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REVIEW ARTICLE

Hydrogels Used As A Potential Drug Delivery System: A Review

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ABSTRACT

Hydrogels, the swellable polymeric materials have been widely investigated as the carrier for drug delivery systems. These biomaterials have gained attention owing to their peculiar characteristics like swelling in aqueous medium, pH and temperature sensitivity or sensitivity towards other stimuli. Hydrogels being biocompatible materials have been recognized to function as drug protectors, especially for peptides and proteins, from in-vivo environment. Also, these swollen polymers are helpful as targetable carriers for bioactive drugs with tissue specificity. Hydrogels are presently under investigation as a delivery system for bioactive molecules, because of their similar physical properties as that of living tissue, which is due to their high water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids. This review presents an overview to the advances in hydrogel based drug delivery that have became the interest of most researchers.

Key Words: Hydrogels, Scanning Electron Microscope, Characterization, Polymerization.

INTRODUCTION

With ongoing research in advanced drug delivery formulation to provide stable and economical drug delivery systems, the focus is on hydrogels that are known to reduce the problems of not only conventional dosage forms but also of delivery systems which require a biocompatible, convenient and stable drug delivery systems for molecules as well as NSAIDS (Non- steroidal anti-inflammatory drugs) or as large as proteins and peptides [1]. There are a number of evidences when such drug delivery devices are imperative such as delivery of insulin at elevated blood sugar levels where it is required to constantly provide the drug in the system. These controlled drug delivery systems are designed for zero- order release kinetics which ensure constant drug release over a prolonged period of time. Drug targeting is achieved by using biocompatible polymers along with drug in micronized form and then attaching certain " homing devices", like antibodies. It leads to exposure of drugs to diseased cells while the normal cells are protected[2]. All these approaches of dosage form designs require a carrier which should be biocompatible and biosensitive like hydrogels which are hydrophobic polymeric network of these dimensional structures consisting of single chain of polymers (monomers) being cross linked. The cross- linking renders these structures insoluble in water due to anionic interaction and hydrogen –bonding[3]. These structures imbibe water or biological fluids in large amount atleast 10-20 times their molecular weight, thus become swollen[4]. Cross- linked hydrogels have sufficient mechanical strength and physical integrity. If water is removed from these swollen biomaterials, they are called xerogels, which are then dried hydrogels. The network structure of hydrogels can be macroporous, microporous or nonporous. Macroporous hydrogels are having large pores of dimension 0.1 to 1 µm. These hydrogels release the drug entrapped inside the pores through mechanism dependent on drug diffusion coefficient. Porosity and tortuosity of the gel network[5]. Microporous hydrogels having small pore size of the gel network, usually in the range of 100-1000 angstrom . The drug releases by molecular diffusion and convection. However, when drugs and polymers are thermodynamically compatible, partitioning of drug through the hydrogel wall is predominant. Nonporous hydrogel are the mesh- like structures of macro-molecular dimension (10 – 100 angstrom) and are formed due to cross- linking of monomer chains. The release of drug is only by diffusion

