Research Article **CODEX: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

NANOPARTICLES AS DRUG DELIVERY SYSTEMS

V. Sivalalitha*[1], G. Yasodalalitha[1], Y. Nagarjuna reddy[1], M. Veerabraham[1]
K. Ramakrishna[2], K. Vinodkumar[1]

[1*]Department of Pharmaceutics, Siddhartha Institute of Pharmaceutical Sciences, Jonnalagadda, Narasaraopet, Guntur, Andhra Pradesh, India.

[2]Department of Pharmaceutical Analysis, Siddhartha Institute of Pharmaceutical Sciences, Jonnalagadda, Narasaraopet, Guntur, Andhra Pradesh, India.

ABSTRACT

Nanoparticles as a drug delivery system has a several advantages over a conventional multi dose therapy much review effort in developing a nano particle as a drug delivery system has been focused on controlled release and sustained release dose forms. The various approaches are available for achieving the nano particle as a drug delivery system. One of the most effective approaches is nano particles of the drug. Nano particles are solid colloidal particles ranging in size from 10-1000nm in which the active principle is dissolved and diffused. Nano particles were prepared by Amphiphilic macro molecule, Cross linking, Emulsion polymerization, Interfacial polymerization, Denaturation of natural macromolecules in an oil emulsion, Chemical dehydration, Solvent evaporation, Solvent deposition, Nanoparticle formation by desolvation of macromolecules and co-accervation. The choice of technique mainly depends upon nature of polymer used, the drug and intended use. By the use of nano particles several drugs has been developed for efficacy, to reduce side effects and drug toxicity, increased therapeutic index and bioavailability for prolonging and controlled release.

KEYWORDS

Nanoparticles, Macromolecules, Bioavailability, Drug delivery and Amphiphilic.

Author for Correspondence:
V. Sivalalitha,
Department of Pharmaceutics,
Siddhartha Institute of Pharmaceutical Sciences, Jonnalagadda, Narasaraopet, Guntur,
Andhra Pradesh, India.
Email: vslalitha2011@gmail.com

INTRODUCTION

Nanoparticles are solid colloidal particles ranging in size from 10-1000nm in which the active principle is dissolved, entrapped, encapsulated and/or to which the active principle is adsorbed and attached. Drug targeting can be achieved by the development of colloidal drug carriers known as nanoparticles.

Nanoparticles are specially designed to release the drug to target tissue. In addition they could be controlled as being bystanders, burst, controlled, pulsatile or modulated. The formulation and clinical application of nanoparticles is based on the physic-chemical, pharmacokinetic and pharmacological properties of a drug. Up to 40% of New chemical entities (NCE's) are poorly soluble or lipophilic compounds. Low drug solubility often manifests itself in a host of in consequences including decreased bioavailability, increased chance of food effect, incomplete release from the dosage form and higher interpatient variability, severely limited choices of delivery technologies and complex dissolution testing with limited or poor correlation to the in vivo absorption. Reducing the particle size of an active pharmaceutical ingredient has been an effective method of improving the bioavailability of relatively insoluble drugs.

Advantages

Reduction of toxicity and adverse reaction.
Better drug utilization.
Controlled rate drug release.
Specific site of drug release
Better patient compliance
Enhancement of the therapeutic effectiveness of the drug.
The overall pharmacological response per unit dose.
Method of preparation is reproducible.
Easy handling of nanoparticles prepared in the powder form.
Pharmaceutical nanoparticles should be free from toxic impurities, should be easy to store and administer and should be sterile if parenteral use is advocated. Polymers are the building blocks of nanoparticulate composites. They delong to either natural or synthetic origin. Natural hydrophilic polymers can be divided into proteins and polysaccharides.

Methodology of nanoparticles[5,6]

1. Amphiphilic macromolecule cross linking
   a. Heat cross linking
   b. Chemical cross linking
2. Emulsion polymerization
   a. Emulsion polymerization in continuous aqueous phase
   b. Emulsion polymerization in continuous organic phase
3. Interfacial polymerization
4. Denaturation of natural macromolecules in an oil emulsion
5. Chemical dehydration
6. Nanoparticle formation by desolvation of macromolecules and coacervation
7. Solvent evaporation
8. Solvent deposition.

