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# An Overview Of Protein Nanoparticles For Targeted Drug Delivery.

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**ABSTRACT**

Protein nanoparticles as drug carriers offer enhancement in the delivery of drugs, [1] especially targeted delivery to site-specific tissue, cells or organs. This can be achieved through ligand attachment, sustained and triggered release of the pharmacologically active drug. This review focuses on the recent developments in protein nanoparticles through self-assembly in drug targeting which is advantageous over conventional drug delivery methods.

**Keywords:** Protein nanoparticles, self assembly, protein carriers, targeted drug delivery, sustained release.

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## INTRODUCTION

For the past several years, great achievements have been made on the development of novel drug delivery system (NDDS) [2] [3] using nanoparticles [4]. .Nanotechnology has given a new insight to pharmaceutical formulation – one of the prominent features is the formulation of drug delivery system at nano size, which permits the drug molecule easy accessibility to anatomical sites through phagocytosis and entering tiny capillaries.

Nanoparticles have generated immense excitement in the field of drug delivery as they provide new opportunities to overcome the limitations of conventional delivery methods with regards to the drug. The novel formulations have improved bioavailability, reduction in toxicity, and allow alternative route of administration, sustained delivery, protection from physical and chemical degradation and effectiveness in delivery of both hydrophilic and hydrophobic drug molecule.

Nanoparticles and nanoemulsions are colloidal systems with particle size ranging from 10nm-1000nm. The pharmaceutical nanoparticles are sub-micron sized, less than 100nm in diameter. The nanospheres are of a matrix type structure in which the active ingredient is dispersed throughout whereas the nanocapsules have a polymeric membrane and an active ingredient core.

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants or can be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size.

Nan emulsions and nanosuspensions are used as drug delivery systems to increase the solubility of the drug to be incorporated there by increasing the bioavailability of the drug.

**Disadvantages over Nanoparticles:**

**Nan emulsions:-**

1) Use of large concentration of surfactant and co-surfactant is necessary for stabilizing nanoparticles.
2) Limited solubilizing capacity for high melting substances
3) Nanoemulsification stability is influenced by environmental parameters such as temperature and pH.

**Nanosuspensions:-**

1) The drug has to be soluble in atleast one solvent and that this solvent should be miscible with a nonsolvent in case of precipitation technology.
2) Possible contamination of the product from the wall of the homogenizer
3) Prolonged milling may induce the formation of amorphous leads to instability
4) Physical stability, sedimentation and compaction can cause problem

Nanoparticles are commonly polymeric colloidal carrier of drugs in nanosize that are being extensively tried to deliver proteins as they can protect the protein from metabolizing enzymes and can sustain the release and target specific tissues by incorporating surface ligand moieties(Muller and Keck 2004).

**Proteins and peptides-**

Therapeutic proteins and peptides have received significant alteration due to their potential to treat and prevent diseases. As they are very unstable as colloids and are rapidly cleared, they may have serious side-effects.

To overcome this, nanocarrier based drug delivery system have been developed to improve their bioavailability and reduced toxicity. Proteins and peptides are organic building blocks of life and have been the drug of choice in treating many hazardous ailments including cancer,[5,6] auto immune disease, Alzheimer's disease, mental diseases, hypertension and certain cardiovascular and metabolic diseases, which offer several advantages over the conventional small molecule drugs.

Therapeutic proteins and peptides have a significant role in every field of medicine, especially in targeted drug delivery system. Protein nanoparticles exhibit high loading capacity of various drugs due to multiple binding sites present in their molecules.

**Sources of pharmaceutical protein-**

Main sources of pharmaceutical protein are of plant and animal origin. Proteins which are used in therapy are of biotechnologically derived molecules. Recently, protein nanoparticles, especially albumin nanoparticles, a commonly used protein for targeted drug delivery, have been used as a novel drug carrier due to its high binding capacity and negligible side effects.

