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A Review On Nanoparticle Penetration Barrier In Cell, Tissue: Current Challenge And Future Direction

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ABSTRACT: -

Nanoparticles Possess come an effective approach for treating colourful conditions, similar as cancer, cardiovascular conditions, and seditious diseases. Different types of Nanoparticle like Poly patches, micelles, liposome, dendrites, and amount blotches, carbon nanotubes and gold nanoparticle have been developed and examined for medicaluse. Still, one major challenge for NPS is reaching the target point in the right quantum while avoiding accumulation in unwanted areas. The distribution of NPS in the body iscontrolled by colourful natural walls. For NPS delivered into the bloodstream, walls include (1) concurrence by the vulnerable system within the spleen and liver, (2) passing into the endothelium the target Atkins, (3) moving through the towel interstitial, (4) uptake by target cells through endocytosis, (5) prolixity within the cell's (6) The entering to the nexus, if demanded. NP scan also be delivered through other routes like the mucosal membranes and skin in the lungs, nose bowel, and the vagina, but in these situations, towel opposition to can hamper delivery, this evaluation looks at the presentknowledge of how the nanoparticle pass through these Natural walls, fastening on transport walls rather than vulnerable walls. It also discusses strategies for designing NPS to overcome these challenges.

Keywords: - (NP) Nanoparticles, Liposomes, Skin Mucosal Membrane,penetration

INTRODUCTION: -

Treatment using targeted drug based on nanoparticles are designed to transport drugs directly to the diseased area, ensuring that the right amount of medication reaches the target. However, this process is hindered by several natural barriers in the body. Thesebarriers, which are part of the body's defence system, are meant to prevent foreign substances from entering. When nanoparticles (NPs) are injected into the bloodstream,the first obstacle they face is the body's defences system, particularly the liver and spleen, which quickly remove them. [1] Another challenge is getting the NPS to pass through the walls of blood vessels into the target tissues.
In healthy conditions, NPS usually cannot cross these walls. However, in cases like inflammation or cancer, the blood vessel walls become more porous due to certain chemicals that cause inflammation, creating gaps between the cells [2]. These gaps allow the NPS to move from the bloodstream to the affected area. After

leaving the blood vessels, nanoparticles (NPS) encounter a challenging barrier as they movethrough the crowded, gel-like to get extracellular matrix (ECM) and interstitial space toreach their target cells. [3-5].

The ECM is made up of a network of elastic and collagen fibers, and other proteins, with interstitial fluid filling the gaps between these components. While the ECM normally helps maintain tissue structure, diseases like liver fibrosis and tumour can increase collagen levels, making the ECM stiffer [6]. This increased rigidity can make It harder for NPS to travel from the blood vessels to their target cells.

Once nanoparticles (NPs) reach their target cells, they face more challenges, startingwith getting through the plasma membrane. NPS can't just diffuse into cells; they aretaken in through processes like pinocytosis, phagocytosis, or endocytosis [7], whichdepending on the nanoparticle surface properties and size the type of cell. After beingtaken up, nanoparticle travel in early stage vesicles endosomes regarding late endosomes and finally to the lysosomes. If they can escape from these compartments, they move into the cell's cytoplasm and might even enter the nucleus, though they canonly get through nuclear pores if they are smaller than 9 nm [8].

Additionally, if the NP delivery needs to cross skin or mucosal membranes, these barriers are very effective at stopping foreign materials, including NPS, from passing through. Despite the challenges at the cellular and tissue levels, many nanoparticle based methods have been created and have the potential to revolutionize medicine [9- 14]. We will also discuss how NP scan be designed to overcome these barriers for treating diseases like cancer, atherosclerosis, and skin conditions.

While we won't cover immunological barriers, such as NP interactions with macrophages in the RES (Reticular endothelium system) organs, as these have been addressed in other [1, 16] reviews, this review will focus on the physical barriers that restrict NP transport.