Heat cross linking

It involves the emulsification of bovine serum albumin or human serum albumin or protein aqueous solution in oil using high pressure homogenization or high frequency sonication. The water in oil emulsion thus formed is then poured into preheated oil. The suspension in preheated oil maintained above 100^0C is held stirred for a specified time in order to denature and aggregate the protein contents of aqueous pool completely and to evaporate the water. The protenaceous sub-Nanoparticles are thus formed where the size of the internal phase globules mainly determines the ultimate size of particulates. The particles are finally washed with an organic solvent to remove any adherent or adsorbed oil traces and subsequently collected by centrifugation.

Chemical cross linking

A chemical cross-linking agent (gluteraldehyde) is incorporated into the system at a 3%v/v level. Removal of residual cross-linking agent makes the method cumbersome. The aggregation in the process during emulsification, following emulsification or cross-linking results into variable size of nanoparticles. Albumin containing water droplets is

stabilized using cross linking agent. The droplets of aqueous phase are firstly emulsified in ethyl cellulose in chloroform by homogenization followed by the addition of gluteraldehyde. The emulsion system is then stirred for several hours. The resultant nanospheres are then washed with toluene or isopropyl alcohol with water and finally freeze dried.

Emulsion polymerization

The monomer is emulsified in a nonsolvent with or without any emulsifier.

Emulsion polymerization in continuous aqueous phase

The monomer is dissolved in the continuous phase, usually an aqueous solvent. Additional monomer can be stabilized in surfactant micelles or be emulsified in larger monomer droplets. The polymerization process is initiated by free radical or ion formation. Initiation occurs when a monomer molecule, dissolved in the continuous phase, collides with an initiator molecule which may represent an ion or a free radical.

Emulsion polymerization in continuous organic phase

In organic media, the conditions for the different phases are reversed and water-soluble monomers are used.

Interfacial polymerization

Here the polymerization process takes place at the interface between two immiscible phases. The monomer and the lipophilic drug are dissolved in oil. The organic phase is slowly added through a small tube under permanent stirring to the aqueous phase containing a surfactant.

Denaturation of natural macromolecules in emulsion

An aqueous solution containing a natural macromolecule and the drug to be entrapped is emulsified or homogenized in an oil emulsion; nanoparticles of the macromolecules are formed by heat denaturation or by cross linking.

Chemical dehydration

Bovine serum albumin nanoparticles with a narrow size distribution in hydroxypropyl cellulose solution in chloroform was used as a continuous phase of emulsion a chemical dehydrating agent 2,2 dimethyl propane is used to convert internal aqueous phase into a solid particulate suspension. The method reportedly avoids coalescence of droplets and could produce nanoparticles of smaller range (300nm), probably due to sonification time required for comminution and to keep internal phase well dispersed is reduced considerably.

Nanoparticle formation by desolvation of macromolecules or coaceration

The desolvation of protein or polysaccharide from an aqueous phase can be achieved by change or change in temperature or by adding some appropriate counter ions. This process is called as coacervation, a new phase is formed. The coacervate phase when treated with a cross linking agent produces nanoparticles.

Solvent evaporation

In this process, a polymer is dissolved together with a hydrophobic drug in a volatile, water immiscible organic solvent. The latter is dispersed in water by stirring and evaporated. The polymer precipitates in the form of microspheres containing the drug. Nanoparticles can be formed if the organic mixture is emulsified to form submicron size droplets using a dispersing agent and high energy homogenization.

Solvent deposition

Polymer with phospholipids is dissolved in acetone. A solution of the drug in benzyl benzoate is then added to the organic phase and this mixture is subsequently poured into water containing 0.5% poloxamer 188 under moderate stirring. Nanocapsules with an oily core are formed instantaneously. This suspension then has to be concentrated to about 10ml final volume by evaporation of solvent and partial removal of water.

Wetting milling or communition

API particles were mixed in 250ml bottle with water, HPC and Yittria-stabilised Zirconium beads (125ml). The weight of the slurry (API+MPC+H20) was 62.5g and the concentration of API in water was 16wt%. Ball milling at 84rpm for 5days to produce nanosuspension, which is later spray dried using Buchimini B-191 spray drier. Its inlet and outlet

temperatures were 100°C and 63°C respectively. During spray drying, suspensions were kept under mechanical stirring. Here Yittria-stabilised Zirconium beads act as milling media. In the wet milling process, communition continually fractures organic crystals while HPC polymer chains adsorb onto the fresh surface and stabilize each broken particle. The surface coverage of HPC can be obtained by dividing the amount of adsorbed HPC by the surface area of nanoparticles.

