



A REVIEW ON DIFFERENT PREPARATION METHODS USED FOR DEVELOPMENT OF CURCUMIN NANOPARTICLES

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ABSTRACT:-

A design and development of herbal (i.e. Curcumin) nanoparticles it has become a extremes research in the Nano formulation field. Curcumin, an orange crystalline powder which derived from the herbs of *curcuma longa* linn (Zingiberaceae), it is natural hydrophobic polyphenol compound mainly applied in Chinese medicine and some of the food industries, which supply different biological and pharmacological activity including antioxidant, anti-inflammatory, anti-microbial, anti-neoplastic, anti diabetic and chemo preventive properties. Curcumin shows therapeutic efficacy against many human illness and diseases but clinical application of this compound is limited due to its poor bioavailability, poor water solubility, fast metabolism, susceptibility to degradation in the alkaline medium.

One of the most important technique/ method to improve the poor biopharmaceutical properties of the curcumin is to enhance aqueous solubility, bioavailability by using nanotechnology and nanoparticles, having a small size in nanometer range. In this review, there are various methods used for preparation of curcumin nanoparticles are briefly discussed.

KEYWORDS: - Curcumin, Methods of preparation, Nanoparticles.

INTRODUCTION:-

Curcumin is a polyphenol compound, which is extracted from curcuma long Linn, (Zingiberaceae) rhizome. It is also known as turmeric in Indian culinary art. Curcumin longa also contains three main curcuminoids such as curcumin, desmethoxycurcumin, bismethoxycurcumin which includes 3-5% of the turmeric preparations. Practically the available curcumin contains 75-80% curcumin, 15-20% desmethoxycurcumin and 3-5% bis-desmethoxycurcumin.

From the thousands of year, this is used in Indian traditional medicine (Ayurveda), Chinese medicine against the several diseases, such as rheumatism, skin diseases, body pains, hepatic diseases, inflammation, and asthma. Currently it is used in the food industry as flavouring, preservative and colouring agent. This grows extensively in Africa and Southwest India. It is commonly used as a spice in the South and Asian countries, due to its flavour and yellow colour. ^[1]

It is natural phytochemical which shows good medicinal properties in different biomedical areas. Curcumin also shows therapeutic values including antioxidant, anti-inflammatory, antimicrobial, antineoplastic, anti-diabetic, chemo preventive properties.

Another advantages of curcumin is minimum side effects, do not causes any toxicity; it is safe in higher doses of curcumin drugs. ^[2]

Curcumin is a practically insoluble in aqueous solutions, readily soluble in organic solvents such as alcohols, ketones, esters and organic acids. Thus the hydrophobic character of the curcumin which shows pharmacokinetic limitations such as low absorption, poor bioavailability by the oral route, fast metabolism and rapid elimination.

There are the main scheme which is used to overcome the phytochemical limitations of curcumin and to increase its bioavailability which are based on the loading the compounds in the nano carriers, such as liposomes, polymeric micelles, phospholipid complexes and polymeric nanoparticles. ^[3]

Nanotechnology is a one of the most consistent fields in the element techniques, because of the rapid expansion. Depends upon the nanotechnology, scientists are adequate to find out and operate the materials in atomic and molecular distribution expanded of the fields. Nanomaterials are designed by the different procedures under the high control using on the basis of physical and chemical properties and developing the different characteristics that give benefits to their purpose.

Nano medicine is technological activation one and other in the development of new drugs/ formulation and reformulation of extant ones, and also enhancing their potency, (i.e. specificity, tolerability and therapeutic index) low risk of toxicity, reduces side effects, concede the use of reactive substances such as curcumin. ^[1]

Nanoparticles also increase their solubility, permeability and also increase the permeability of the curcumin towards the metabolic processes. It also produces longer circulation times, protects the molecule from incomplete degradation and develops controlled Drug release and drug targeting. ^[3] In the formulation, mostly poorly soluble drugs are one of most important/ major problem in the pharmaceutical industry. Because duo to low solubility, permeability, low bioavailability, faster metabolism. There are

different types of techniques which are used before for enhancing the solubility and dissolution rate of poorly soluble drugs.

Nanoparticles which have one of most favourable way which have used in last many years According to Whitney-Noves Equation, reduction in the drug particle into nanoscale material size that results in higher dissolution rate and higher surface area and are efficient for drug release and drug loading. Nanoparticles size generally ranges from 20-500 nm consisting of large specific entities, all characteristics appearance which are implement for in medicine technology.

Therefore efforts have been made to improving these features. The promising approaches to increasing bioavailability of curcumin include the use of nanoparticles, liposomes, micelles and phospholipid complexes. The application of nanoparticle formulation to enhances of solubility, stability, bioavailability, pharmacological activity, and ability to avoid physical and chemical degradation. In the introduction of nanotechnology in curcumin provides a solution to increase its bioavailabilty and therapeutic efficacy. [4,5]

In this review, we have discussed the different methods used for the preparation of Curcumin nanoparticles shown in table no. 1.