HISTORY: -

1. In (1960s-1980s) the nanoparticles began gaining traction with develop of electron microscopy, which allow scientist to observe structure at Nano-scale early research focused fundamental properties of nanoparticle such as size, shape, surface early Studied primarily concerned themselves with how particle interact with biological system.

2. The advance in nanotechnology (1990s-2000s) - the advance technology led to the creation of nanoparticle designed targeted drug delivery. Research began to explore nanoparticle could be engineered to cross cell membrane & penetrate tissue. During the period was significant progress understanding biological barrier such as cellmembrane & blood brain barrier.

3. In early 21 century innovation – The researcher developed technique to alter the characteristics of nanoparticle surface enhance capacity to cross cellular &tissue barrier. This include coating nanoparticle with ligand &polymer. New experimental model & imaging technique such as advanced fluorescence microscopy & in vivo imaging provided deeper insight into nanoparticles interact.

NANOPARTICLE PENETRATION THROUGH ENDOTHELIUM:-

The protective qualities of a healthy endothelium-

Endothelium is a single layer of cells lines lymph vessels and blood [17]. It can be ongoing, with no gaps; fenestrated, with small holes; or discontinuous [18], with largergaps the majority of the arteries, veins, and capillaries in the muscles, lungs, skin, and brain have a continuous endothelium. In a healthy state, these cells are attached to a solid base layer and tightly joined together [17]. Fenestrated endothelium, which has tiny pores, is found in the renal glomeruli, endocrine and exocrine glands, and the digestive tract some renal tubules.

Discontinuous endothelium, with larger gaps (100–200 nanometres) and a less organized base layer, is mainly found in sinusoidal blood vessels in the liver, as well asin the bone marrow and spleen. [17, 18] The body's tightest endothelium is found withinthe central nervous system (CNS) and is known as the blood-brain barrier

(BBB). This special barrier closely regulates the movement of particles between the brain and blood to keep the brain inside the environment stable [19].

The endothelial cells in the brain's tiny blood vessels have a very tight membrane and are only about 0.3 micrometres apart [20]. The space between these cells is just about 0.8 nanometres wide. The cells have many mitochondria, no small openings (fenestration), very little pinocytosis (cell drinking), and tight junctions that keep themclosely connected.

Enhanced Permeability and Retention (EPR) Effect inDisrupted Endothelial Barriers: -

- Below is a discussion of two significant pathologies that are relevant tomedicine delivery-

1.Cancer: -

Blood vessels around a tumour have leaks and have unevenly high permeability and poor lymphatic outflow in contrast to healthy tissues [3, 4]. This leakage allows nanoparticles (NPs) to enter and stay in the tumour more easily, a phenomenon called the enhanced permeation and retention (EPR) effect. The pores in the leaky blood tumours Range from 380 to 780 nanometres in size. So, nanoparticles that use the EPReffect to tumour tumours should be smaller than this size range.

Nanoparticles using the EPR effect are widely utilzed in medicine [21, 22]. For eg. Albumin-bound by paclitaxel (Abraxane) nanoparticles, authorized by the FDA in 2005 for breast cancer therapy [23], are 130 nanometres in size. This size works well for taking advantage of the EPR effect. Liposomes with a diameter smaller than 400 nanometres have been found to pass through blood vessels into adenocancer in human tumours placed inside the naked mice [24].

2. ARTHEROSCELEROSIS: -

The Enhanced permeability and retention effect is also observed in the case of atherosclerosis, a condition linked to long-term inflammation in the arteries [25]. Whenthe blood vessel lining on the inside is exposed to free radicals, high blood pressure, oroxidized LDL cholesterol, it can contribute to the development of atherosclerosis [26, 27].

Researchers have tested nanoparticles (NPs) of various sizes and types to deliver drugs directly to atherosclerotic plaques. For example, in studies with rabbits, inflammation in these plaques was treated using prednisolone phosphate drugs inside PEG-liposome

NPs. These liposomes target the clot through the enhanced permeability and retention (EPR) effect [28]. Additionally, among different types of polymeric NPs, those made from poly(D,L-lactide-co-glycolide) (PLGA) and sized at 100 nm showed over three times more uptake in a test model of canine carotid arteries compared to 275 nm NPs [29].

