



# Preparation And Evaluation Of Mefenamic Acid Nanoparticles By Continuous Addition Method Using Butanol As Desolvating Agent

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## Abstract

The aim of the present investigation is to prepare mefenamic acid nanoparticles by desolvation technique using butanol as desolvating agent. To 1% aqueous solution of mefenamic acid the desolvating agent was added continuously at the rate of 1 ml per minutes till the solution become turbid. Then a cross linking agent was added and kept for stirring for a period of 8 hours. The obtained nanoparticles were evaluated for product yield, Drug content, entrapment efficiency and loading capacity. The SEM images clearly reveals that the particles were found to be spherical in shape. The product yield, drug content, entrapment efficiency and loading capacity was found to be 85.6%, 53.7%, 85.05% and 83.52% respectively.

## Introduction

### Introduction to the Nanoparticles

Nanoparticles are sub-nanosized colloidal structures composed of synthetic or semisynthetic polymers. They are nanospheres, nanocapsules and nanocrystals. Nanospheres are solid core spherical particulates which are nanometric in size. They contain drug embedded within the matrix or adsorbed onto the surface. Nanocapsules are vesicular system in which drug is essentially encapsulated within the central volume surrounded by an embryonic polymeric sheath. In nanocrystals drug is mainly encapsulated in the solution system [1].

### Natural Hydrophilic Polymers

Albumin, gelatin, legumin polysaccharides like alginates or agarose. Natural hydrophilic polymers are studied because of their intrinsic biodegradability and biocompatibility. Natural polymers are classified as proteins and polysaccharides. Proteins are gelatin, albumin, lecithin, legumin and vicilin. Polysaccharides are alginate, Dextran, chitosan, agarose and pullulan.

They suffer some disadvantages

- batch to batch variation
- conditional biodegradability
- antigenicity

### Synthetic Hydrophilic Polymers

Polymers in nanoparticle preparation are those which are used in the preparation of microsphere. The polymers used are either pre-polymerized or synthesized before or during the process of nanoparticle preparation [2].

Two types of systems are present

- 1) Consisting of an entanglement of oligomer or polymer units. ( nanoparticles/nanosphere)
- 2) Reservoir type of system comprised of an oily core surrounded by an embryonic polymeric shell.

### Criteria For Ideal Polymeric Carriers For Nanoparticles And Nanoparticle Delivery System

#### Polymeric Carriers

- 1) Easy to synthesize and characterize
- 2) Inexpensive
- 3) Biocompatible
- 4) Biodegradable
- 5) Non-immunogenic
- 6) Nontoxic
- 7) Water soluble

## Nanoparticle Delivery System

- 1) Simple and inexpensive to manufacture and scale up
- 2) No heat high shear forces or organic solvents involved in their preparation process
- 3) Reproducible and stable
- 4) Applicable to a broad category of drugs, small molecules proteins and polynucleotides
- 5) Ability to lyophilize
- 6) Stable after administration
- 7) Non-toxic

## Different Techniques For Preparation of Nanoparticles

- 1) Amphiphilic macromolecule cross-linking
  - a. heat-cross linking
  - b. Chemical cross linking
- 2) Polymerization based methods
  - a. Polymerization of monomers
  - b. Emulsion polymerization
  - c. Dispersion polymerization
  - d. Interfacial condensation polymerization
  - e. Interfacial complexation
- 3) Polymer precipitation methods
  - a. Solvent extraction
  - b. Solvent displacement
  - c. Salting out

## Nanoparticle Preparation By Cross-Linking Of Amphiphilic Macro Molecules

### Mechanism

The technique of preparation involves aggregation of amphiphile followed by further stabilization either by heat denaturation or chemical cross linking [3].

### Cross Linking In W/O Emulsion

The cross-linking method is used for the nano-encapsulation of drug. The method involves the emulsification of bovine serum albumin (BSA/Human serum albumin) or protein aqueous solution in oil using high pressure homogenization. The water in oil emulsion so formed is then poured into preheated oil. The suspension in preheated oil maintained above 100 degrees is held stirred for a specific time in order to denaturate and aggregate the protein contents of aqueous pool completely and to evaporate water. Proteinaceous sub-nanosopic particles thus formed where the size of the internal phase globule 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. The factors which govern size and shape of nanoparticle are mainly emulsification energy and temperature [4].

### Emulsion Chemical Dehydration

It is used for producing BSA nanoparticles with a narrow size distribution. Hydroxy propyl cellulose solution in chloroform was used as a continuous phase of emulsion. A chemical dehydrating agent 2, 2-dimethyl propane was used to translate internal aqueous phase into a solid particulate suspension. This method avoids coalescence of droplets and could produce nanoparticles of small size.

### Phase Separation In Aqueous Medium

The protein or polysaccharide from an aqueous phase can be desolvated by pH change or change in temperature or by adding appropriate counter ions. Cross-linking may be affected simultaneously or subsequent to the desolvation step. It contains three steps. Protein dissolution, protein aggregation and protein deaggregation. The appropriate levels of desolvation and resolvation, the aggregate size could be maintained and finally these aggregated nanoparticles are cross linked using glutaraldehyde. Sodium sulphate is the main desolvating agent. Alcohol, Ethanol, isopropanol are added as desolvating agents. The addition can be optimized turbidometrically using nephelometer. Only desolvation gives the final product as nanosphere. Desolvation deaggregates the protein and turns the suspension colloidal and hence milky in appearance. Both lipophilic and hydrophilic drugs can be entrapped in nanoparticles using this technique [5].