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mechanism [3]. In a chemical hydrogel , all polymer chains are cross-linked to each other by covalent bonds, and thus, the hydrogel is one molecule regardless of its size. For this reason there is no concept of molecular weight of hydrogels, and hydrogels are sometimes called infinitely large molecules or super macromolecules. One of the unique properties of hydrogel is their ability to maintain original shape during and after swelling due to isotopic swelling. Swelling only changes the size of the original shape. Hydrogels, have been used widely in the development of biocompatible biomaterials, and this is mainly due to the low interfacial tension and low frictional surface by the presence of water on the surface. The dried hydrogels (also called xerogels) are usually clear, and swelling in water takes a long time. The slow swelling process is due to slow diffusion of water through the compact polymer chains. It is this slow swelling property that has been useful in controlled drug delivery[4]. For a glassy hydrogel of a size equivalent to a stack of five pennies, it will take hours before the hydrogel shows appreciable swelling. Their ability to absorb water is due to the presence of hydrophilic group such as –OH, -CONH , -COOH. The water content in the hydrogels affect different properties like permeability, mechanical properties, surface properties, and biocompatibility. Hydrogels have similar physical properties as that of living tissue, and this similarity is due to the high water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids. The ability of molecules of different size to diffuse into (dry loading), and out (release drug) of hydrogels, permit the use of hydrogels as delivery systems. Since hydrogels have high permeability for water soluble drugs and proteins, the most common mechanism of drug release in the hydrogel system, is diffusion. Factors like polymer composition, water content, crosslinking, density, and crystallinity, can be used to control the release rate and release mechanism from hydrogels. An ideal biodegradable, polymeric scaffold for tissue engineering should be biocompatible,biodegradable and dimensionally stable until the functionally active extacellular marix is generated. The scaffold should have porous, with interconnecting pore structure to enable the migration of nutrients, accommodation of large number of cells within the structure and their organization into a functioning tissue. Since soluble drugs and proteins, the most common mechanism of drug release in the hydrogel system, is diffusion. Factors like polymer composition, water content,crosslinking density, and crystallinity, can be used to control the release rate and release mechanism from hydrogels. The beginning of modern hydrogel research is considered to be the synthesis of poly(hydroxyl ethyl methacrylate). Since then , considerable progresses have been made in the synthesis and applications of hydrogels. The preparation of hydrogel formulations to aid in the processing of the drug delivery system during its manufacture, protect support,bioavailability or delivery of the drug during storage or use[6].

Characterization of Hydrogels :

Generally hydrogels are characterized for their morphology, swelling property and elasticity. Morphology is indicative of their porous structure. Swelling determines the release mechanisms of the drug from the swollen polymeric mass while elasticity affects the mechanical strength of the network and determines the stability of these drug carriers. Some of the important features for characterization of hydrogels are as follows [5,6].

Morphological Characterization:

Hydrogels are characterized for morphology which is analysed by equipment like stereomicroscope. Also the texture of these biomaterials is analysed by scanning electron microscope to ensure that hydrogels,especially of starch, retain their granular structure. The scanning electron microscope is an instrument that produces a largely magnified image by using electrons instead of light to form an image. A beam of electrons is produced at the top of the microscope by an electron gun. The electron beam follows a vertical path through the microscope, which is held within a vacuum. The beam travels through electromagnetic fields and lenses, which focus the beam down toward the sample. Once the beam hits the sample, electrons and x- rays are ejected from the sample. Detectors collect these x-rays, backscattered electrons, and secondary electrons and convert them into a signal that is sent to a screen similar to a television screen[7].

x-ray diffraction:

It is also used to understand whether the polymers retain their crystalline structure or they get deformed during the processing pressurization process. The diffraction analysis is quite a popular study for the morphological characterization of hydrogels. The retention of crystalline structure or their deformation during pressurization has played a vital role.Diffraction analysis is the estimation of crystalline or amorphous characteristics. The appearance of new peaks in powder pattern is

characteristic of drug – excipient interaction. X-ray diffraction is particularly used for the determination of broad halos that is a characteristic of impurities in powder that determines the pattern of the arrangement in which the hydrogel layers are distributed[8].

In – Vitro Diffraction:

Since hydrogels are the swollen polymeric networks, interior of which is occupied by drug molecules, therefore, release studies are carried out to understand the mechanism of release over a period of application. The in- vitro diffraction study is quite popular for studing the release profile of hydrogel. One that basis the bioequivalence study is carried out to estimate the release of dosage forms. The parameters are matched with the standard plot so that the equivalence between the drug solution is carried out.In – vitro diffraction of type-1 collagen hydrogel containing bioactive glass and silica sol-gel micromeritics particles are formulated and their invitroapatite- forming ability have been simulated by body fluids that is assessed[9].

FTIR (Fourier Transform Infrared Spectroscopy):

Any change in the morphology of hydrogels changes their IR absorption spectra due to stretching and o-H vibration. Formation of coil or helix which is indicative of cross linking is evident by appearance of bonds near 1648cm-1. The stretching or bending vibrations are basically responsible for the changes in IR absorption spectra. FTIR is an important technique in organic chemistry. It is an easy way to identify the presence of certain functional groups in a molecule. Also one can use the unique collection of absorption bands to confirm the identity of a pure compound or to detect the presence of certain impurities[10].

