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A REVIEW ON PROTEIN DRUG DELIVERY SYSTEM

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ABSTRACT

Protein and Peptide drug delivery system are the Novel drug delivery System. Proteins and peptides are the most abundant components of biological cells. They exist functioning such as enzymes, hormones, structural element and immunoglobulin. The twenty different naturally occurring amino acids join with each other by peptide bonds and build polymers referred to peptides and proteins. Although the distinction between peptides and proteins are peptide contains less than 20 amino acids, having a molecular weight less than 5000, while a protein possesses 50 or more amino acids and its molecular weight lies above this value. The most of pharmaceutical proteins and peptides are absorbed intramuscular IM, intraventricular IV and subcutaneous route of absorption, but the oral route is more convenient for absorption of protein as compared to other. Several approaches available for maximizing pharmacokinetic and pharmacodynamics properties are chemical modification, formulation vehicles, mucoadhesive polymeric system, use of enzyme inhibitors, absorption enhancers, penetration enhancers etc. The Present review is described structure, classification of protein, need, advantages, function of protein and peptide drug delivery system. route of absorption, pharmaceutical approaches, Incorporation of DDS, Stability aspect, applications, recent advances and marketed formulation of protein and peptide drug delivery system are also described.

KEYWORDS: Protein, Peptide, Parenteral, Non-Parenteral, Pharmaceutical approaches.

INTRODUCTION

Proteins and amides are the novel drug delivery system. Proteins and peptides are the foremost long ingredients of the living system and biological cell. Its functions embrace

hormones, enzymes, structural components, and immune serum globulin. Several metabolic processes conjointly play a crucial role in immunogenic defense, additionally as participate in several biological activities. Macromolecule is one in every of the foremost long organic molecules within the biological systems, Macromolecule word was first utilized in Bercelius. The word macromolecule is holding on to the primary place by suggests that of a Greek word Proteins.

Proteins and peptides are the biopolymers that yield two or additional amino acids on chemical reaction. Peptides and polypeptides are the principal elements of the substance of cells and are high mass compounds consist of alpha amino acids connected along by amide linkages. Proteins could have thousands of organic compound residues. Though the terms "protein" and "polypeptide" are typically used interchangeably, molecules named as polypeptides usually have molecular weights below ten, and referred to as proteins have higher molecular weights.

Molecular size of proteins is bigger than those in ancient prescribed drugs, and that they have secondary and tertiary structures, that build them terribly vulnerable to physical and chemical degradation.

Molecular weight and size greatly influence the diffusion of medicine through the animal tissue layer.one in of the challenges in operating with amide medical specialty is their tiny size, which usually equates to a brief current life. it's incontrovertible fact that the lower the mass of the amide, the shorter the period is. Most of therapeutic proteins and peptide-based drugs are administered by the parenteral route, that is, via an injection. The obvious downside of this delivery method is patient acceptance and compliance, limiting most macromolecule development to indications in which the need to use invasive administration routes are not outweighed by the associated expenses or inconvenience.

Protein and peptides when delivered orally would not achieve therapeutically acceptable bioavailability because of the enzymatic barriers, the intestinal epithelial and vascular endothelial barriers, which typically digest them with the help of the GI system.[1]

STRUCTURE OF PROTEIN

Primary structure: The first structure of the macromolecule is named due the variety, nature and sequence of amino acids with peptide chains, during this structure, the N terminal of

organic compounds is usually the left finish of peptide and also the right amino acid shown within the right facet. The simplest example structure of primary is associate degree hypoglycemic agent molecule.