METHOD OF PREPARATION:-

1. Single Emulsion-Solvent Evaporation Technique.
2. Thin Film Hydration Method.
3. Micro Emulsion Method.
4. Desolvation Method.
5. Agitation and Sonication Method.
6. Cross Linking Method.
7. Freeze Dried Anti Solvent Crystallisation And High Pressure Homogenizer Method.
8. Co-Precipitation Method.
9. Electrospraying Method.

1. Single Emulsion Solvent Evaporation Technique

Curcumin loaded nanoparticles were prepared by using single emulsion solvent evaporation technique.

In glass tube, to take 100-200 mg of PLGA polymer was dissolved in 5 ml of dichloromethane (DCM), then 10 or 20 mg curcumin powder dissolved in solvent mixture and intermittent vortex for 30 min. The mixture of drug/polymer was added in glass tube containing 10 ml of aqueous PVA solution. After, adding the drug/polymer mixture in PVA solution then vortex for more 10 sec at high speed. This polymer mixture was emulsified in ice water bath for 7 min at 40 % amplitude by using probe sonicator. This emulsified mixture was poured into 30 ml of 0.5% aqueous solution under magnetic stirring.

Dichloromethane was evaporated under high magnetic stirring at 800 rpm for 3 hrs. The nanoparticles were collected by using centrifugation at 20,000 rpm for 15 min and washed for 3 times with distilled water. Then supernatants were collected, pellets of the nanoparticles was resuspended in 5 ml distilled water. Schematic diagram for preparation of curcumin nanoparticle by single emulsion solvent evaporation technique shown in figure 1. [3]

2. Thin Film Hydration Method

The drug loaded lipid nanoparticles was prepared by using a thin film hydration method. In this technique, lipid phosphatidylcholine, cholesterol, curcumin are mixed in the methanol and chloroform desired ratio. Then rotatory evaporator apparatus are used for evaporation of solvent mixture under the reduced pressure at 45°C for 15min at 70 rpm speed. In the solvent mixture containing elements are removed by vacuum pumping for 3 to 4 hrs then thin film is formed.

Finally, thin film of drug loaded lipid nanoparticles are hydrated for 1 hrs by using pH 7.4 phosphate buffer solutions. This lipid mixture are sonicated for probe sonication and filtrated by 0.45 µm membrane filter and finally well appropriated drug loaded lipid nanoparticles are formed and store at 4°C. Schematic diagram of lipid loaded Curcumin nanoparticles by thin film hydration method shown in figure 2. ^[6]

3. Micro emulsion-sonication Method

The Curcumin nanostructure lipid carriers (NLC) are prepared by using Micro emulsion method. In this method, sonicator is used. The lipids of steric acid (SA) and capric triglycerides (CA) are heated to 75 °C, the surfactants of tween 80 and plutonic F127 are added in melted lipid solution until the solution is clear. Another 1 ml of distilled water and non ionic surfactants are heated to 75 °C and to melted lipid solution containing curcumin under the continuous stirring. The formed emulsion are added in 2 to 4 °C cold water then they are solidified and the solidified emulsion are homogenised at 8000 rpm for 5 min. Finally well distributed curcumin nanostructure lipid carriers are formed. Schematic diagram of lipid loaded Curcumin nanoparticles by Micro emulsion method shown in figure 3. ^[7]

4. Desolvation Method

The curcumin nanoparticles are prepared by using the desolvation technique. In this technique aqueous polysaccharide solution of ethanol precipitation are used for the preparation of curcumin polysaccharide nanoparticles. Essentially absolute ethanol is a desolving agent and curcumin as the active substances with arranged concentration of absolute ethanol, and 0.1% of tween 20 emulsifying agent is used.

To dissolve 5mg/ml of chitosan, 0.1% tween 20 in deionised water and continuous stirring for 1 hour at 90°C. Then the desolving agent of absolute ethanol is added drop wise to the chitosan solution under mixing at 70°C. The nanoparticles formed suspension is centrifuged at 10,000 rpm for 2 min. After centrifugation to separate large particles, supernatant are collected and again centrifuge for 15,000 rpm for 15 min, then resulting nanoparticles precipitate are washed with 1 ml of desolving agent of absolute ethanol and to remove free curcumin.

Certainly, the formed nanoparticles are resuspended in deionised water and freeze dried to form a well distributed polysaccharide curcumin nanoparticles. Schematic diagram of polymer loaded Curcumin nanoparticles by desolvation method shown in figure 4. ^[8]

5. Agitation and Sonication Method

The curcumin nanoparticles are obtained by two methods one as Agitation and second as sonication. In agitation method, 0.05g mL^{-1} of curcumin are added in ethanol then 100 ml of this solution are added in predefined volume of deionised water. Then this solution is agitated for 2 hrs at 200-1000 rpm for 50°C . After agitation this solution is lyophilised to obtain a yellow colour TY] powder of curcumin nanoparticles. The nanoparticles are obtained from ethanol and agitation process is known as NEA.