Nanoparticles used for imaging have enhanced the identification of atherosclerotic plaques by including agent of contrast like Gd (gadolinium) [30]. Lipoproteins with a high density (HDLs), which are about 7–13 nanometre in size, utilized to visualize the macrophages inside these clots by adding Gd [31,32], gold (Au) Nano crystals[33], ironoxide[34], or quantum dots (QDs)[34,35]

Techniques to improve NP penetration via healthy endothelium:-

1. Delivery mediated by receptors –

The method is one of the majority of studied ways to improve how nanoparticles can enter blood vessels. Researchers tested nanoparticles made from poly (lactic acid) (PLA) and poly (ethylene glycol) (PEG) that were designed to target PSMA (prostate- specific membrane antigen) in a phase I clinical investigation [36].

PSMA, which is present on the surface of tumor blood vessels, is added to [37], anothertarget that is often overexpressed in a lot of tumors is the transferrin receptor (TfR) [38].Researchers have developed polymer nanoparticles (NPs) that target TfR, leading to higher absorption of siRNA (small interfering RNA) by cancerous cells [10, 39, and 40]. In a patient study, this approach was used to deliver siRNA to inhibit the expression of the RRM2 cancer gene via a linear vector of cyclodextrin polymer combined with PEG (poly ethylene glycol) adamantine along with a ligand for transferrin.

Researchers have developed different types of nanoparticles (NPs) that use molecule ofIntercellular Adhesion,

like ICAM-1 to target inflammatory blood vessel lining [41]

The purpose of nanoparticles is to traverse the blood-brain barrier (BBB) using endocytosis mediated by receptors [19, 42, and 43]. Researchers have looked at different receptors to enhance their transport into the brain, including as the insulin receptor (IR),low-density lipoprotein (LDL) receptors, and transferrin receptor (TfR).

Azidothymidine (AZT) an antiviral medication, was linked to transferrin-albuminnanoparticles (Tf-albumin NPs) and found to accumulate in the brains of rats. However,targeting the transferrin receptor (TfR) is challenging because it is already occupied bya high amount (25 μM) of natural transferrin (Tf) in the body. Antibodies 8D3 and RI7-217 have been found to be more potent than OX26 at targeting the brain. [44]

2. NANOPARTICLES PROPERTIES CONTROL: SHAPE AND SIZE –

The ability of nanoparticles to penetrate tumours is affected by their shape, size, andsurface charge. Smaller nanoparticles can penetrate tissue better, those smaller than 10nm however are quickly removed by the kidneys or immune system. NPs around 100nm tend to stay in circulation longer than those that are smaller or larger. A newapproach to address both of these challenges is to create multi-layered NPs, like 100 nmgelatine NPs that have 10 nm quantum dot (QD) NPs inside their core. Polystyrenenanoparticles (NPs) of 20 and 40 nm were able to spread evenly throughout the tumour,100 and 200 nm particles however, had limited penetration. [45].

10–20 nm-sized PEGylated phospholipids enhanced tumour penetration and the effectiveness of the cancer drug DOX by distributing better within the tumour [45].
Nanoparticles (NPs) can come in different shapes like spherical, disc-shaped, rod-like,or filamentous. These specific shapes can be created using techniques such as Particle replication in non-wetting templates (PRINT) [47,48], jet and flash imprint lithography(J-FIL), and film stretching [46]

Few examples. Comparing rod-shaped NPs coated with Herceptin to spherical NPs, the former have demonstrated superior binding to HER2-overexpressing breast cancer cells [49, 50].