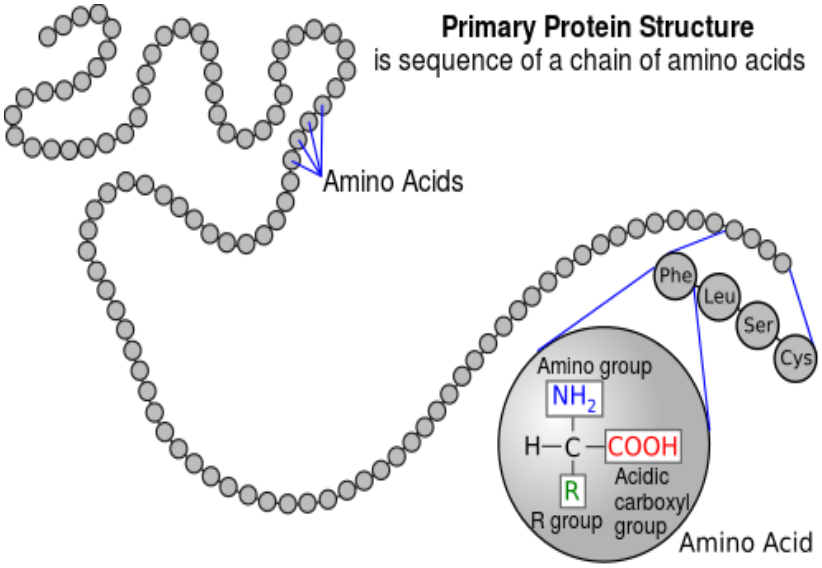

Fig1: Primary structure of protein.

Secondary structure: Secondary structure of the macromolecule during which long peptide series is collapsible or collided in several geometrical arrangements.[2] sorts of macromolecule alpha spiral structure and secondary structure of beta folded sheet area unit organized.

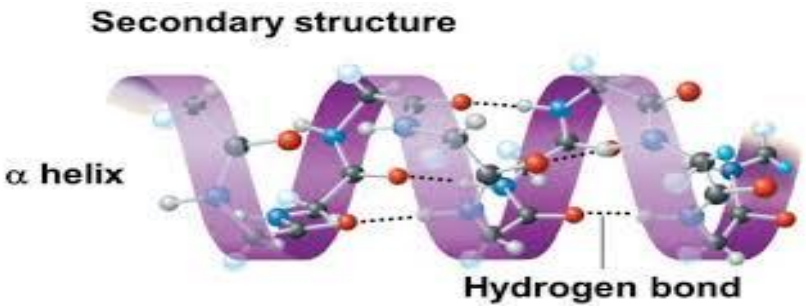

Fig 2: Secondary structure of protein.

Tertiary structure: In tertiary structure of proteins area unit the 3-dimensional whorled and folding of the chain, stable by the interaction between the sequences of amino acids. This folding result the (R-) cluster is facet chain amino acids, these interaction area unit primarily (H-) secured Interactions. the ultimate form of the tertiary structure of macromolecule is associate degree go on, globe and the other irregular form.

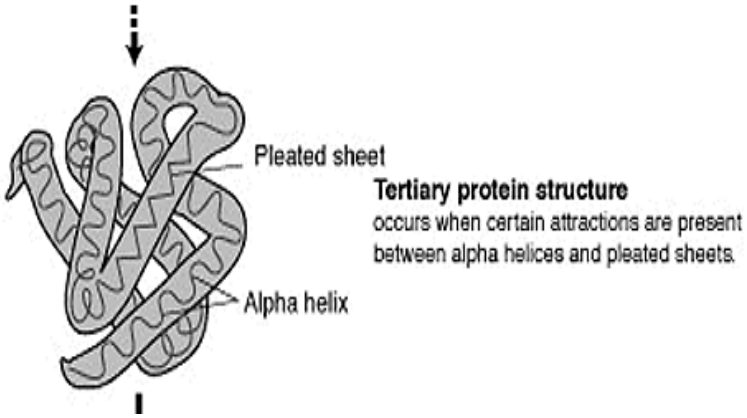

Fig 3: Tertiary structure of Protein.

Quadrilateral structure: In Quaternary structure of Proteins area unit the 2 or additional peptide chain hold along by non - chemical bond to provide the quaternary structure of the proteins, hemoglobin has Example of Quaternary structure of Proteins. Proteins and amide area unit applicable endogenous functioning to keep up the biological environments. the invention of various Hormones and Peptides area unit Applicable for the pharmaceutical and biopharmaceuticals.[2]

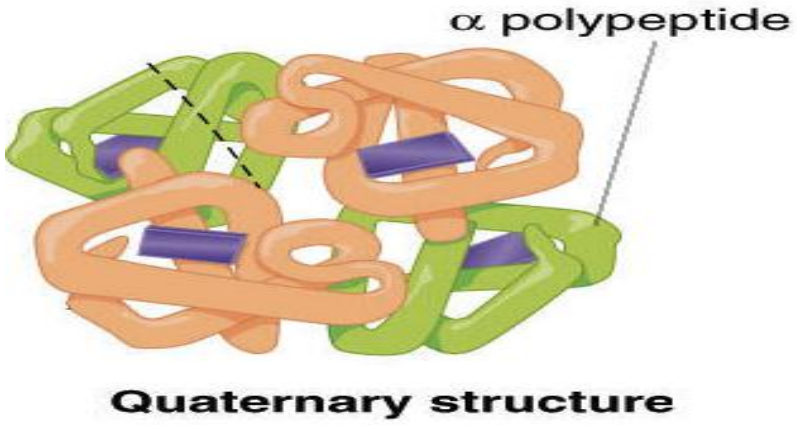

Fig 4: Quaternary structure of Protein.