In sonication process, 0.10g mL^{-1} of curcumin are added in ethanol then 100 ml of this solution are added in predefined volume of deionised water. Then this solution was sonicated (120W) for 2 hrs at 50°C . After sonication this are lyophilised to obtain well distributed yellow colour curcumin nanoparticles and second part are maintained as solution. The nanoparticles are obtained from chloroform and sonication is known as NES. Schematic diagram of Curcumin loaded nanoparticles by Agitation method shown in figure 5. ^[1]

6. Cross-linking Method

The curcumin loaded human serum albumin (HSA) nanoparticles are prepared by cross-linking method. Firstly, to prepare the human serum albumin nanoparticles and then to load the curcumin in human serum albumin nanoparticles and to form curcumin loaded HSA nanoparticles. In this method, 1% solution human serum albumin added in 2 ml of phosphate buffer saline and to prepare different concentration of dithiothretol (DTT 1-10 mM) and Sodium deoxycholate (NaDS 5-30 mM). Then this solution was incubated for 1 hrs at 30°C . After, incubation of this solution 1 ml of ethanol was added drop by drop to the solution and constant stirring. After the addition of ethanol the solution are again incubated for 10 min at 37°C , then solution are stored at room temperature for 2 hrs. Thereafter, dialysis is performing for 24 hrs under the constant stirring and to remove the unbound or unreacted DTT and NaDS using PBS dialysing agent.

After dialysis, take 0.2-2 mg of curcumin mix in 1 ml of ethanol and they are added in alternately to HSA nanoparticle solution. This solution is equilibrated for 15 min and then performs the dialysis process for 12 hrs to remove the unbounded or unreacted curcumin. Finally curcumin loaded human serum albumin (HSA) nanoparticles are form. Schematic diagram of HSA loaded Curcumin nanoparticles by cross-linking method shown in figure 6. ^[9]

7. Freeze dried anti solvent crystallization method (CRS-FD), Freeze dried Anti solvent crystallisation method followed by high pressure homogenizer.

Stabilizer loaded curcumin nanoparticles are prepared by anti solvent crystallisation method. In this method, 1 gm of curcumin was added in 20 ml of acetone and to dissolve. Then this solution are added in the 200 ml of aqueous solution containing different weight concentration of stabilizer such as PVP, HPMC at a rate 5 ml per/min by using a burette. Then this solution was stirred for 600 rpm for 25°C , the final concentration of curcumin and stabilizer suspension is formed in different ratio. Then the final

suspension are instantly freeze dried at -70°C for 48 hrs, then to form stabilizer loaded curcumin nanoparticles by freeze dried antisolvent crystallization method.

In high pressure homogenizer, prepared suspension of curcumin and stabilizer in different ratio are homogenized. In 1st step the pressure are adjusted at 500 bars, pass the suspension for 5 times in a homogenizer and final step pressure are adjusted for 1000 bars, pass the suspension for 10 times in a homogenizer. The final obtained suspension is instantly freeze dried at -70°C for 48 hrs, then. To form stabilizer loaded curcumin nanoparticles freeze dried anti solvent crystallisation method followed by high pressure homogenizer. Schematic diagram of Stabilizer loaded Curcumin nanoparticles by anti solvent crystallisation method shown in figure 7. ^[10]

8. Co-Precipitation Method

Amorphous Calcium Phosphate (ACP) loaded curcumin nanoparticles are formed by co-precipitation method. In this method firstly, calcium nitrate are dissolved in 29 ml of deionized water to form 1 mM aqueous solution. Then ammonium hydrogen phosphate was added drop by drop in this and to form a white suspension.

The raw materials are arranged in calcium and phosphate ration at 1.5 and pH maintained for 8 by the addition of 1 M Sodium hydroxide solution at 30°C , then formed nanoparticles are washed with deionized water and to remove any other ions and samples are centrifuged and freeze dried.

After forming a ACP nanoparticles then, 5 mg/ml of curcumin are loaded in calcium nitrate solution then, mixture are stirring for 1 hrs under slowly addition of sodium hydrogen phosphate then mixture are stirring again for 15 min at 30°C , resulting suspension are centrifugated to form a ACP loaded curcumin nanoparticles. Schematic diagram of ACP loaded Curcumin nanoparticles by co-precipitation method shown in figure 8. ^[4]

9. Electro spraying Method

The nanoparticles are prepared by the Electro spraying technique. In this technique, curcumin as the active ingredient, zein, chitosan, piperazine as the biopolymer used for preparing curcumin, piperazine loaded zein, chitosan nanoparticles. In the preparation of nanoparticles, firstly to prepare zein unloaded micro particles then unloaded zein nanoparticle without addition of curcumin, chitosan, piperazine.

Preparation of zein unloaded micro and nanoparticles:-

Zein are dissolved in 70 % ethanol:water v/v ratio and continuously stirring at room temperature up till dissolve completely.