Swelling Behaviour:

The hydrogels are allowed to increase in aqueous medium or medium of specific pH to know the swellability of these polymeric network. These polymers show increase in dimensions related to swelling. The hydrogels swell in water to form the polymeric network. The formation of this polymeric network is responsible for the morphological characterization of drug. Polymers are characterized by viscosity method, osmometry, light scattering and size exclusion chromatography[11].

Rheology:

Hydrogels are evaluated for viscosity under constant temperature of usually 4c by using Cone Plate type viscometer. This viscometer is highly specific for the evaluation of viscosity. The viscosity is determined by the simple equation of determining the angle of repose through that height and length is determined [12].

Preparation Of Hydrogels:

Several techniques have been reported for the synthesis of hydrogels. The first approach involves copolymerization/ crosslinking of co-monomers using multifunctional co-monomers, which act as crosslinking agent. The polymerization reaction is initiated by chemical initiator. The polymerization reaction is initiated by chemical initiator. The polymerization reaction can be carried out in bulk, in solution, or in suspension. The second method involves crosslinking of linear polymers by irradiation, or by chemical compounds. The monomers used in the preparation of the ionic polymer network, contain an ionisable group, a group that can be ionized, or a group that can undergo a substitution reaction after the polymerization is completed. As a result, hydrogels synthesized contain weakly acidic groups like carboxylic acid, or a weakly basic group like substituted amines, or a strong acidic and basic group like sulfonic acids, and quaternary ammonium compounds. Some of the commonly used cross linking agents include divinylbenzene, and ethylene glycol dimethacrylate[13].

Solution Polymerization/ Cross Linking:

In solution, co- polymerization/ crosslinking reactions, and ionic or neutral monomers are mixed with the multifunctional crosslinking agents. The polymerization is initiated thermally, by uv light, or by redox initiator system. The presence of solvent serves as heat sink, and minimizes temperature control problems. The prepared hydrogels need to be washed with distilled water to remove the unreacted monomers, crosslinking agent , and the initiator. The best example is preparation of poly(2-hydroxy ethyl methacrylate) hydrogels from hydroxyl ethyl methacrylate, using ethylene glycol dimethacrylate as crosslinking agent. The hydrogel can be made pH sensitive or temperature sensitive by incorporating methacrylic acid, or N-isopropylacrylamide as monomers[14,15].

Suspension Polymerization:

This method is employed to prepare spherical hydrogel microparticles with size range of 1 um to 1 mm. In suspension polymerization, the monomer solution is dispersed in the non solvent forming the fine droplets, which are stabilized by the addition of stabilizer. The polymerization is initiated by thermal decomposition of free

radicals. The prepared microparticles then washed to remove unreacted monomers, crosslinking agent and initiator. Hydrogel particles of poly(vinyl alcohol) and poly(hydroxyl ethyl methacrylate) have been prepared by this method.

Polymerization By Irradiation:

High energy radiation like gamma and electron beam, have been used to prepare the hydrogels of unsaturated compounds. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains, resulting in the formation of macroradicals. Recombination of macroradicals on different chains results in the formation of covalent bonds, and finally a crosslinked structure is formed [16,17].

Type Of Hydrogels:

pH – Sensitive Hydrogels:

These hydrogels respond to changes in pH of the external environment. These gels have ionic group (which are readily ionisable side groups) attached to impart peculiar characteristics. Some of the pH sensitive polymers used in hydrogels preparations are polymethylmethacrylate (PMMA), polyacrylamide (PAAm), polyacrylic acid (PAA) , polydimethylaminoethylmethacrylate (PDEAEMA) and polyethylene glycol[18,19].

Temperature Sensitive Hydrogels:

The hydrogels being cross-lined polymers are temperature sensitive. These hydrogels are pharmaceutically well accepted owing to large number of temperature sensitive drugs being delivered in these dosage forms. Temperature sensitive hydrogels is particularly targeted for the formulation of temperature sensitive hydrogels that is particularly defined[20].