Types of protein

Depending on the number of amino acids they are classified as follows:

- Polypeptides
- Oligopeptides
- Fibrous proteins
- Globular proteins
- Oligomeric proteins

Need of Protein and Peptide Drug Delivery System

- Proteins and peptides are vital in biological cells and organic molecules.
- In the Absence of proteins and peptides causes diseases like DM. (Caused as a result of the shortage of macromolecule referred to as INSULIN)
- R-DNA technology and somatic cell techniques conjointly utilized in macromolecule and amide primarily based prescribed drugs.

Advantages of Protein and Peptide Drug Delivery System

- Erythropoietin is especially used for the assembly of blood corpuscle.
- Heart attack, macromolecule tissue plasminogen substance is employed for stroke.
- Bradykinin peripheral circulation will increase.
- Somatostatin trauma in peptic ulcer.
- Gonadotropin brings biological process.
- Insulin maintains the amount of glucose.

Functions of Protein and Peptide drug delivery systems

- Transport and storage of tiny molecules and biological molecules.
- Coordinated speed through muscular contraction.
- Mechanical support from fibrous proteins.
- Production and transmission of nerve impulses.
- Enzymatic catalysts in organic chemistry reactions.
- Immune Protection Through Antibodies.
- Control of growth and variation through hormones.

Path of absorption

The Proteins and amide drug delivery system during which most of the pharmaceutical proteins and peptides Formulations area unit the developed as an answer, suspension, Emulsions and that they area unit delivered in Invasive or epithelial duct route like intra muscular route (IM), endogenous route (IV) intravenous and connective tissue route (SC) Injections. But, these all routes area unit arises its own difficulties like, poor patient compliance, the pain and discomfort associated during this route (to inject injection in same web site once more and once more it will arise Pain) and it's an Inconvenience to treat the medical specialty patients. The oral route of administration in protein and peptide is appropriate as compared to epithelial duct route.

The oral route having a 1 of the foremost convenient route of drug administration, during this style of route no pain and discomfort was arises and maintained the upper Patient compliances or acceptance.[3]

Oral protein and peptide drug delivery arises many issues for his or her oral administration of medicine. There unfavorable and undesirable chemistry properties area unit like the big molecular size of the drug molecules, drug undergoes susceptibleness to biological and catalyst degradations, the oral drug having a brief plasma 0.5 life as compared to alternative medicine, it will be having high immunogenicity, the tendency of macromolecule undergoes aggregations, surface assimilation and it will undergo denaturation's, the foremost drawback orally administered. Proteins and peptides are having a lesser bioavailability or less bioavailability has about a hundred and twenty fifth. the opposite route of administration of macromolecule and amide is made success for the administration of proteins and peptide medicine, the routes are oral, buccal administration Intranasal administration, pneumonic administrations, percutaneous, body part and ocular administrations of proteins and peptide.

Properties of Protein and Peptide

Irrespective of their structural or functional role, all **proteins** are built from the same fundamental blocks, the amino acids. The physico-chemical **properties** of the constituent amino acids **determine** the structure and biological function of **proteins**.

PHARMACEUTICAL APPROACHES

Proteins and peptides have four completely different approaches that they're listed below.

- Chemical correction
- Enzyme inhibitors
- Penetration Enhancers
- Forming vehicle
- Modular compound Systems

Pharmaceutical approaches-for protein drug

1. Chemical Reform

The chemical corrections of the macromolecule and amide drug delivery system of medicine are vital for protein stability beside membrane compliance. It's applicable to reducing immunogenicity.

Chemical modification involves 2 sorts of changes

1. Organic compound change
2. Hydrophilization

Amino Acid Modifications: Organic compound change is one in every of the vital approaches during which replace proteins of D-amino acids and L-amino acids are vital in dynamica the physical properties of the amide drug delivery system. **Example:** There are 2 vital analogues for dysmoprocin and diminovasprocene vasopressin; within the past, it's necessary to incorporate the replacement of the last L-ergin de-erginin to provide 1st amino acids and demonovascoscarsin.