Herceptin-coated Nano rods were absorbed by breast cancer BT-474. Cells moreeffectively than spherical or disk-shaped nanoparticles. PEG hydrogel cross-linked withcations. Nanoparticles, measuring 150×450 nm, were absorbed by HeLa cells [47] faster than smaller ones sized 100×300 nm. Similarly, Mesoporous silica in the Shape of a rodnanoparticles, 450 nanometre (nm) in length, were better absorbed by A375 human melanoma cells compared to shorter 100 nm spherical particles or 250 nm rods. [51].

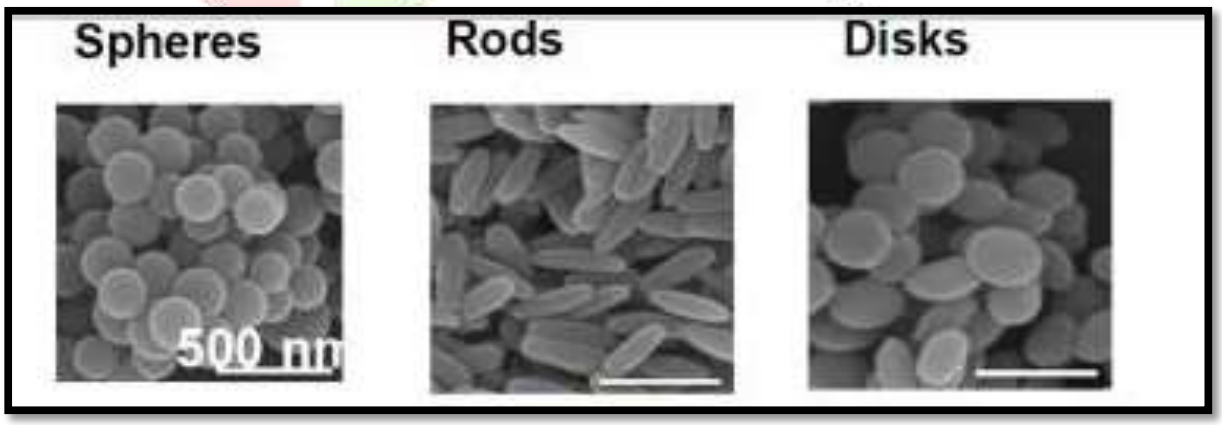

Fig- Shape of Nanoparticles

FACTORS GOVERNING NP TRANSPORT: -

1. MATRIX OF DENSE EXTRACELLULAR: -

The ECM (extracellular matrix) in tumours is denser than in normal tissue because it contains more collagen, higher levels of the enzyme LOX (lysyl oxidase) and more receptors [52]. The high level of collagen in the tumour extracellular matrix make it difficult for nanoparticles (NPs) [6, 53] to move through. LOX strengthens the ECM bycrosslinking collagen, which makes the ECM stiffer [53].

The tumour's extracellular matrix (ECM) contains more fibroblasts, which produce growth factors, chemokine's, and adhesion molecules that help tumour cells grow [54].

The thick ECM acts as a significant barrier to the movement of nanoparticles in solid tumours. Additionally, some drugs can bind to the ECM, further slowing down their transport [3].

2. THE INTERSTITIAL SPACE DISTANCE: -

Nanoparticles can pass via the interstitial space by both convection and diffusion. But for nanoparticles bigger than 4 nm. Diffusion is a primary way they move [4, 54, and 55]. This diffusion process controls how NPs are distributed locally and throughout thetumour, but it is slowed down by the dense, micro porous network of collagen and elastin in solid tumours [56]. Nanoparticles (NPs) like liposomes and viruses, which arearound 100 nm in size, are unable to move through the dense extracellular matrix [57, 58].

3. INTERSTITIAL FLUID PRESSURE (IFP) –

IFP (Interstitial fluid pressure) results in pressure gradient that facilitates the movementof waste materials, nutrients, and oxygen from capillaries enter the lymph nodes via theinterstitial space. [3, 4, 54] This process generates normal tissues have a slightly

Negative pressure (-3 to 3 mm Hg), which is necessary to preserve tissue health and equilibrium.