**Advantages of plant protein over animal protein-**

- Plant protein reduces the risk of spreading disease
- Antigenicity /toxic effects can be reduced
- Universally accepted as they can be used even by people who are pure vegetarians

**Various proteins that have been used for protein nanoparticles formulation [19] include:**

- Albumin - Includes ovalbumin (from egg white), bovine serum albumin (BSA) [7, 8] and human serum albumin (HSA). It serves as a depot and transporter of protein which is freely soluble in water. Albumin nanocarriers are biodegradable, easy to prepare, have defined sizes and reactive functional groups on their surface which can be used for ligand binding and surface modification.
- Gelatin - It is a widely used animal protein obtained by controlled hydrolysis of collagen (component of skin, bone and connective tissue). Based on hydrolysis, two types of gelatin can be produced, Type A and Type B. It is non-toxic and can be easily modified chemically. It is inexpensive, has low antigenicity and can be sterilized.
- Elastin - It is an essential component of connective tissue. There are two types of elastin derived polypeptides, namely α-elastin and elastin-like polypeptide (ELPs), which have been used for drug delivery applications.
- Gliadin and legumin - Gliadin, a gluten protein, found in wheat shows bioadhesive property and has been used for oral and topical drug delivery application. It is also a good polymer for mucoadhesive nanoparticles preparation. Legumin, one of the main storage proteins in pea seeds, is an albuminous substance that can undergo self assembly to form nanoparticles after aggregation.
- Zein - it is a protein found in the endosperm of the corn kernel. This hydrophobic protein is used for films and coatings. Nanoparticles formulated with this protein includes those which include several drugs like Ivermectin, Coumarin, 5-fluorouracil.
- Soy protein - Nanoparticles with soy protein can be prepared using simple coacervation method. The enriched form of soy protein is known as soy protein isolate (SPI).
- Milk protein - The two milk proteins that have been identified for drug delivery applications are β-lactoglobulin (BLG) and casein. BLG is an ideal natural polymer for drug delivery applications due to its good gelling property. Casein micelles can withstand heat and mechanical forces.
- Whey protein - The use of whey proteins, mainly BLG, is as a drug delivery carrier.
- New plant proteins -The proteins present in root and stolon of various plants are the area of interest for self assembling nanoparticles drug delivery.
- Silk fibroin and protein isolated from various other sources are the new areas of interest as protein carriers in targeted drug delivery systems.[9]

**Structure of protein –**

- Primary structure: Each protein has a characteristic linear sequence of amino acids, which are linked together through peptide bonds.
- Secondary structure: It is important to understand the secondary structures of protein and how these can be used for self assembly. Two most prominent types of secondary structures of proteins are (a) α-helix and (b) β-pleated sheet.

a. α-Helix: In which amino acid have a tendency to form hydrogen bonds between carbonyl group and the amide group which is not a stable confirmation but by assembling with other α-helices a stable structure is created.

b. β-pleated sheet: The β-pleated structure is stabilized by inter-chain hydrogen bonding

- Tertiary structure: Refers to the overall three dimensional structure or native conformation. The tertiary structure is stabilized by hydrophobic interactions, ionic bonds, van der Waal's forces and hydrogen bonds.

**Self assembly of protein and peptides [10]–**

Protein self assembly presents a convenient and inexpensive method for creating functional nanomaterials for a variety of applications including use as biomaterials. The components of a system assemble themselves through local interaction such as hydrogen bonding, hydrophobic, vander Waal's forces and π-π interactions to form a large functional unit. The spontaneous formation of well-ordered nanostructures by a process of self-association represents the core part of modern nanotechnology.