Application: Organic compound change is very important for enhancing membrane permeableness and maintaining catalyst stability.

Hydrophilization: This is often a crucial approach to lipophilicmitiges. Ex: NOBEX hypoglycemic agent.

Example description: it's vital feature of hypoglycemic agent molecule to one, 3-dipedityloglycerol, to attach the free organic compound cluster of glycine, mono and hypoglycemic agent to the phenoilanelline and essential amino acid molecules that are very important for transferring hypoglycemic agent across the mucus membranes of the big internal organ. It's vital to enhance stability against catalyst degradation.[5]

Enzyme ambient (protease)

The protein (protease) inhibitors are the catalyst approach of the protein and peptide drug delivery systems. GIT and liver play vital role in metabolization of the protein and peptides into smaller fragments of the 2 to 10 amino acids with the assistance of the variability of chemical action. This proteolytic enzyme inhibitors are CO-administered with protein and peptide to change the setting for the protein stability to suppress the chemical action activity. The protein proteases inhibiters are divided into four varieties they're Aspartic Proteases (Pepsin, Rennin), Cysteinyl Proteases (Papain, Endopeptidase), Serinyl Proteases (Thrombin, Trypsin), and Metallo Proteases (Carboxypeptidase).

Penetration enhancers

Penetration enhancers are the one in every of the foremost vital part of macromolecule and peptides formulation and is liable for the disruption of the tissue layer barriers and applicable

to enhance the membrane permeations of enormous organic compound substances lie proteins and peptides. Numerous sections of compounds are primarily used like surface-active agent (Polysorbate, SLS, Pluronic F-68), chelating agents (EDTA), fatty acids (Sodium Carprate), mucoadhesive compound system (thiomers, polyose derivatives), lipid could be a transit scientific instrument (PC). The essential mechanisms for increasing penetration are.[6]

Detergent and surfactant molecules increase the transcellular transport of the drug material, the lipoid membrane is liable for obstructing the structure of the lipoid bilayer and additional perm ableness. Another mechanism metal chelate is liable for the advanced formation of metal ions and that they are passing through tight junctions and that they are fascinating the paracellular transport of deliquescent medicine. Fatty acids are vital for improving paracellular absorption by control Phospholipids C activation and intracellular metal ions; simple protein is leading the contraction of globulin filaments.[7]

Transport vehicles

Protein and amide drug delivery systems are vital for oral delivery of proteins and peptides, as a result of it will be with success achieved exploitation completely different carrier systems,

1. Dry emulsion
2. Microsphere
3. Liposome
4. Nanoparticles

1. Dry emulsion: It is vital application in drug delivery system to stop the instabilities of the future storage of multiple emulsions. The novel approach at that multiple emulsion is replaced by dry emulsions. Dry Emulsion is ready by the Spray drying, Lyophilization and Evaporation Techniques. In dry emulsion preparation application of the pH responsive polymers like HPMCP, is very important for the emulsions area unit the enteric coated and web site specific achieved.[8]

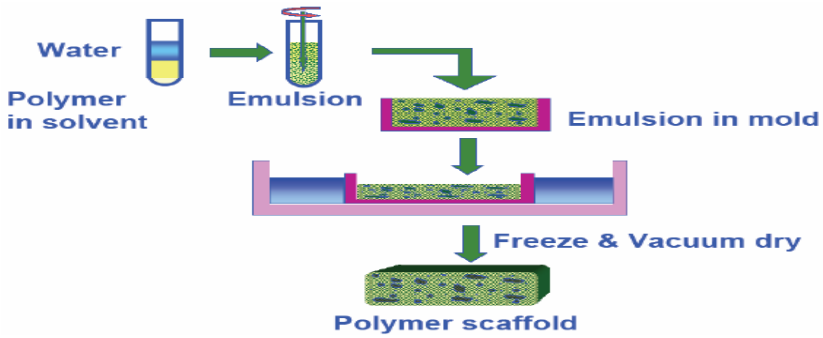

Fig5: Preparation of Dry emulsion.