Glucose Sensitive Hydrogels:

These hydrogels are sugar sensitive and show variability in response depending upon the presence of glucose. One of such pharmaceutical hydrogel system is the cross linked poly (methacrylamide phenyl boronic acid)-coacylamide hydrogel which liberates the drug in a controlled manner only when the concentration of glucose is high in the surrounding environment causing swelling of the hydrogel. Glucose-sensitive phase- reversible hydrogel is formulated by the interaction between polymer- bound glucose and concanavalin A . Glucose sensitive hydrogels has been characterized by the release of model proteins by insulin and lysozymes through the hydrogel membrane as the free glucose concentration in the environment has been changed. Glucose sensitive hydrogels is particularly useful for the determination of the sensitivity of hydrogel that is particularly useful for the determination of the viability of compound of compound that is particularly useful for the presence of glucose or fructose[21].

Nanohydrogels:

Nanohydrogels are the hydrogels which are prepared in water by self aggregation of polymers of natural origin like dextran. These types of hydrogels are formed from natural polysaccharide like dextran, pullulan, or cholesterol- containing polysaccharide. The hydrogels are prepared by the aggregation of particles called miscelles[22].

Pharmaceutical Applications Of Hydrogels:

To provide sustained or controlled drug delivery into systems, the hydrogels are designed, modulated and characterized for the expected invivo results. These hydrogels have gained existence in drug delivery through parenteral, ocular, rectal ,vaginal, dermal and nasel route. The biomedical application of hydrogel is a polyvinylalcohol that is of great interest because of its many desirable characteristics that is specifically for various pharmaceutical and biomedical applications. The crystalline nature of the polyvinyl alcohol has been of specific interest particularly for physically cross-linked hydrogels prepared by repeated cycles of freezing and thawing that is produced by conventional crosslinking[23].

Wound Healing:

A modified polysaccharide that occurs in cartilage has been used in formation of hydrogels to treat cartilage defects has been developed. Polyethylene glycol fumarate hydrogels is formulated for wound healing. Wound healing is particularly useful for the determination and elucidation of the structure of hydrogel that is the estimation of the particular structure of hydrogel. Hydrogel is a crosslinked polymer matrix which has the ability to absorb and hold water in its network structure. Hydrogels act as a moist wound dressing material and have the ability to absorb and retain the wound exudates along with the foreign bodies, such as bacteria, within its network structure[24].

Colon Specific Hydrogels:

Colon specific hydrogels of polysaccharide have been specifically designed because of presence of high concentration of polysaccharide enzymes in the colon region of GI. (gastrointestinal tract). Dextran hydrogel is formulated for colon- specific drug delivery.The diisocyanate that is proposed for the equilibrium degree of mechanical strength[25].

Cosmetology:

For aesthetic purpose, hydrogels have been implanted into breast to accentuate them. These hydrogels swell invivo in aqueous environment and retain water. These breast implants have silicone elastomer shell and are filled with hydroxyl propyl cellulose polysaccharide gel . Pharmaceutical companies are focussing on advanced drug delivery formulations to provide stable and economical drug delivery systems polymers that is backbone in designing the modified release dosage forms due to various properties that hydrogels have attained[26].

Topical Drug Delivery:

Hydrogels have been used to deliver active component like Desonide which is a synthetic corticosteroid usually used as an anti-inflammatory. Instead of conventional creams, the hydrogels have been formulated for better patient compliance. Topical drug delivery device for the formulation of corticone drugs like Budenoside is particularly important for the delivery device of hydrogels[27].

Ocular Drug Delivery:

For ocular drug delivery of pilocarpine and timolol, the polymer which form gel such as xyloglucan have been used for sustained drug delivery. A number of anticholinergic drugs are available like timolol, atenolol, that is particularly useful as the polymer for the formulation as well as preparation of hydrogel. Ocular drug delivery device like that of anticholinergic drugs like Atenolol is particularly important for the drug delivery devices[28].

Industrial Applicability:

Hydrogels have been used as absorbents for industrial effluents like methylene blue dye.Methylene blue dye is particularly useful as absorbant for the industrial applicability of hydrogel that is used as absorbent for the industrial effluent for a large number of compounds that are particularly useful for a large variety of hydrogels. Hydrogels are used as absorbant for industrial effluents like methylene blue dye. Another example is adsorption of dioxins by hydrogel beads[29].

Modified Dosage Forms:

An interesting research in the field of drug delivery is of bio- macromolecules like insulin delivered to the site of absorption with hydrogels of poly (methacrylamide co – itaconic acid) [30].