Preparation of curcumin loaded zein nanoparticles:-

After the development of zein concentration, the different weight ratio of curcumin are added to zein solution (curcumin:zein) ratio ranges from 1:10, 1:20. Then curcumin are dissolved in 70 % ethanol and needed relation of zein to curcumin solution (1:10, 1:20, 1:30)

Preparation of curcumin and piperazine loaded zein-chitosan nanoparticles:-

For the preparation of curcumin and piperazine loaded zein-chitosan nanoparticles, the solution of zein and curcumin are added in the inner fluid of core, the blunt end of needle syringe which are attached to the positive electrode of the direct current supply and second solution of chitosan, piperazine are added in the outer fluid of shell. The solution was feeding to the injection needle by using a syringe pump. The distance between the needle tips to aluminium foil covered plate is about 10 cm; this covered plate is connected to direct power supply. Then apply the voltage 15 kV and slowly increases to 17.5 to 20 kV and maintaining the flow rate at 0.3 ml/h. ^[11]

CONCLUSION:-

Recently nanotechnology is advanced technique in the drug delivery system, because of its greater stability, functionality and also the pharmacokinetic and pharmacodynamic of the drug significance. Curcumin is the poly phenolic hydrophobic compounds; it's used in different medicinal properties such as anti-inflammatory, anticancer, antiseptic, anti-diabetic, anti-microbial etc. But curcumin have limited advantages in clinical applications because it's low solubility, low bioavailability. There are the main system which is used to affected the phytochemical condition of curcumin to increase its solubility, stability, bioavailability, its ability to avoid physical and chemical degradation, solubility of the curcumin by nanoparticles, such as the polymeric nanoparticles, polymeric micelles, liposomes, phospholipid complexes.

In this review we have discussed the different methods which are used for the preparation of curcumin nanoparticles and its drawbacks and its advantages. We have also discussed the new reported methods for the preparation of curcumin nanoparticles in last five years. The described methods, in this review are best suitable methods for the preparation of curcumin nanoparticles, its methods are less expensive as compared to other methods.

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Table no.1 Different methods used for the preparation of Curcumin nanoparticles

Sr. No	Name of Method	Types of prepared Nanoparticle	Advantages	Uses
1	Single Emulsion-Solvent Evaporation Technique	Curcumin loaded poly(lactic-co-glycolic acid) PLGA Polymeric Nanoparticle PNP	The PNPs have excellent endocytosis efficiency, passive tumor-targeting, high encapsulation efficiency, improve solubility, protects the molecules from degradation, biocompatibility	Use to treat of colon cancer. PNPs used for oral colon delivery purposes.
2	Thin Film Hydration Method	Curcumin loaded liposomic Nanoparticle (CLL)	Enhance the bioavailability of drug, Reduction the dose of drug	Use to treat of Wound Healing.
3	Micro emulsion-sonication Method	Curcumin loaded Nanostructured Lipid carriers(NLCs)	High drug encapsulation efficiency and high drug stability without use in organic solvent. Its inexpensive and easy method to scale-up.	Use to treat of Gastric disease.
4	Desolvation Method	Curcumin Loaded polysaccharide Nanoparticle (CLPNPs)	Increased stability of volatile pharmaceutical agents, easy and cheap fabrication in large quantities by a multiple method.	Use to treat of anti-cariogenic activity (dental caries)
5	Agitation and Sonication Method	Curcumin loaded nanoparticle (CLP)	Increases bioavailability. Nanoparticle obtained in small size than other method.	Anti-Inflammatory, Anti-oxidant, Anti-microbial.
6	Cross-linking Method	Curcumin loaded albumin nanoparticle	Optimum size for cellular uptake of entice drug. It's helpful in the future design of novel drug delivery system for the hydrophobic drugs	Use to treat of lung cancer.
7	(CRS-FD), Freeze dried Anti solvent crystallisation method followed by high pressure homogenizer. (CRS-FD),	Curcumin loaded polymeric (HPMC, PVP) Nanoparticle	Obtain the modifiable curcumin Nanoparticle. It shows the better solubility.	Anti-cancer, Anti-inflammatory Activity
8	Co-Precipitation Method	Curcumin loaded calcium phosphate nanoparticle (ACP nanoparticle)	High drug loading capacity and good pH responsive drug released properties And controlled drug released behavior. Good biodegradability	Anti-oxidant activity
			It shows good cytotoxic	

9	Electrospraying Method	Chitoson, Curcumin and piperzine loaded zein	effect, Improves stability and protect drugs against degradation	Anti-cancer activity
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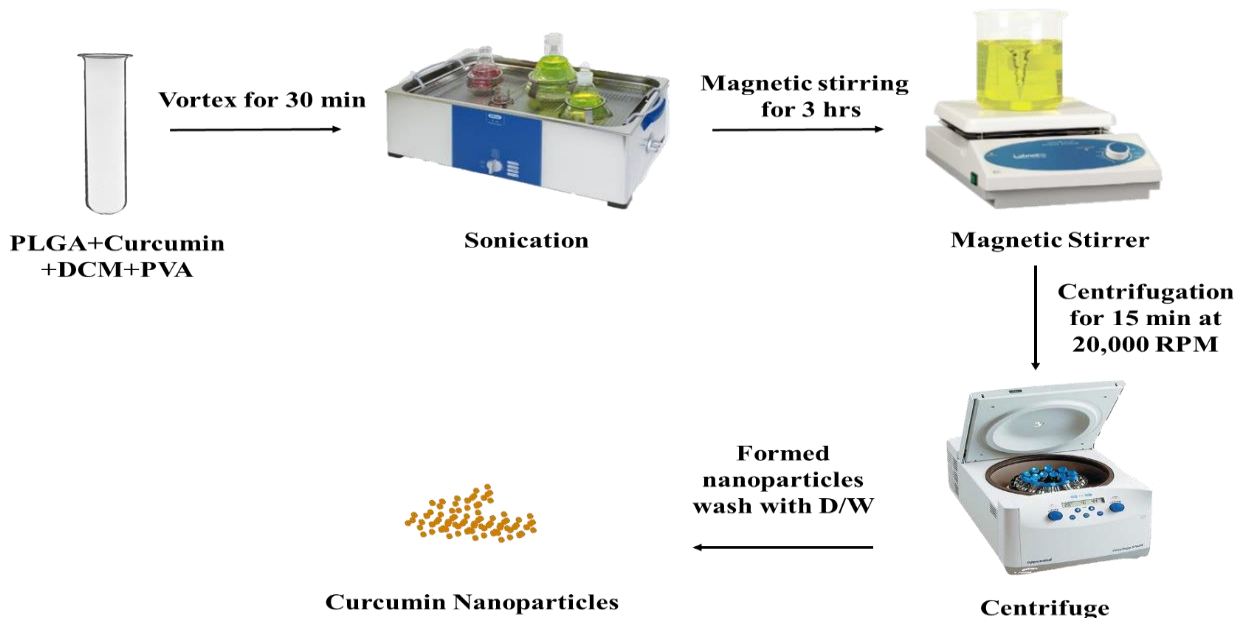