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5. pH: -

The extracellular pH of tumors is lower (6.0–7.0). Compared to normal blood and tissue(pH 7.4). In the low-oxygen environment of tumour, cancer cells produce energy (ATP)primarily through glycolysis, which occurs without oxygen, instead of using the TCA cycle, which requires oxygen.

Techniques to Enhance Nanoparticle Moving through the InterstitialSpace

The movement of nanoparticles within the tumour tissue can be improved by looseningthe dense ECM (extracellular matrix) [59, 60] and reducing interstitial fluid pressure (IFP). One way to achieve this is by using enzymes like hyaluronidase and collagenaseto break down matrix. These enzymes have been shown to enhance the penetration of molecules like IgG and dextran into tumours. [6, 61, 62]

Additionally, Hyaluronidase has used to increase the uptake of the liposomal medication (doxorubicin) Doxil in tumours.

Hyaluronidase increased the distribution of DOX (a chemotherapy drug) throughout theentire tumour by 2 to 8 times compared to Doxil alone, without affecting its transport into the cell nuclei. Similarly, experiments using fluorescent polystyrene nanoparticles(NPs) of different sizes (20–200 nm) in 3D human cervical cancer cell (SiHa) spheroidsshowed that smaller NPs (20–40 nm) were able to reach the centre of the spheroids after treatment with collagenase. This was because collagenase increased the spaces betweencells and loosened them up. Without collagenase treatment, the NPs were only able to penetrate the outer layer of the spheroid. [63]

Matrix metalloproteinase (MMPs), especially MMP2 and MMP9, are found at higher levels in the areas surrounding tumour cells. [64] Scientists have created peptide Sequences that respond to these enzymes to attach chemotherapy drugs or other large molecules, making it easier to deliver treatments directly to the tumour. For example, DOX has been linked to albumin using an MMP-2 sensitive connector and used to treat A375 human melanoma tumour. [65]

The pro-inflammatory cytokine tumour (TNF-α) or necrosis factor- α raises the blood vessel wall's pressure. The boosts 5–6 times the PEG-liposome delivery rate. Additionally, radiation therapy can also make the blood

vessels in solid tumours more permeable, helping nanoparticles (NPs) reach the tumour more easily. [66, 67]

Nanoparticle Penetration through the Skin: -

1. Skin structure-

The biggest organ in the human body is the skin. Occupying 1.2–1.3 square meters of space and is less than 2 mm (millimetre) thick. [68] There are three primary layers. Thedermis, hypodermis, and epidermis. [69] The top layer of the epidermis, called the stratum corneum, acts as a barrier that limits the movement of substances through the skin.

This layer is made up of fat like Triglycerides, cholesterol, free fatty acids, and ceramides. A dermis, located beneath the epidermis, contains elastin and collagen fibresthat give the skin its strength and elasticity.

2. Liposome: -

The movement of liposomes through a skin has been studied, but exact way they movethrough the skin is still not fully understood. Generally, the liposomes don't pass through skin as whole vesicles. [69, 70] The liposomes have been used to treat skin conditions like infections, psoriasis, acne, and other conditions. [71] The ethosomes, on the other hand, are vesicles made from lipids or surfactants combined with ethanol. [72]

Drugs encapsulated in ethosomes have been shown to exhibit systemic absorption anddeep skin penetration. The phospholipid structure's high ethanol content (~30%) not Only produces a flexible bilayer but also permits deposition and subsequent stratum corneum bilayer breakage.

3. Solid lipid NPs (SLNs) –

The Solid lipid nanoparticles (SLNs) have been utilized for the therapy for a topical skininflammation, skin break out, psoriasis and rheumatoid joint pain. Of late, a strong lipid nanoparticle (SLN) gel was made to provide the pharmaceutical meloxicam (MLX) utilizing a miniaturized scale conflation mild. (73) The entrance of MLX was tried in alab utilizing rodent skin with a framework called the Franz prolixity cell. SLNs have too been utilized to provide isotretinoin (74).