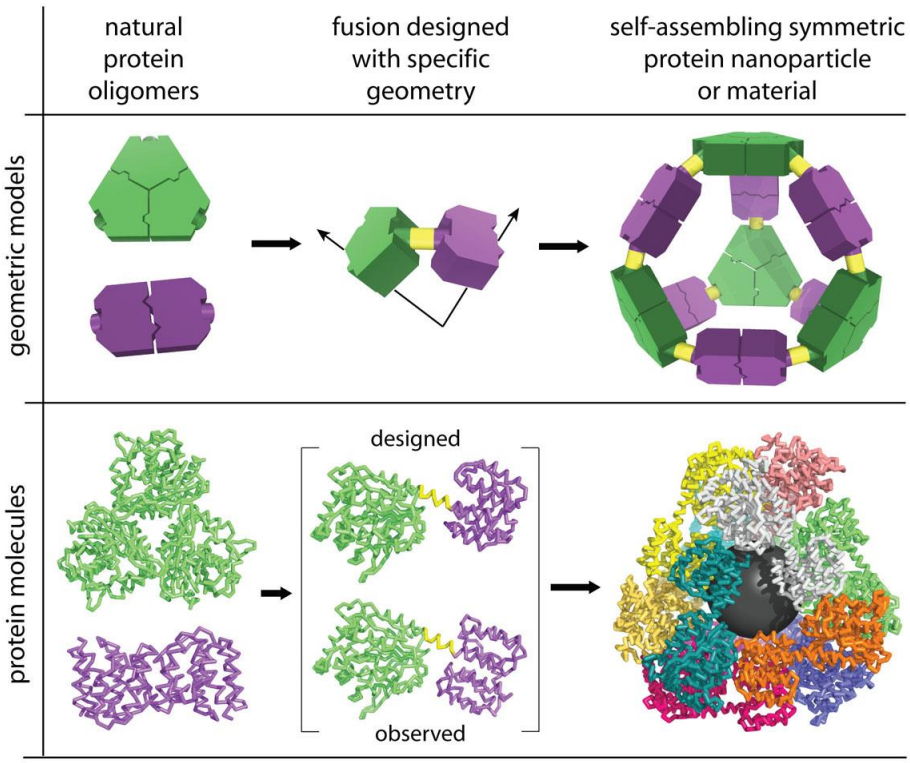


**Fig 1: Self assembly of proteins**

Self assembled structures can be formed by a variety of building blocks, [11] both organic and inorganic. Peptides are the most useful ones among organic building blocks as they possess biocompatibility and chemical diversity and can be readily synthesized on a large scale. In a "bottom-up" process, simple building blocks interact with each other in a coordinated way to form large and complex supramolecular assemblies. The process of molecular recognition and self assembly direct the way in which relatively simple building blocks recognize each other, associate and form ordered one-dimensional, two- dimensional and three- dimensional nanostructures and macroscopic objects with nanoscale order. Peptides therefore, offer a unique platform to design self assembled materials with controllable structural features at the nanoscale due to the flexibility and versatility afforded by amino acids sequence. [12]

**Mechanism of self assembly –**

Although self assembly involves a variety of physical forces, it is the hydrophobic forces that play an integral role in driving this process. It is found that the degree of hydrophobicity affects the nucleation and

elongation rates of self assembly. The higher the number of hydrophobic groups, the faster the self assembly process and improvement of the mechanical properties of the system.

Drug targeting: A Targeted drug delivery system is preferred in the following situation [18]:

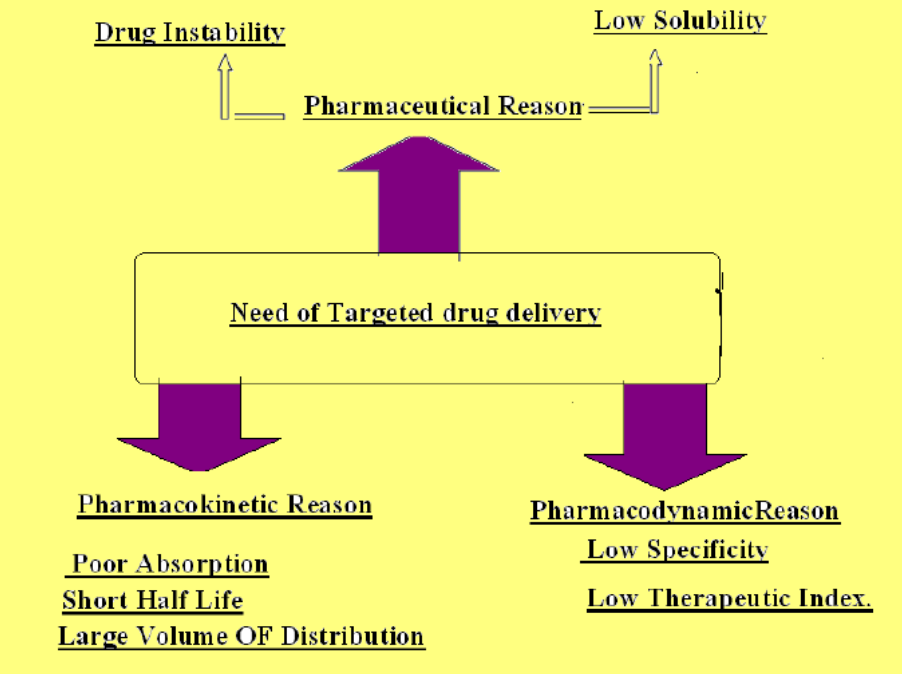


**Fig 2: Components of targeted drug delivery include a target and a carrier [13, 14]**

- Target – It include a specific organ, cell or tissues which is in a chronic or an acute condition and needs treatment.
- Carrier – It is the specific molecule or system which is essential for effective transportation of loaded drug to the specific sites
  Targeting in Nanotechnology refers to the spatial localization of the nanoparticles within the intentional sites and is distinct from molecularly targeted drugs. Targeted drug means blocking essential biochemical pathways or mutant that are required for tumor cell growth.

Strategies of drug targeting:

Passive targeting – These drug delivery systems are targeted to systemic circulation.
Inverse targeting – In this, an attempt is made to avoid the passive uptake of colloidal carrier by RES. Hence the name inverse targeting.
Active targeting – In this particular approach, the carrier system with drug reaches the specific site on the basis of surface modification, rather than normal uptake by RES.
Dual targeting – In dual targeting, carrier molecule itself has its own therapeutic activity and increases therapeutic activity of drug.
Double targeting – When spatial methodologies are combined in order to target a carrier system, it is called double targeting.

Drug delivery devices based on nanotechnology includes nanotubes, [15] nanoshells, quantum dots [16] and dendrimers.

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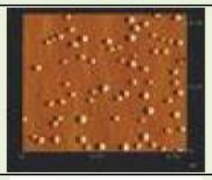
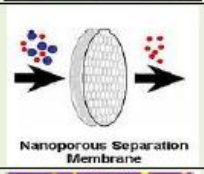
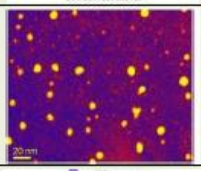
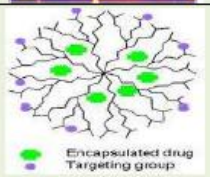
**Table 1: Nanoparticles and their applications [17]**

Nanoparticles and their Applications

| S. no | Nano carrier | Description | Image Structures | Application |
|---|---|---|---|---|
| 1 | Nano Tubes | They are hollow cylinder made of carbon, atoms which can be filled and sealed for potential drug delivery. |  | Cellular scale needle for attaching drug molecule to cancer cells. As an electrode in thermo cells. |
| 2 | Nano wires | the nanowire pinpoint damage from injury and stroke, localize the cause of seizures, and detect the presence of tumors and other brain abnormalities |  | Technique has potential as a treatment for Parkinson's and similar diseases. |
| 3 | Nanoshells | Nanoshells are hollow silica spheres covered with gold. Scientists can attach antibodies to their surfaces, enabling the shells to target certain shells such as cancer cells |  | Technique has potential for targeting cancerous drug. |
| 4 | Quantum dots | Quantum dots are miniscule semiconductor particles that can serve as sign posts of certain types of cells or molecules in the body. |  | Technique has potential for targeting cancerous drug. |
| 5 | Nano pores | Engineered into particles, they are holes that are so tiny that DNA molecules can pass through them one strand at a time, allowing for highly precise and efficient DNA sequencing. |   | Potential in genetic engineering and bio technology. |
| 6 | Gold Nano Particle | Scientist uses gold nanoparticle to develop ultrasensitive detection system for DNA and protein markers associated with many forms of cancer, including breast prostrate cancer. |  | In cancer Treatment and Genetic engineering |
| 7 | Dendrimers | Dendrimers precisely defined, synthetic nanoparticles that are approximately 510 nm in diameter. They are made up of layers of polymer surrounding a control core. The dendrimers surface contains many different sites to which drugs may be attach. |   | In gene transfection, medical imaging |