Figure 1: Schematic diagram for preparation of curcumin nanoparticle by Single Emulsion Solvent Evaporation Technique.

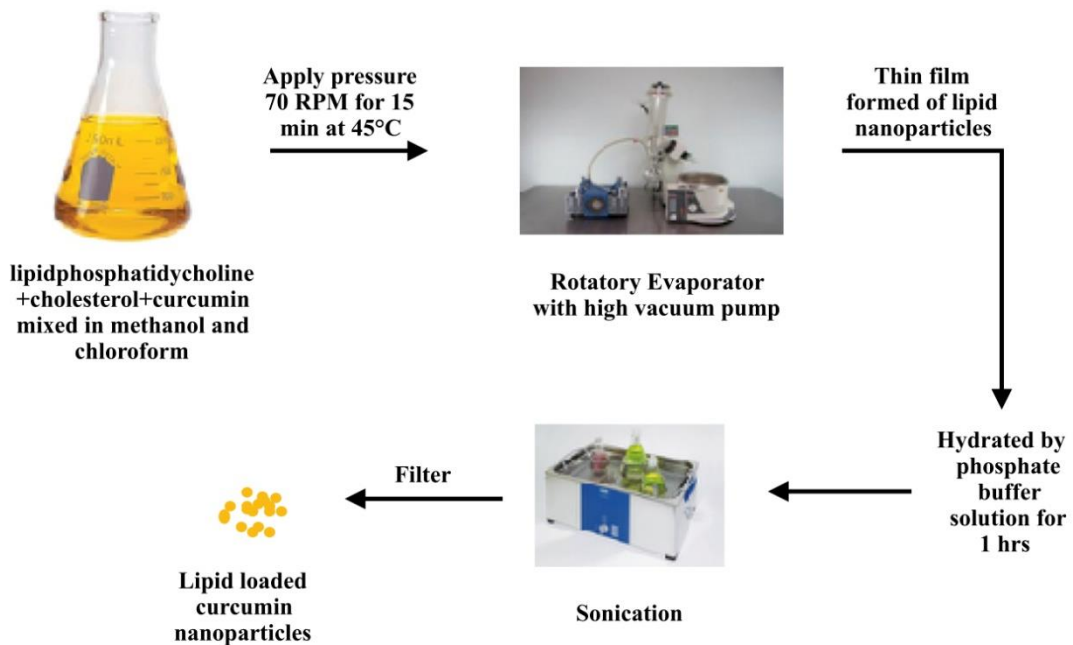


Figure 2: Schematic diagram of lipid loaded Curcumin nanoparticles by thin film hydration method