Super critical fluid processes

SCF are fluids whose temperature and pressure are greater than its critical temperature and critical pressure, allowing it to assume the properties of both a liquid and a gas. Once the drug particles are solubilised with in SCF, they may be recrystalised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to submicron levels.

Solid lipid nanoparticles

The solid lipid nanoparticles (SLN's) are submicron colloidal carriers (50-1000nm) which are composed of physiological lipid, dispersed in water or in an aqueous surfactant solution. There are two well-established methods reported in literature for the production of SLN. Hot homogenization technique homogenization of melted lipids at elevated temperature is termed as hot homogenization technique. Cold homogenization technique in case of too low solubility of the hydrophilic drug in the melted lipid, surfactants can be used of solubilisation of the drug. It is suitable for thermo sensitive and thermolabile Hydrophilic drug.

Hydrogel nanoparticles

Hydrogel nanoparticles are formed in water by self-assemblage and self-aggregation of natural polymer amphiphiles such as hydrophobised polysaccharides like cholesterol pullulan, cholesterol manna and cholesteroyldextran.

Purification of nanoparticles

Impurities in the nanoparticle suspension-organic solvents, residual monomers, polymerization initiators, electrolytes, stabilizers and large polymer aggregates must be removed, by gel filtration, ultra-centrifugation or "Cross flow filtration method, the nanoparticle suspension is filtered through membranes, with the direction of fluid being tangential to the surface f the membrane. The clogging of the filters is avoided. Depending upon the type of membrane used either microfiltration or ultra-filtration can be performed.

Freeze drying

It involves the freezing of the nanoparticle suspension and subsequent sublimation of its water content under reduced pressure given a free flowing, stable, readily dispersible, elegant, product.

Sterilization

Nanoparticles intended for parenteral use should be sterilized and be pyrogen free. Sterilization by filtration does not work for nanoparticles. Sterilization of nanoparticles is done by aspetic technique in preparation and processing and formulation and/ or by subsequent sterilizing treatments like autoclaving or γ-irradiation.

Table No.1: Drugs developed as nanoparticles

S.No	Application	Medicament studied
1	To increase the efficacy	Acitinomycin-D 5-fluorouracil Amphotericin-B Pilocarpine Cyclosporine Primaquine and Metronidazol
2	To reduce side effects	5-fluorouracil
3	To reduce drug toxicity	Doxorubicin Dehydro emetine
4	To enhance therapeutic index	Doxorubicin
5	To improve or enhance Bioavailability	Avarol Pefloxacin mesilate Ofloxacin
6	For prolonging drug action	Insulin Influenza whole virus Influenza
7	For controlled release	Theophyline Indomethacin Ibuprofen and Propranolol
8	For targeting	Phthalocyanines and napthalocyanines Monoclonal Antibodies
9	Miscellaneous	Cyclosporin-A Somatoliberin

Table No.2: Therapeutic uses by using nanoparticle drugs

S.No	Application	Purposes
1	Cancer therapy	Targeting, reduced toxicity, enhanced uptake of Antitumoragents, improved in-vitro and *in vivo* stability
2	Intracellular targeting	Target reticulo endothelial systems for Intra cellular infections
3	Prolonged systemic circulation	Prolong systemic drug effect, Avoid uptake by the reticulo endothelial system
4	Vaccine Adjuvant	Enhances immune response, Alternate acceptable adjuvant
5	Per oral absorption	Enhanced bioavailability, protection from gastro intestinal enzymes
6	Ocular delivery	Improved retention of drug or Reduced wash out
7	DNA delivery	Enhanced delivery and significantly higher expression levels
8	Oligo Nucleotide delivery	Enhanced delivery of oligo nucleotide
9	Other Applications	Cross blood - brain barrier Improved absorption and permeation Enzyme immuno assays Radio-imaging Oral delivery of peptides