Soft Contact Lenses:

The first commercially available silicon hydrogels adopted two different approaches.First approach by Bausch and Lamb was a logical extension of its development of silicon monomers with enhanced compatibility in hydrogel forming monomers. The second of ciba vision was the development of siloxy monomers containing hydrophilic polyethylene oxide segment and oxygen permeable polysiloxane units [31].

Tissue Engineering:

Micronized hydrogels are used to deliver macromolecules(phagosomes) into cytoplasm of antigen presenting cells. This property is also utilized in cartilage repairing. Natural hydrogel materials used for tissue engineering include agarose, methyl cellulose and other naturally derived products[32].

Drug Delivery In GI Tract:

Hydrogels deliver drug to specific sites in the GIT . Drugs loaded with colon specific hydrogels show tissue specificity and change in the pH or enzymatic actions cause liberation of drugs. They are designed to be highly swollen or degraded in the presence of microflora[33].

Application Of Hydrogels In Tissue Engineering:

There are several applications in regenerative medicine where hydrogels have found utility. Langer and vacanti were among the first to elucidate the basic technique used in tissue engineering to repair damaged tissues as well as the ways the polymer gels are utilized in these techniques. To date, hydrogels in regenerative medicine have been used as scaffolds to provide structural integrity and bulk for cellular organisation and morphogenic guidance, to serve as tissue barriers and bioadhesives, to act as drug depots, to deliver bioactive agents that encourage the natural reparative process, and to encapsulate and deliver cells[34].

Hydrogels As Scaffold Materials:

Hydrogels are an attractive scaffolding material because their mechanical properties can be tailored to mimic those of natural tissues. As scaffolds, hydrogels are used to provide bulk & mechanical constitution to a tissue construct whether cells are adhered to or suspended within the 30 gel framework. The fundamental obligation of a tissue scaffold is to maintain cellular proliferation and desired cellular distribution throughout the expected servicelife of the construct. Therefore a critical design consideration for hydrogels in regenerative medicine is the transition in functional dependence between the scaffold and the emergent tissue during scaffold biodegradation and the healing process[35].

Hydrogels as barriers:

To improve the healing response following tissue injury, hydrogels have been used as barriers in order to prevent restenosis or thrombosis due to post-operative adhesion formation. It has been shown that forming a thin hydrogel layer intravascularly via interfacial photopolymerization will prevent restenosis by reducing intimal thickening and thrombosis. The thin hydrogel layer is able to reduce intimal thickening because it provide a barrier to prevent platelets, coagulation factors, and plasma proteins for contacting the vascular water[36].

Hydrogels with drug delivery capabilities:

Hydrogels are often used as localized drug depots because they are hydrophilic, biocompatible, and their drug release can be controlled and triggered intelligently by interactions with biomolecular stimuli. Macromolecular drugs such as proteins or oligonucleotides that are hydrophilic are inherently compatible with hydrogels.By controlling the degree of swelling, crosslinking density, and degradation rate, delivery kinetics can be engineered according to the desired drug release schedule[37].

Hydrogels for cell encapsulation:

Cell transplantations can be achieved with hydrogels because they can provide immunoisolation while still allowing oxygen, nutrients, and metabolic products to diffuse easily into the hydrogel. The development of a bio-artificial endocrine pancreas, photopolymerized PEG diacrylate (PEGDA) hydrogels have been fabricated to transplant islets of langerhans[38].

Test For Hydrogels:

Biocompatibility Test:

Generally hydrogels are biocompatible and non-irritant in nature. The biocompatibility of the hydrogels is generally associated with the hydrophilic nature of the same, which helps in washing of the toxic and un- reacted chemicals during synthesis. The presence of water in the system makes it soft and rubbery which offers least frictional irritation and provides a soothing effect when in contact with the physiological system. In this method, the material whose biocompatibiliry has to be determined is placed in direct contact with the host environmental cells and is subsequently incubated for a specific period of time at 37c. In the second method, the material is placed in a suitable physiological solution and is incubated for a specific period of time at 37c to allow any leaching from the material. The leachates, so obtained, are used to carry out the biocompatibility tests in the presence of cells[39].