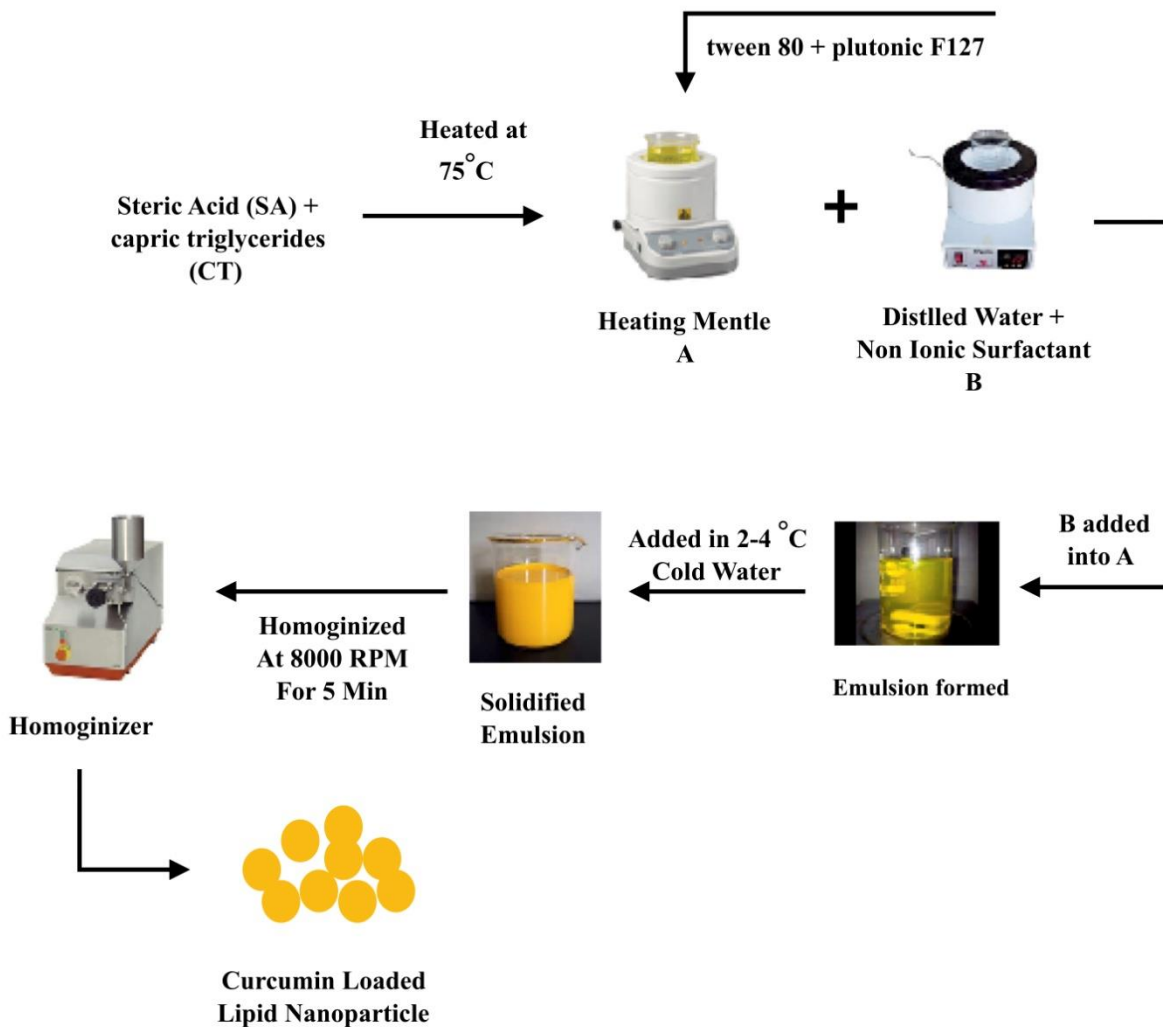


Figure 3: Schematic diagram of lipid loaded Curcumin nanoparticles by Micro emulsion method

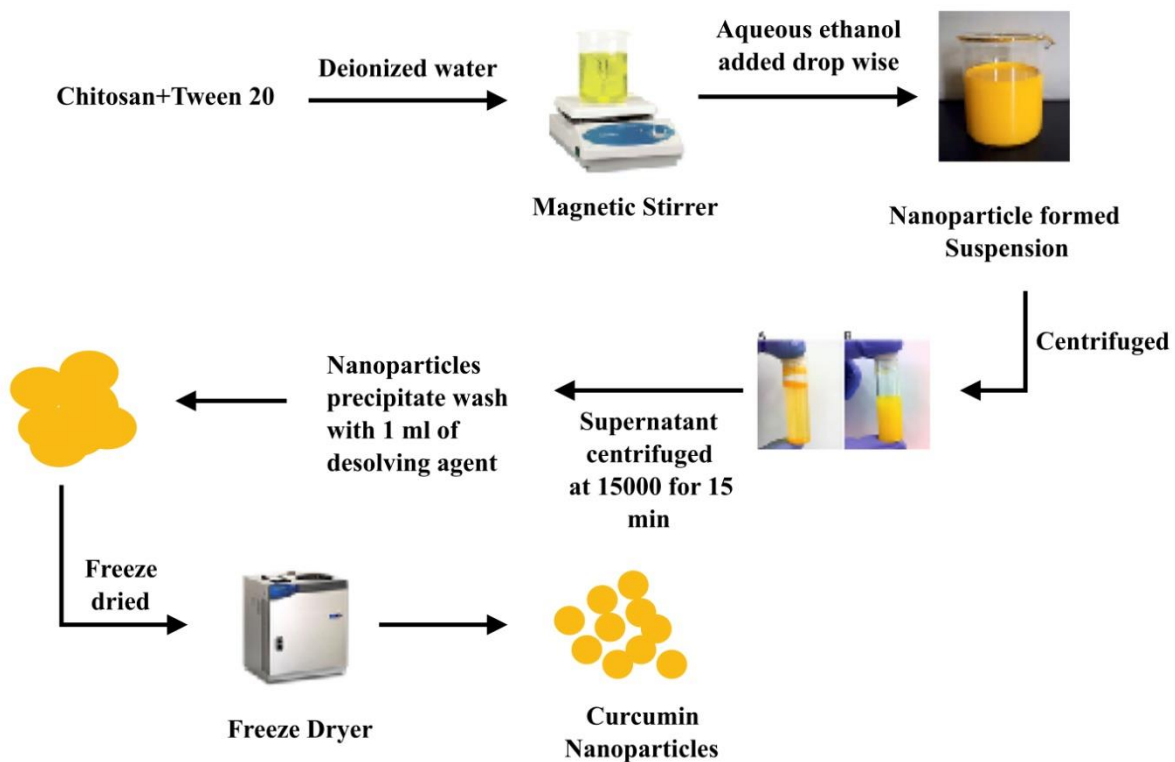


Figure 4: Schematic diagram of polymer loaded Curcumin nanoparticles by desolvation method