### pH Induced Aggregation

The protein phase also be separated through pH change. The pH -induced aggregation to prepare nanoparticle has been extensively used for the preparation of nanoparticles.

## Materials and Methodology

Mefenamic acid was obtained as a gift sample from Dr. Reddy Labs. Ltd, Hyderabad. BSA acetone and glutaraldehyde were supplied from S.D Fine Chemicals Ltd, Mumbai.

### Preparation of BSA Nanoparticles By Continuous Addition Of Acetone As Desolvating Agent

Requisite amount of BSA was dissolved in 100 ml water. In continuous addition method butanol (desolvating agent) was added at the rate of 1ml per minute. The solution was stirred at a speed of 500 rpm until the solution become slightly turbid. pH of the solution was maintained at 7. One Drop of 6 % glutaraldehyde was added for cross linking of resultant nanoparticles. Solvent was removed by Rota evaporator [6].

### Characterization and Evaluation

The obtained nanoparticles were evaluated for Particle size, product yield, Drug content, entrapment efficiency and loading capacity.

## Determination of Particle Size

### Study of Surface Morphology Of Nanoparticles By Scanning Electron Microscope (SEM)

The prepared amorphous nanoparticles were dispersed in deionized water and sonicated for 30 minutes. A circular metal

plate is taken on to which carbon double tape (1mm×1mm) is stickered; a drop of the resultant nano dispersion is placed on to the tape and allowed to dry for a while. Then it is scanned under SEM for morphology. The obtained nanoparticles were found to be spherical in shape [7] (Figure 1).

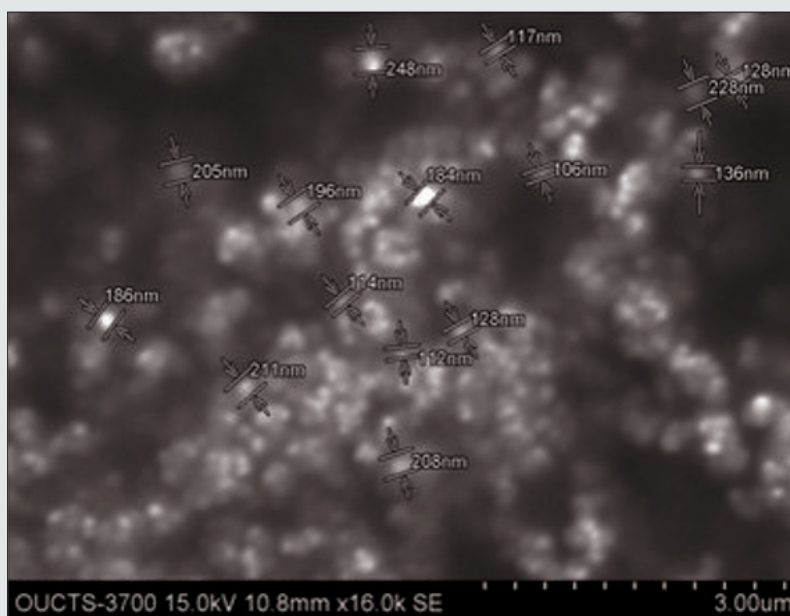


Figure 1: SEM images of BSA nanoparticles by continuous addition method.

### Product Yield

The yields of the prepared nanoparticles were calculated. The dried nanoparticles were weighed, and the yield of nanoparticles was calculated using the formula:

$$\text{Percentage yield} = \frac{\text{Amount of nanoparticles obtained}}{\text{Theoretical amount}} \times 100$$

The product yield was observed as 87.9%

### Drug Content

To determine the drug content, 50mg drug equivalent to formulation was weighed accurately and transferred into three necked RBF containing 50ml of methanol. The solution was stirred at 700rpm for 3hrs by using magnetic stirrer [8]. The resultant solution was filtered and the amount of the drug in the filtrate was estimated after suitable dilution by ultraviolet (UV) spectrophotometer at 285nm. The drug content was found to be 53.7%.

### Entrapment Efficiency

Entrapment efficiency indicates the amount of drug encapsulated in the formulation. The method of choice for drug content determination is separation of free drug by ultracentrifugation, followed by quantitative analysis of the drug

from the formulation. The samples were centrifuged by using ultracentrifuge at 17640 rpm for 40min [9,10].

Percentage entrapment efficiency may be calculated from the following formula:

$$\text{Entrapment efficiency} = \frac{\text{Amount of drug encapsulated in the formulation}}{\text{Total amount of drug in the formulation}} \times 100$$

The entrapment efficiency of the formulation was found to be 85.05%.

### Loading Capacity

The loading capacity (LC) refers to the percentage amount of drug entrapped in nanoparticles [11]:

$$\text{Loading capacity} = \frac{\text{Total amount of drug} - \text{Amount of unbound drug}}{\text{Nanoparticle's weight}} \times 100$$

The loading capacity was observed as 83.52%

### Conclusion

Mefenamic acid loaded BSA nanoparticles were prepared by desolvating technique using butanol as desolvating agent. Continuous addition method was followed for the addition of desolvating agent to the aqueous solution of BSA. The product

yield, drug content, entrapment efficiency and loading capacity was found to be 85.6%, 53.7%, 85.05% and 83.52% respectively. Mefenamic acid nanoparticles were prepared by desolvation technique successfully using butanol as desolvating agent by continuous addition method.

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