Melting of the lipid

↓

Dissolution of the drug in the melted lipid

↓

Mixing of the preheated dispersion medium and the drug lipid melt

↓

Premix using a stirrer to form a coarse pre-emulsion

↓

High pressure homogenization at a temperature above the lipids melting point

↓

O/W-Nano emulsion

↓

Solidification of the nano-emulsion by cooling down to room temperature to form SLN

Figure No.1: Flow chart for hot homogenization technique

Melting of the lipid

↓

Dissolution or solubilization of the in melted lipid

↓

Solidification of the loaded lipid in liquid nitrogen or dry ice

↓

Grinding in powder mill (50-10) m particles

↓

Dispersion of the lipid in the cold aqueous dispersion medium

↓

Solid lipid nanoparticles

Figure No.2: Flow chart for solid liquid nanoparticle preparation by cold homogenization technique

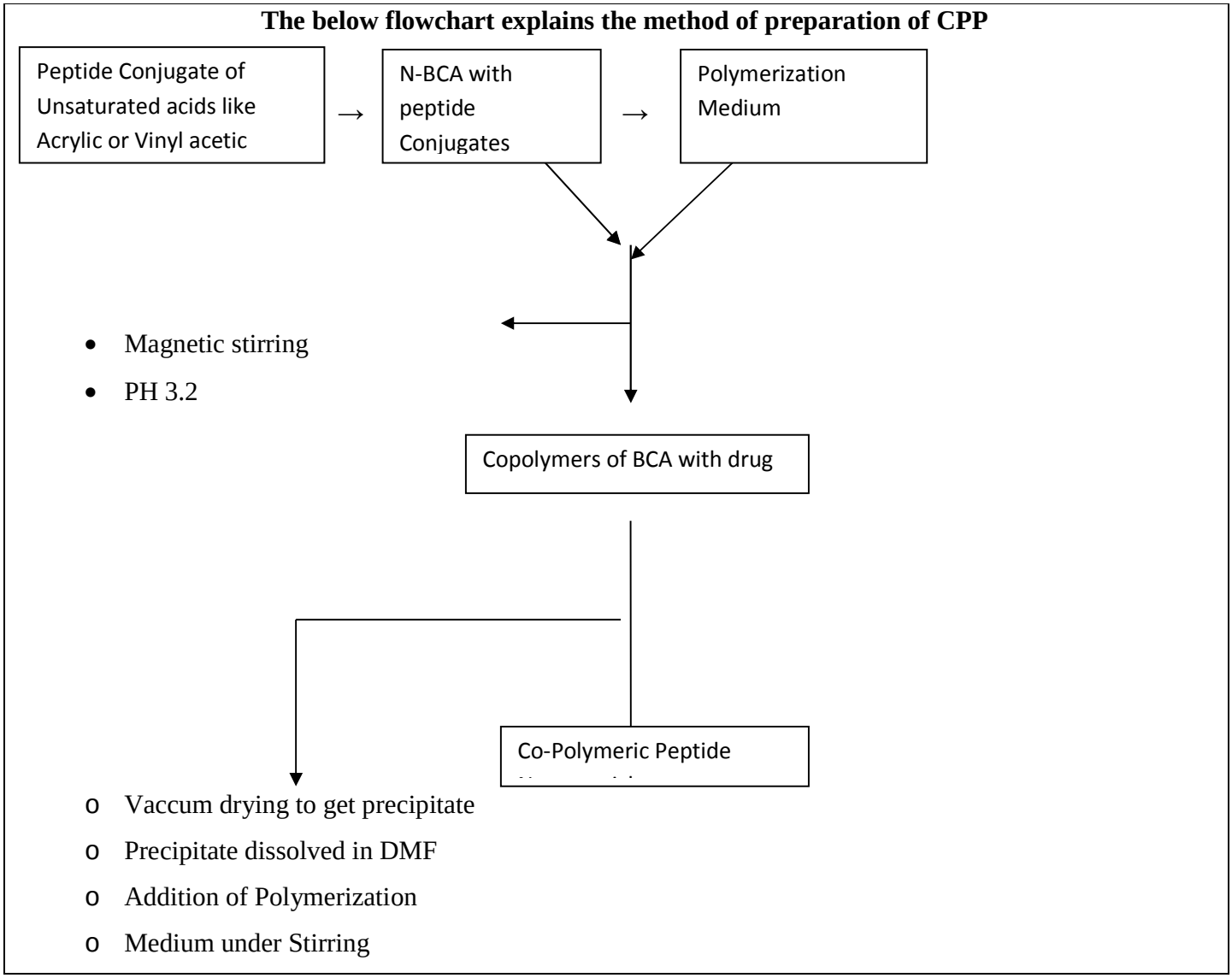

Figure No.3: Flow chart for copolymerized peptide nanoparticles technique

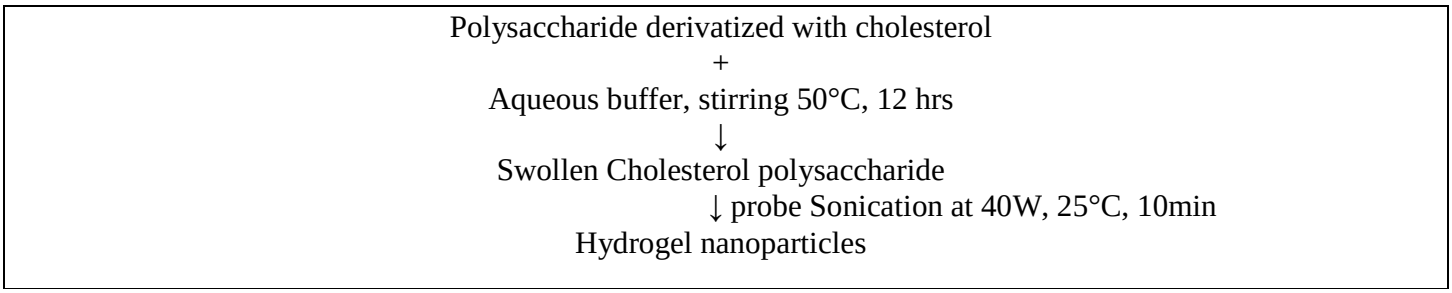

Figure No.4: Flow chart for hydrogel nanoparticles technique

CONCLUSION

Nanoparticles are solid colloidal particles in nanometer range acts widely as the drug carriers for controlled drug delivery. Drug targeting can be achieved by the development of colloidal drug carriers, Nanoparticles are specially designed to release the drug to target site, Nanoparticles improve the bioavailability of relatively insoluble drugs and used to increase the efficacy and reduce adverse effects of the drugs. By using the drugs in the form of nanoparticles, they have several advantages in the medicinal aspects such as cancer therapy, DNA delivery and prolonged systemic circulation, as a whole now a day's nanotechnology is one of the emerging technologies to deliver the drugs to the desired site.