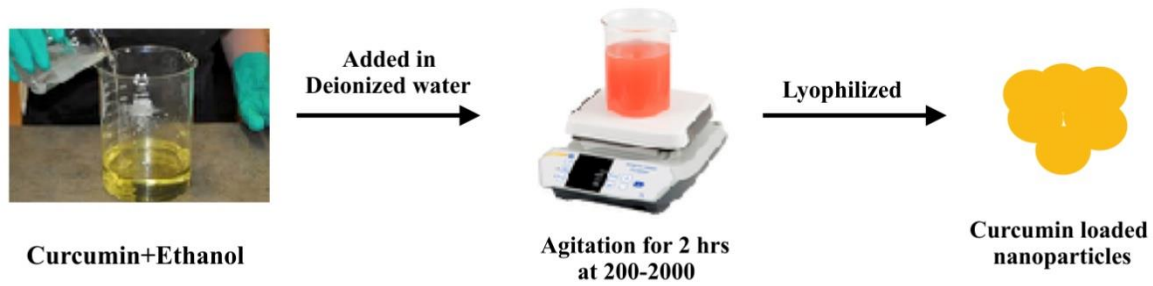


Figure 5: Schematic diagram of Curcumin loaded nanoparticles by Agitation method

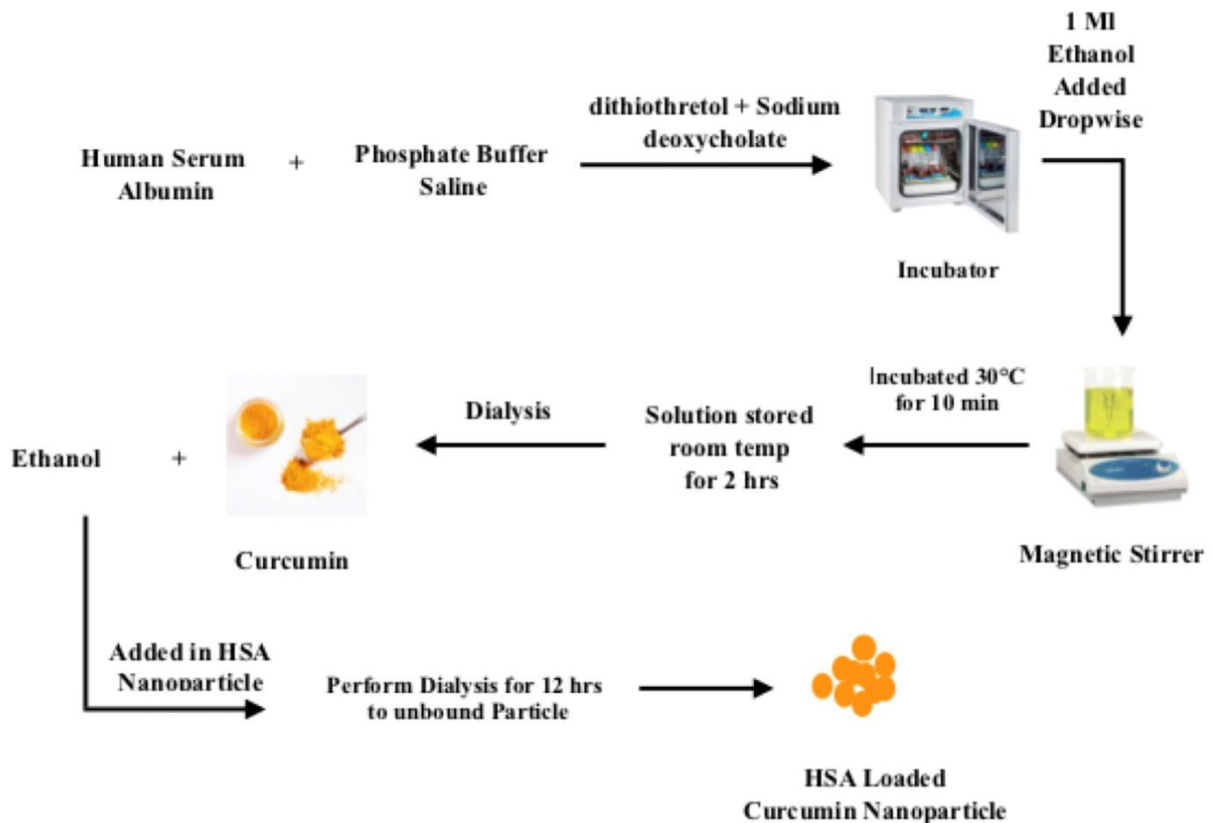


Figure 6: Schematic diagram of HSA loaded Curcumin nanoparticles by cross-linking method