2. Microsphere: The identical distribution of the drug within the delivery of oral drugs within the macromolecule peptides drug is understood as microspheres. The pH counter written magnifier is primarily accustomed shield the abdomen from protective chemical action degradation in oral delivery and protective the tiny intestines from the chemical action degradation.[9]

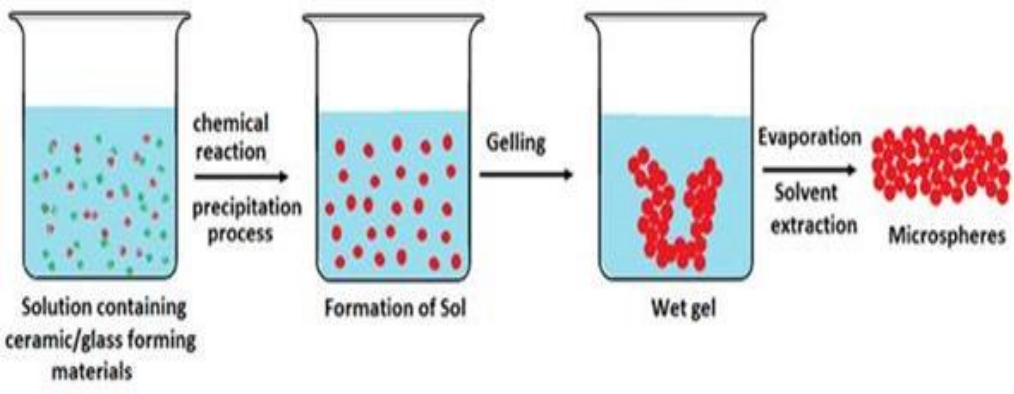

Fig 6: Preparation of Microsphere.

Liposome: Liposome are the tiny microscopic vesicles during which liquid volume is entirely closed by the membrane composed lipoid molecules. Liposome's in drug delivery system,the encapsulation of the hypoglycemic agent with sugar chain portion of glycoprotein and PEG fully suppressed the degradation of the hypoglycemic agent molecules in internal organ fluid. The uncoated from of cyst are suppressed on surface coating of the cyst molecules in PEG or glycoprotein gained resistances against digestion by salts and raised the soundness of alimentary canal.

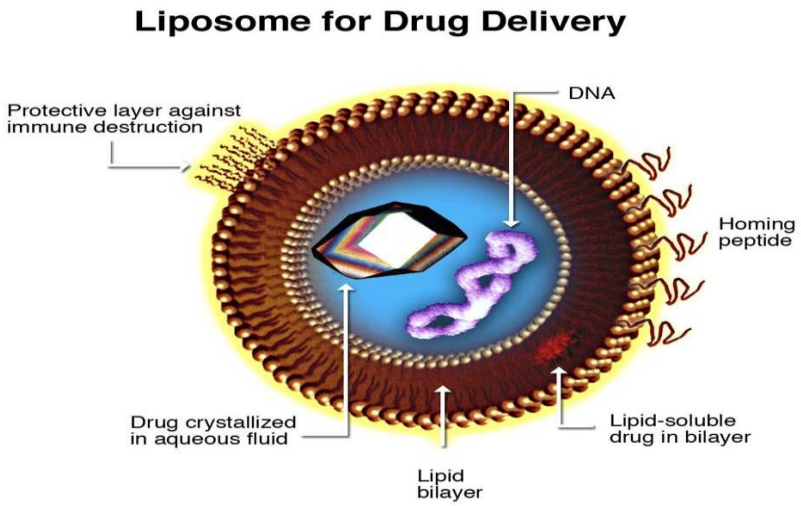

Fig 7: Liposomes drug delivery.

4. Nanoparticles: Nano-shaped mixture structure formed size is 10-1000 nm. The particles within the manometries-shaped particles are preserved by the animal tissue of the intestines and that they are uless liable to catalyst degradation. Charging of particle size surface, affects the speed of the Nanoparticles system in GI path.

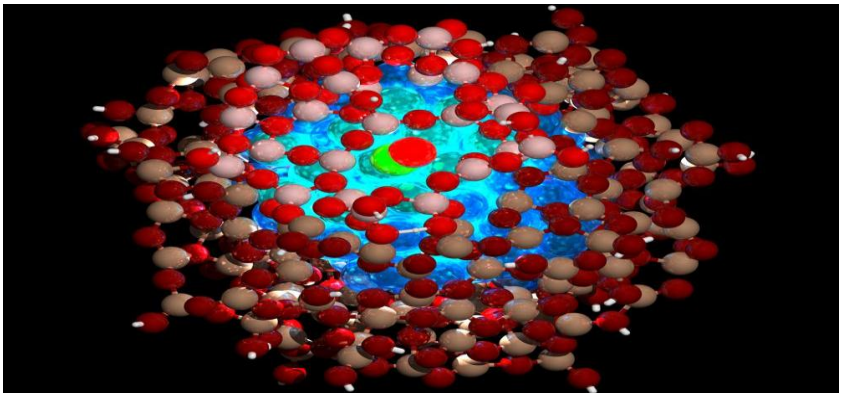

Fig 8: Nanoparticle.