ACKNOWLEDGEMENT

We are thankful to our respective secretary Mr. K. Gurukishan, Director Mr. J. Prabhakar Rao, for providing us the books facility and also to our Principal Dr. R. Srinivasan who given permission to carry out the work. We are also thankful to Librarian staff that spared their time with us.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Martin's. A book of physical pharmacy and pharmaceutical sciences, *Wolters Kluwer Health(India) Pvt.Ltd, New Delhi,* 5th edition, 2007, 496, 625.
2. Aulton. A text book of pharmaceutics for the design and manufacture of medicines, *Elsevier's health sciences rights department, USA,* 3rd edition, 2009, 14.
3. Remington. A text book of science and practice of pharmacy, *Wolters Kluwer Health (India) Pvt.Ltd, New Delhi,* 21st edition, 1, 2011, 954, 960.
4. Suresh P Vyas and Roop K Khar. A text book of controlled drug delivery, *Vallabh prakashan C-S, New Delhi,* 2nd edition, 2012, 527.
5. Vyas S P. A text book for theory and practice in novel drug delivery system, *CBS publishers and distributors Pvt.Ltd, New Delhi,* 2nd Edition, 2011, 226.
6. Mohanty sivasankar and Boga pramod kumar. Role of nanoparticles in drug delivery system, *International Journal research for pharmaceutical biomedical sciences,* 1(2), 2010, 41-66.

Please cite this article in press as: Sivalalitha V. *et al*. Nanoparticles as drug delivery systems, *International Journal of Research in Pharmaceutical and Nano Sciences,* 1(2), 2012, 281-289.