## CONCLUSION

Extensive research is focused on developing new drugs and new ways to release them to patients in a less invasive route, with the help of Nanotechnology such possibility is increasing day by day healthcare.

Self assembled peptide nanostructures offer a promising alternative to existing delivery vehicles due to their low toxicity, high biocompatibility and ability to target therapeutic small drug molecules and proteins. These drug delivery systems have shown potential outcomes when used to deliver drugs targeted to the brain, eye, cardiovascular system, bone tissue and cancerous cells. However, this delivery system requires further investigation before they are being used in clinical studies.

## REFERENCES

[1] Sravya Nella,Kiran Babu Uppuluri, Formulation and In-Vitro Evaluation of Piroxicam Loaded BSA Nanospheres by Desolvation, Nanomedicine & Nanotechnology,2015; 6:3. Cited on 11/02/18

https://www.omicsonline.org/open-access/formulation-and-invitro-evaluation-of-piroxicam-loaded-bsa-nanospheres-by-desolvation-2157-7439-1000289.pdf

[2] Ajazuddin, S.Saraf, Application of novel drug delivery system for herbal formulations-review, Fitoterapia, 2010; 680-689. Cited on 11/02/18.

[3] Jaydip Kumbhani, Chintan Tank et al., Nanoparticle: A Promising carrier for Novel Drug Delivery, International Journal of Pharma Research & Review, Feb 2016;5(2):27-40 ISSN: 2278-6074. Cited on 15/02/18
http://www.rroij.com/open-access/nanoparticle-a-promising-carrier-for-novel-drug-delivery-.pdf

[4] Suriyakala Perumal Chandran, Satheesh Babu Natarajan et al., Nano drug delivery strategy of 5-fluorouracil for the treatment of colorectal cancer, Journal of Cancer Research and Practice Volume 4, Issue 2, June 2017, Pages 45-48. Cited on 15/02/18
https://www.sciencedirect.com/science/article/pii/S2311300616301847

[5] Journal of Control Release, 2005, jul II: Technol Cancer Res: Treat, 2005 Aug, 4 (4), 407-416. Cited on 28/02/18
https://onlinelibrary.wiley.com/doi/epdf/10.1002/cncr.22035

[6] Sreemanti D, Anisur Rahman Khuda-Bukhsh et al., PLGA-loaded nanomedicines in melanoma treatment: Future prospect for efficient drug delivery, Indian J Med Res 144, August 2016, pp 181-193 DOI: 10.4103/0971-5916.195024. Cited on 03/03/18
http://www.ijmr.org.in/temp/IndianJMedRes1442181-3446994_005726.pdf

[7] T.Feczkó, J.Tóth et al., Optimization of protein encapsulation in PLGA nanoparticles, Chemical Engineering and Processing: Process Intensification, Volume 50, Issue 8, August 2011, Pages 757-765. Cited on 07/03/18
https://www.sciencedirect.com/science/article/abs/pii/S0255270111001498

[8] Biswajit Mukherjee, Kousik Santra et al., Preparation, characterization and in-vitro evaluation of sustained release protein-loaded nanoparticles based on biodegradable polymers, International Journal of Nanomedicine 2008:3(4) 487–496. Cited on 10/03/18
https://www.dovepress.com/getfile.php?fileID=4214