Mucoadhesive Polymeric Systems

Mucoadhesive chemical compound system is very important for preventing the matter related to Presystemic metabolism or earlier metabolism and to keep up its therapeutic effectualness. Increase or decrease in continuance and drug approval rate of this drug delivery system on the location of action.

Examples: Thiomers, polyacrylic acid derivatives and polyose derivatives. The stronger Mucoadhesive properties of thiomers area unit believed to be supported valence bonds between thiol teams of the thiomer and cysteine- wealthy domains of mucous secretion

glycoproteins. (Higher quantity of thiol teams is liable for the stronger Mucoadhesive properties).

Incorporation into drug delivery matrix

The drug incorporate within the macromolecule and amide drug delivery system undergoes 3 strategies they as follow.

1. Emulsification

In this method, soluble drugs are dissolved in liquid (water solution) and it's soluble in organic solvent solutions are mixed with the suitable magnitude relation to supply w / o emulsion. This ready primary emulsion is created in blended wetter w / o / w emulsion within the solution. In the end, the organic solvent is especially far from the emulsion as a result of the depression of the filtration by the solvent evaporation and temperature.[10]

2. Extrusion and spray drying

The extrusion and spraying is used to from microspheres and also the core material or matrix containing drug, incorporated as resolution and also the Particulate is especially ejected from the passage of fine tubes, syringe or nozzles to from small droplets. the scale of drop is especially depending upon the Properties of Liquid (melt, resolution and suspension) and passage diameter to jet rate.[11]

3. Chemical process

Polymerization in hydrogels has a chemical compound drug delivery system preparation by the blending of chemical compound with the drug associate degree leader and a cross linking agents. The Intravascular delivery of the macromolecule via hydro system that's photograph polymerized in place on the inner surface of vessel. The radiation is manufacturing harmful impact on integrity of macromolecule molecules one in every of the downside of macromolecule and amide drug delivery systems.[12]

Stability aspects

Protein and amide stability are determined by macromolecule degradation, they're 2 pathways of corrosion of proteins and amide molecules during this drug delivery system.

1. Path of physical decline (instability)
2. Chemical degradation pathway (instability aspects)

Chemical degradation the foundation or root structure of the macromolecule is modified by the modification of its primary structure of macromolecule molecules.

By the physical decline, the essential or original structure of the macromolecule is modified or the structure of the macromolecule (secondary, tertiary or quadrilateral structure) has been replaced by high order.[12]

Physical orientation: The first symptoms of the physical instability of macromolecule molecules in the case of physical degradation. Within the case of global proteins, hydrophobic residues are buried in internal and deliquescent residues. The denaturation of the molecule refers to the loss or injury to the global structure of the molecule so the macromolecule is open. as a result of physical denaturation, changes in setting of macromolecule molecules like temperature, pH.eg Urea, guanidine HCl Alcohol, Acetic acid.

Denaturation: Any non -proteolytic modification of the unique structure of a native protein thatϖ effects definite changes in physical, chemical, and biological properties. Peptides and proteins are comprised of both polar amino resides and non-polar amino acid residues.[13]

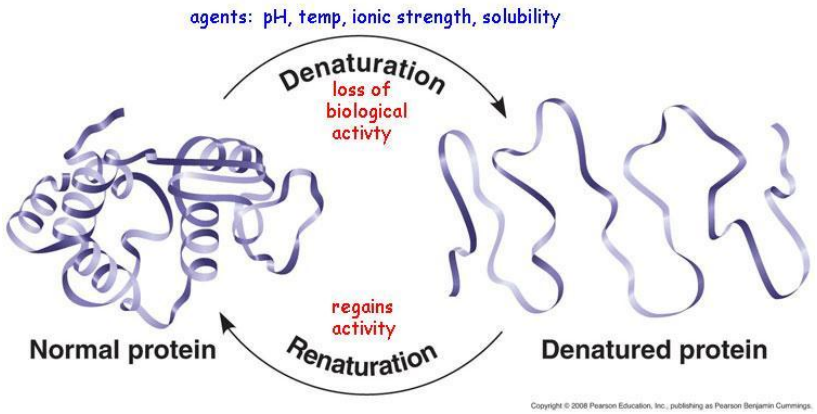

Fig 9: Process of Denaturation.