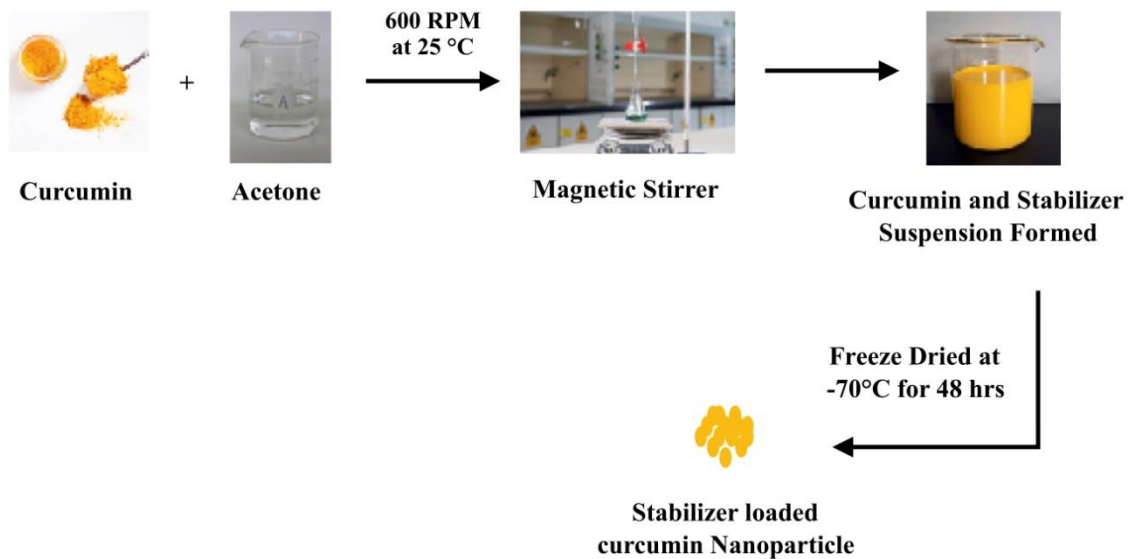


Figure 7: Schematic diagram of Stabilizer loaded Curcumin nanoparticles by anti solvent crystallisation method.

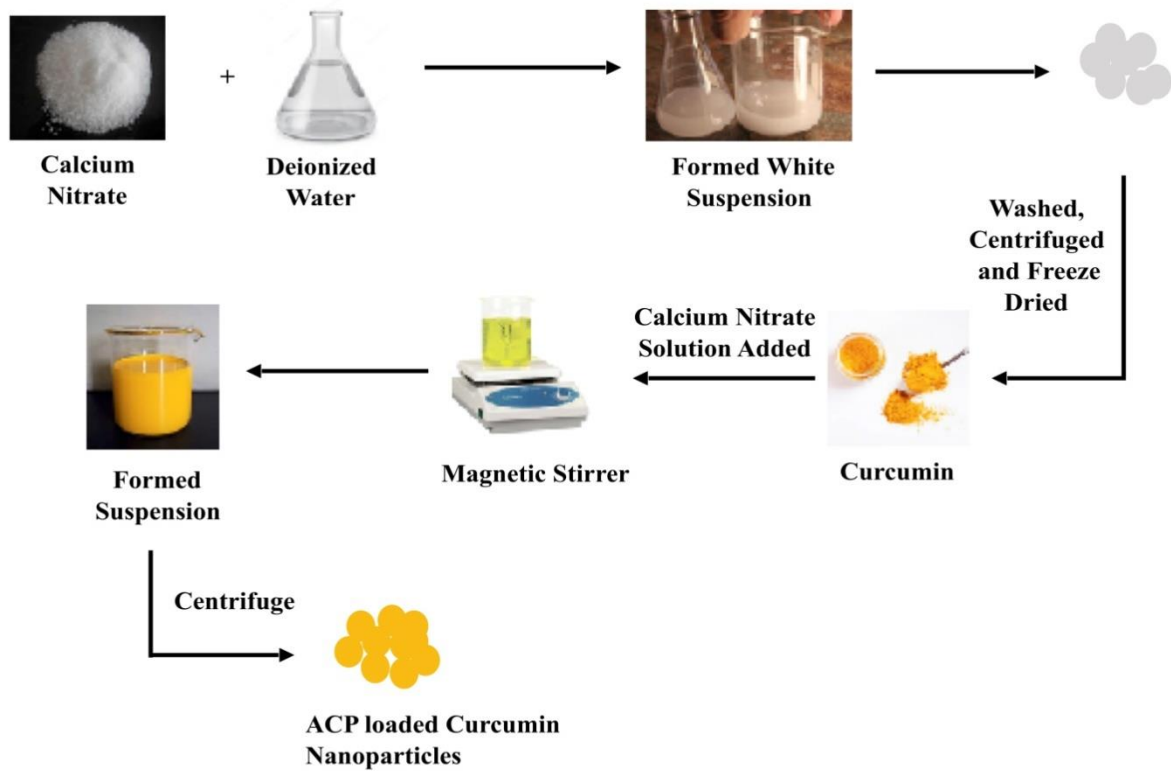


Figure 8: Schematic diagram of ACP loaded Curcumin nanoparticles by co-precipitation method