Water Vapour Transmission Rate:

Water vapour transmission rate (WVTR) is defined as the quantity of the water vapour under specified temperature and humidity conditions , which passes through unit area of film material in fixed time.Water vapour transmission rate is measured in grams per square meter over a 24 hours period. It is inversely proportional to the moisture retentive nature of a wound dressing i.e the wound dressing with lower water vapour transmission rate will be able to retain wound surface moisture.Typically, a wound dressing material showing WVTR less than 35g/m2/hr is defined as moisture retentive and helps in a rapid healing [40].

Mechanical Properties:

It is important to characterize the hydrogels for their mechanical properties. This is because the hydrogels could be used in various biomedical applications, viz. Ligament and tendon repair, wound dressing material, matrix for drug delivery and tissue engineering and as cartilage replacement, which require hydrogels with different properties .FDA also provides strict guidelines for the same depending upon the type of application. As for example, a drug delivery device should maintain its integrity during the lifetime of the application, unless it has been designed to degrade[40].

Chemical And Physical Analysis:

Since presence of different functional groups play an important role in the water holding capacity of the hydrogel, hence it become necessary to analyse the presence of different functional groups in a newly synthesized hydrogel. Also, determination of the functional groups can provide some information on the composition of the polymeric network.The various techniques which are used for the purpose include infrared (IR) spectroscopy. UV- visible spectroscopy, nuclear magnetic resonance (NMR) and mass spectrometry. The chemical bonds in a molecule are always either in stretching or in bending motion.The IR spectroscopy involves excitation of the functional groups with IR radiation of a particular wavelength which results in the increase in the amplitude of vibrations (bond stretching and bending) of the functional group[41].

Surface Topography:

The surface morphology of a hydrogel can reveal minute important details. The monitoring of the surface properties of materials can either be done by contact profilometers or by non –contact

profilometers.Atomic forced microscopy (AFM) is commonly used for determining the surface properties of the hydrogels & xerogels. AFM is a contact profilometer and can be operated either in contact mode or tapping mode. In the static mode, the tip of the AFM instrument drags over the sample surface. The surface properties are measured as a function of the tip deflection as it moves over the surface. The deflection of the tip is generally measured using a laser beam detector which detects the reflected laser beam from the upper surface of the cantilever holding the tip.While in the tapping mode, the tip of the cantilever has a piezoelectric element. The cantilever is oscillated in the resonance frequency of the piezoelectric element. As the tip approaches the surface of the material, there is an increased interaction between the surface of the tip thereby resulting in the decrease in the amplitude of oscillation[42].

CONCLUSION

There are enough scientific evidences for the potentiality of hydrogels in delivery of drug molecules to a desired site by triggering the release through an external stimulus such as temperature, pH , glucose or light. These hydrogels being biocompatible and biodegradable in nature, not having toxic or injurious effect or biological function, are excellent candidates for controlled release devices and bioadhesive devices, applicable as drug and cell carrier, and as tissue engineering matrices. The release of therapeutic agent can be regulated by controlling water swelling and crosslinking density and have been used in the development of nanobiotechnology products and have maryelous applications in the field of controlled drug delivery as well.They can be injected in – vivo as a liquid that gels at body temperature. The grating of hydrogels with good mechanical properties onto biomaterials have paved the way for hydrogels with good mechanical strength and toughness after swelling. The characterization of hydrogel into morphological pattern demonstrate the x- ray diffraction, fourier transform infra red spectroscopy, rheology and the swelling behaviour of hydrogels. A part from this they have gained wide applicability in the field of wound healing , colon specific drug devices, cosmetology, topical drug devices, ocular drug devices and modified dosage forms . Wound healing & ocular drug delivery are the processes that estimates the presence of hydrogels and their incorporation with hydrogels by using anticholinergic drugs.The ocular drug delivery device is particularly useful as synthetic hydrogels.The industrial applicability of hydrogel have paved the way for a large number of synthetic hydrogels that is particularly useful for the large number of synthesis of hydrogels. Modified dosage forms of hydrogels have paved the way for a large number of formulations and thus have gained tremendous approach in the field of science.There are methods like solution polymerization, suspension polymerization and polymerization by irradiation for the preparation of hydrogels . That is why these turn- able biomedical drug delivery devices are gaining attention as intelligent drug carriers.

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