test substance are stirred in a water bath and incubated. After a certain time, tissue removed from the solution and is dried and weighed. Then the amount of drug harvested by tissues is measured by counting radioactive or other methods(52).

4.1.2.2. Returned intestinal bags:
This method is also similar to returned loops method. Thus, a 2-4 cm section of the intestine at one end is closed and is returned using the glass rod (53).Similar to returned loops method mucosal part is in the outer part of membrane and is in contact with the incubation medium. But unlike returned loops method, just the mucosal part in contact with the combination solution is considered.

5.1.2.2. Cell diffusion using tissue:
From the early 1950s, side-by-side cells diffusion cells have been used to determine the passage of drugs in live tissues that one of the earliest of them is using chambers. In this method, small pieces of intestine (about 2 cm) is kept by clamp between two glass containers filled with buffer and foods such as glucose in 37C. The test combination is added to the container, which can be part of serous or mucous. Then the combination accumulation is measured in the other side of the membrane means in the receiver part as a function of time(54).

6.1.2.2. Cultured cells:
One of the advantages of cell culture is that in monolayer state, just as in vivo state show polarization state. The initial cell culture ha spoor viability and dose not form coherent monolayer in which cells put together by tight intracellular junctions(55). Today, most of cell culture models are of immortalized cell lines which have been generated from normal cells, induced tumor cells, or colon cancer cells. Colon cancer cells due to differentiation capability and the formation coherent monolayers and polarizing in culture medium are most widely used.Caco-2 cells among them that have been used for the first time in 1970 have the most usage(56). The advantage of these cells is that they can form monolayer on the porous filter in culture medium in a few days and then differentiated to intestinal absorptive cells by typical morphology (with study margins and tight intracellular junctions).

7.1.2.2. Perfusion in situ
The study the absorption of drugs was posed for the first time in the late 1960s(57).In these studies, parts of the intestine cannulated anesthetized animal are perfused by the drug solution. Then the amount of drug absorbed from the intestine is determined by concentration reduction of effluent solution and effective permeability of the drug is calculated from this formula(58):

$$P_{eff} = \frac{-Q \ln(C_{out}/C_{in})}{2\pi rl}$$

Where Q is the speed of inflow to the intestine in terms of centimeters per second, Cin and Cout are inlet and outlet concentrations of intestine, respectively, r is radius of the small intestine in terms of centimeters, and ℓ is also the length of the study part of intestine in terms of centimeters. For calculating amount of water entry and exit of intestine and correction of permeability resulting from non-absorbable materials is used simultaneously. Phenol Red is a coarse colored molecule that has been frequently used for this purpose(49, 59-61).

Rat intestine is often used in perfusion studies. The advantages of this method are increased viability of tissue and the presence of a large number of sampling sites in the intestine. In addition, in this method all the natural obstacles in the way of absorption from the intestine to reach the portal vein blood flow are exactly preserved equal to the in vivo state. Although intestine perfusion method has been used to determine the adsorptive properties of various drugs(59),however, it seems that the large number of drugs screening in the manufacturing process of new drugs, the above method cannot be used routinely. Of course, to confirm the results obtained from simpler examining methods of absorption, such as Caco-2 cells (which often lacks some specific properties of intestine in vivo state such as the presence of mucus) have widely used this method.

2.2.2. Vivo methods:
One of the major disadvantages of each in vitro system is its inherent variability that appears in the permeability data. The results showed that rat intestine perfusion and cell culture model showed the correlation between the model and the most significant relationship with the fraction absorbed in humans. Furthermore, the results of research conducted by Zakeri Milani and colleagues also indicates high correlation between coefficients of Peff drugs in rats with permeability coefficients corresponding in humans (R2 = 0.91), as well as with fraction values of dose absorbed in humans (R2 = 0.91)(61).

CONCLUSION

Several sciences have fundamentally and basically focused on properties of nanoparticles, which are being called nanotechnology. Most studies have been focused on materials science, ceramics, electronics and biomedical fields. It was thought that practically distinct no differences to be seen in physical behavior of nanoparticles and coarser

materials. Two main effects which created in nanoparticles compared to coarse materials are their surface to volume ratio, which is very significant in this materials and the other is quantum effects.

Fortunately, in recent years, many researches have been done on the phenomenon of nanoparticles, and most of the fundamental questions were answered. These beneficial uses led to the development of drug delivery technologies of new drugs. A very small number of fundamental studies in pharmacy were conducted on the use of nanoparticles in drug delivery. Many methods are available to measure the permeability of drugs but none of them cannot study the effect of all involving factors simultaneously unless using alive and intact human or animal. In recent years, various models have been offered for in vitro studies of new drugs absorption.

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