4. Polymeric NPs: -

Both manufactured and normal polymers are utilized to convey drugs through the skin.[75] The most common sorts of polymers incorporate PCL, poly(methyl methacrylate), and poly(ε-caprolactone), polylactic corrosive (PLA), poly(glycoliccorrosive), and their combination known as PLGA.[76 ,77] Among these polymers are secure for the body and can break down normally.

Lipid-polymer crossover nanoparticles (CyLiPn) have been created with a center madeof PLGA, a shell made of PEG, a cyclic pyrrolidinium head gather, and a DOPC external layer. These nanoparticles are aiming to provide anti-TNFα siRNA (siTNFα) for treating incessant skin provocative diseases. [78]

The histological segmentation of SiTNFα-CyLipn-treated skin appeared typical skin conduct where the untreated skin appeared expanded thickening of the skin with prolonged epidermal edges in both epidermis and dermis.

5. Peptide: -

The peptides delivery through the skin is confined through the external sub caste calledthe stratum corner. Still, some cell-piercing peptides can successfully cross the skin, conceivably because they contain appreciatively charged amino acids like arginine or lysine. (79, 80).

The attention of hyaluronic acid (HA) in the original skin towel at the operation point was 1000 times advancer than in the blood. This same system also bettered the capabilityof Siena- lipid NATO complexes to access the skin.

Nanoparticle Permeation through Mucosal Barriers: -

Mucus acts as a protective barrier, keeping harmful pathogens and substances away from the cells underneath. It allows only essential nutrients, proteins, and molecules
[81] to pass through. This makes it the first line of defence for mucosal tissues, effectively trapping and removing tiny particles, viruses, and bacteria. Mucosal surfaces protect key entry points in our body, such as the nose, lungs, intestines, gallbladder, reproductive tracts, and bladder [81].
The majority of the mucus layer (90–98%) contains water. along with much mineral salts, lipids, glycoproteins, and proteins (2–5%). The Mucins are special proteins that create thick, gel-like system. Compared to water, mucus is 1,000–10,000 times more viscous. When not disturbed.[82] Abnormal mucus is linked to several conditions, suchas lung cancer, cystic fibrosis, asthma, and eye ailments.
Current research utilizing nanoparticles has proven that even right up to several hundred nanometres in size, can pass via mucus in just a minute. [83, 84]. Beneath the mucus layer, the epithelial cells are tightly packed with very small gaps between them—less than 0.1 nanometres-making it difficult for NPS to pass through.
Nanoparticles have the ability to penetrate epithelial cells. Beneath the layer of mucous through two main pathways: paracellular and Trans cellular. [85]

In the paracellular pathway, substances move between the gaps of adjacent epithelial cells by diffusion. Nanoparticles smaller than 50 nanometres move between cells (paracellular transport), while those between 50 and 200 nanometres are absorbed by enterocytes (intestinal cells). Larger nanoparticles, between 200 nanometres and 5 micrometres, the M cells absorb them in the intestinal Paper's patches. [86]

Nanoparticles penetration into the epithelium -

1. Oral, intestine: -

The most widely used technique for administering drugs is orally. However, it faces several challenges, such as poor drug solubility, stability issues due to varying pH levels in digestive enzymes, the mucous membrane that protects the gastrointestinal (GI) tract. [85, 87] Because of this, oral drug delivery needs innovative designs and formulations to improve how well the drug is absorbed and distributed in the body.

Natural hydrogels like extra, Gelatine, alginate, and chitosan have all been investigated.For delivering oral drugs using nanoparticles. Micelle polymeric nanoparticles made from PEO, PCL, and PLA all possess demonstrated improved absorption. Properly regulated medication discharge at the intended location. After oral administration, nanoparticles are typically absorbed in the small intestine.