[9] Yang Cao, et al, Drug release from core-shell PVA/silk fibroin nanoparticles fabricated by one-step electrospraying, Scientific Reports volume 7, Article number: 11913 (2017) doi:10.1038/s41598-017-12351-1. Cited on 10/03/18
https://www.nature.com/articles/s41598-017-12351-1

[10] Philip D. Tatman, Ethan G. Muhonen,et al., Self-assembling peptides for stem cell and tissue engineering, Biomaterials Science · February 2016. Cited on 11/03/18
https://www.researchgate.net/profile/Ethan_Muhonen/publication/294730778_Self-assembling_peptides_for_stem_cell_and_tissue_engineering/links/578fd4ec08ae4e917cff38d2/Self-assembling-peptides-for-stem-cell-and-tissue-engineering.pdf?origin=publication_detail

[11] Gazit E., Self-Assembled peptide nanostructures: the design for molecular building blocks and their technological utilization, Chem. Soc. Rev.2007,36;1263-1269. Cited on 11/03/18
http://pubs.rsc.org/en/content/articlelanding/2007/cs/b605536m#!divAbstract

[12] Sharareh Eskandari, Thalia Guerin, Recent advances in self-assembled peptides: Implications for targeted drug delivery and vaccine engineering, Advanced Drug Delivery Review,2016. Cited on 11/03/18

[13] E. Bhargav, N.Madhuri, K.Ramesh, Targeted Drug Delivery-A Review, World Journal Of Pharmacy And Pharmaceutical Sciences,2013(3.1); 150-169. Cited on 12/03/18
http://www.wjpps.com/download/article/1388590478.pdf

[14] KirtiRani, SaurabhPaliwa, A Review on Targeted Drug Delivery: its Entire Focus on Advanced Therapeutics and Diagnostics, Scholars Journal of Applied Medical Sciences (SJAMS), Sch. J. App. Med. Sci., 2014; 2(1C):328-331. Cited on 15/03/18
https://www.researchgate.net/profile/Kirti_Rani2/publication/265862863_A_Review_on_Targeted_Drug_Delivery_Its_Entire_Focus_on_Advanced_Therapeutics_and_Diagnostics/links/54e1d3080cf2966637931551/A-Review-on-Targeted-Drug-Delivery-Its-Entire-Focus-on-Advanced-Therapeutics-and-Diagnostics.pdf?origin=publication_detail

[15] Venkatesan M., Yoshimitsu J., et al, Liquid filled nanoparticles as a drug delivery tool for protein therapeutics, Cancer Res. 2005. Jun 15, 65 (12) 5317-29. Cited on 20/03/18
https://www.ncbi.nlm.nih.gov/pubmed/15967493

[16] Zhang X ,Chibli H , KongD, Nadeau J .Comparative cytotoxicity of gold –doxorubicin conjugates.Nanotechnology2012:23:275103. Cited on 25/03/18

https://www.ncbi.nlm.nih.gov/pubmed/22710097
[17] J. Agnihotri, S. Saraf, and A. Khale, "Targeting: new potential carriers for targeted drug delivery system," International Journal of Pharmaceutical Sciences Review and Research, vol. 8, 2011. Cited on 30/03/18 http://globalresearchonline.net/journalcontents/volume8issue2/Article-020.pdf
[18] Gupta Manish and Sharma Vimukta, Targeted drug delivery system: A Review, Research Journal of Chemical Sciences, Vol. 1 (2) May (2011) Res.J.Chem.Sci. Cited on 04/04/18 https://pdfs.semanticscholar.org/7e82/738dca918261f6e3f5b07641a68efb9fe545.pdf
[19] Warangkana Lohcharoenkal, Wang L., Protein nanoparticles as drug delivery carriers for cancer therapy-review, BioMed Research International, 2014. Cited on 08/04/18 https://www.hindawi.com/journals/bmri/2014/180549/
[20] S.K. Pudota, V. Shirisha, and R.H. Kumar, "A review on drug targeting and drug carriers", International Journal of Research in Pharmaceutical and Nano Sciences, Vol. 2, 2013. Cited on 08/04/18