Factor which favors' denaturation

- When solvent changes from an aqueous to organic solvents or to a mixedsolvent.
- PH changes –alters the ionization of the carboxylic acid and amino acids and there by the charges carried by the molecules.
- Alteration in the ionic strength.
- Temperature rise.
- Denaturation may be reversible or irreversible.

- Denaturation may lead to decrease in solubility, alteration in surface tension, loss of crystallizing ability, changes in constituent group reactivity and molecular profile, vulnerability to enzymatic degradation, loss or alteration of antigenicity and loss of specific biological activity.[13]

Chemical instability

The chemical instability of proteins and peptides will cause the subsequent four sorts of reactions.

- Oxidation Reaction
- Chemical action
- Chemical bond geophysical science
- Disulphide exchange

1. Oxidation

Oxidation is one of the foremost vital chemical instability of proteins and amide molecules. Amino acids of proteins and peptides are vulnerable to acid-chain reaction, reaction is created by region O molecules, numerous sorts of metal ions like copper or iron, like oxide, like several reagents.

Example: essential amino acid residues, particularly in acidic conditions, are seemingly to solidify by oxide by the reagents, that turn out essential amino acid sulfoxide. (Hydrogen peroxide is employed to sterilize the formulation vessels or the development area).

2. Deamination: Instability arises in chemical reaction of organic compound chain of bound organic compound residue are primarily includes amino acid and asparagine's', is understood has chemical action. Some conditions area unit like changes in Temperature and pH area unit primarily shown to facillated the method of deamination's of Biological Therapeutic macromolecule and Peptides.

3. Chemical bond chemical reaction: During this chemical bond Hydrolysis method the amino acid residues are heated at 90-1000 C, in pH four (acetate), the chemical reaction of the Asp-X bonds area unit ends up in loss of the Biological activity.

4. Disulfide Exchange: Therapeutic proteins contain amino acid residue that disulphide with bonds. These fashioned bonds are vital elements of structural integrity of proteins. Incorrect

association of amide bonds brings changes within the three-dimensional structure of macromolecule molecules and their biological activity.[14]

Application

- CVS acting medicine, proteins and peptides: (Angiotensin a pair of opposed, captopril) is very important for up pressure and peripheral circulation for heart condition management.
- CNS is very important for the relief of hunger and pain by pressing active proteins and peptides (Cholecystokinin, B-endorphin).
- GI-active proteins and peptides (anti-gastrointestinal, duct gland enzyme) area unit vital for secretion of stomachic acid and it's vital for digestion supplement.
- Immunomodulation of proteins and peptides (burden, cyclosporine, and interferon) is very important for selective lymph cell formulating hormones, preventing the activity of T-lymphocyte antigens in blood cells.
- Metabolism of proteins and peptides (insulin, vasopressin) is very important for the treatment of polygenic disorder treatment and treatment of polygenic disorder acids.

RECENT ADVANCES

PEGylation

PEGylation could be a recent advancement of macromolecule and amide drug delivery systems, PEGylation could be a method of attaching the strands of the compound PEG to commonest peptides fragments that may facilitate to fulfill the macromolecule and challenges of up the security and potency of the many therapeutic macromolecules like macromolecule and Peptides. Itis widely used for the modification of proteins and peptides, protein fragments and oligonucleotides. PEG area unit the non-toxic. And non –immunogenic, it's having as such hydrophilicity and it's having high flexibility. PEGylation is very important to will increase the Bioavailability, it's applicable for the optimized pharmacology, it is very important for Decreasing Immunogenicity, it's vital to Decreases the Frequency of administration.[15]

The PEGylation is very important Mechanism for increasing the mass of the molecules, it will will increase the drug solubility and it's applicable for the protection against chemical action degradations, it's having a crucial mechanism to reducing the dosing frequency and maintain therapeutic activity.