The main cell types of the small intestine include mucus-secreting goblet cells, immune-sampling M cells, and absorbent enterocytes. [88] M cells are linked with various immune cells, such as lymphocytes, immunoblots, plasma cells, and macrophages.

2. Lung: -

Most inhaled particles become stuck in the respiratory tract lining of mucus. Between the nose and the last bronchioles. The mucus layer in the human lungs is divided into two sections. The layer of the periciliary (sol) which is thin and watery, and the luminal(gel) layer, which is thicker and stickier. The sol layer is near the cells, while there are cilia in the gel layer. That help move lungs mucus discharge trapping any foreign particles along the way.

Technique for overcoming the mucus barriers consist of using buccal, mucoadhesive, and mucus-penetrating particle. Conventional hydrophobic particles, such as PCL, PLA, and LPGA tend to stick to mucus while hydrophilic and neutral particles can reduce this attachment of the mucus fibers using Solid lipid nanoparticles (SLNs) combined with rifampicin, isoniazid, and pyrazinamide demonstrated a slowly and steady release of the TB treatment medications in both lab and clinical trials. [89] Administering drugs through the lungs is an effective way to deliver medications.

3. Nose: -

The nasal route provides a simple, painless, and non-invasive way to provide medication. Both locally and throughout the body, with a high absorption rate [90] the nasal cavity is composed of the following parts: the respiratory area, the olfactory region, the nasopharynx, the atrium, and the anterior and posterior vestibules. Additionally, it has mucus-producing glandular epithelial cells. A medication delivery system must get beyond the mucus layer and the endothelium inorder to get through the nasal mucosa. When compared to chitosan-mediated transport, the nasal distribution of insulin in rats was improved by the combination treatment of insulin-loaded chitosan NPs and acetyl cysteine, a mucolytic agent [76].

4. Vagina: -

The composition of vaginal mucus is 95% water, 1% to 2% fibre, and trace amounts ofproteins, enzymes, lipids, salts, and lactic acid. [91] The fibers create viscoelastic gel produced by forming cross-links the water, which can limit the way medications pass through the vaginal canal. Numerous medications, including spermicides, antifungals, hormones used in contraception, and substances that aid in ovulation or abortion, have been developed forvaginal birth. Researchers have used Polystyrene particles coated with PEG that range in size from 200 to 1000 nm to investigate the composition of cervicovaginal mucus (CVM) in humans at various pH values. (1-2, 4, 6-7, and 8-9). [84]

FUTURE DIRECTION: -

1. **Improved Design**: Researchers are working on creating nanoparticles with surface coatings or modifications that make them more likely to cross barriers safely and effectively.
2. Biodegradable Materials: Using biodegradable nanoparticles can reduce toxicity and ensure that they break down safely in the body after delivering their cargo.
3. Targeting Mechanisms: Advanced techniques that help nanoparticles identify and bind to specific cells could improve their penetration and effectiveness.
4. New Delivery Methods: Innovations such as using ultrasound or magnetic fields may help push nanoparticles across barriers more efficiently.
5. Combining Therapies: Using nanoparticles alongside other treatments may help overcome the barriers and boost the effectiveness of medical interventions.

Conclusion: -

Nanoparticles have great potential in medicine, especially for targeted drug delivery and disease treatment. However, getting them to cross cell and tissue barriers effectively is a major challenge. These barriers, like the skin, lungs, and blood-brain barrier, are designed to protect the body and are difficult to bypass. The size, shape, surface properties, and material of nanoparticles all play a role in how well they can penetrate these barriers.

Current research has made progress in understanding these factors and improving nanoparticle design, but there are still many unanswered questions. For example, we need to better understand how nanoparticles interact with cells and tissues and minimize potential side effects. Advanced techniques like surface modifications and biodegradable materials offer promising solutions.

In the future, collaboration between scientists, engineers, and medical professionals will be key. By combining knowledge from different fields, we can overcome these challenges and unlock the full potential of nanoparticles for safe and effective medical treatments.

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