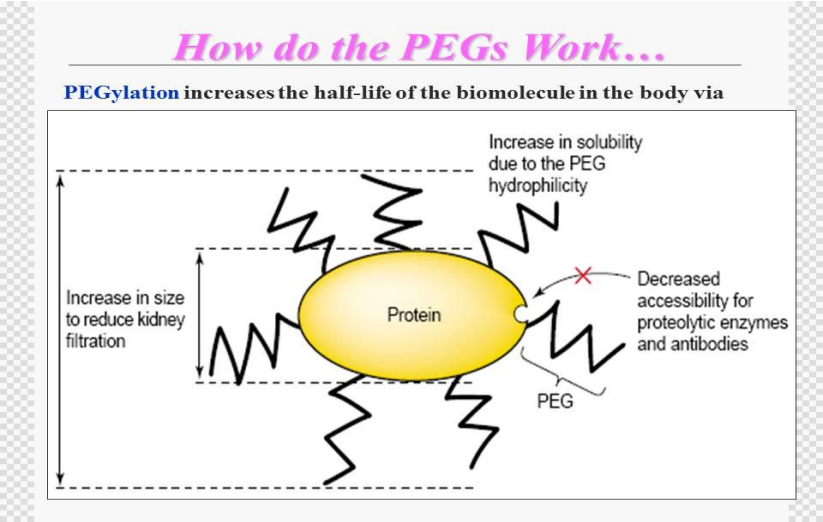

Fig 10: Working of PEGs.

Depot Foam Technology

Therapeutic Proteins and Peptides area unit administered in IV or SC area unit usually too speedy of the Circulation and it's had to be compelled to inject to the frequent order of administration for maintaining their therapeutic level of the blood. numerous sorts of liposomal formulations are usedas drug delivery vehicles for sustained unleash of proteins and peptides likeunilamellar or multilamellar cyst systems however few deals with the multivesicular liposome's area unit referred to as as —Depot-Foam particles.

The Depot-Foam technology is capable of accommodating high drug loading and high recovery of drug material, it's having a high Encapsulation potency, it's vital style of technique is applicable for the sustained delivery of organic compound medicine. a singular feature of Depot-Foam system is that within every Depot-Foam particle, discontinuous internal liquid chambers bounded by a nonstop network of lipoid membranes render a better liquid volume to lipoid magnitude relation and far larger particle diameter as compared to SUV's or MLV's.

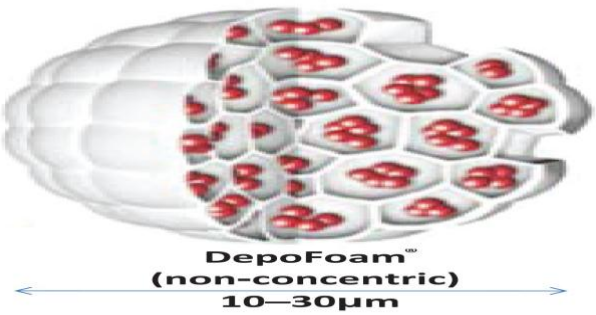

Fig 11: Depo foam.

CONCLUSION

Protein and peptide-based prescribed drugs area unit progressively changing into a awfully vital category of therapeutic agents and within the close to future, there's an opening of fixing several existing organic primarily based prescribed drugs. amide and macromolecule medicine are mass created by biotechnology processes and can be accessible commercially for therapeutic use. it's a direct challenge for the pharmaceutical business to develop a viable distribution system for therapeutic medical delivery of those complexes in biologically active type. Their demand in clinical and clinical areas has accelerated the investigation of their convenient and effective delivery through a non-invasive system. macromolecule and amide drug distribution systems area unit novel drug delivery systems. Proteins and peptides area unit the foremost long elements of biological cells, they're operating like enzymes, hormones, structural components, and immune serum globulin. Twenty completely different natural amino acids connect with amide bonds and type the required polymers for peptides and proteins. though the distinction between amide and macromolecule is a smaller amount than twenty amino acids within the amide, during which there's a mass of but 5000, whereas one macromolecule contains fifty or additional amino acids and its price is on top of its price. Most of the drug proteins and peptides absorb the under-skin absorption of IM, IV, and absorption, however the oral path is additional convenient for the absorption of proteins compared to the opposite. distinctive needs of peptides associate degreed proteins in planning delivery systems an new increase within the field have done plenty of analysis in novel suggests that of drug delivery. seek for those viewers UN agency give stable, bio-available, simply man-readable and patient-friendly formulations, have created major progress within the development of nose and controlled unleash technology.

Some new demands have conjointly been seen within the field of parental solutions technology, and that was a standard space of technology antecedently used, scientific progress has been created to fulfill the wants of those compounds. At constant time, progress in elementary analysis is being exhausted areas of oral delivery, otherwise delivery and 'delivery' areas on the demand of palatial and peptides and proteins.

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