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FACTORS AFFECTING PREPARATION AND PROPERTIES OF NANOPARTICLES BY NANOPRECIPITATION METHOD

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Abstract:

Nanoprecipitation technique for preparation of nanoparticles has emerged as one of the most viable methods of all available methods, owing to its advantages such as simple, rapid, economical and surfactant free preparation method. Several kinds of polymers, lipids, proteins, and cyclodextrins can be used as matrix for encapsulation of drug. Moreover, it can be employed to prepare nanoparticles of drug product itself without use of any polymer. Nanoprecipitation is achieved by slow addition of an organic solution of the polymer with or without drug in an aqueous solution (non-solvent) with moderate stirring at moderate temperature. Nanoparticles are hardened due to evaporation of organic solvent which are then collected by filtration, centrifugation or freeze drying. This article summarizes several parameters that may influence preparation of nanoparticles include types and proportion of solvent and anti-solvent, types and proportion of polymer and drug, rate of addition of solvent, stirring speed and processing temperature.

Keywords: *Nanoprecipitation, Nanoparticles, Nanocapsules, anti-solvent, stabilizers, surfactants.*

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INTRODUCTION:

The nanoprecipitation was first developed by Fessi for the preparation of nanoparticles of hydrophobic drug [1]. Drug or polymer or drug and polymer both are dissolved in the common organic solvent which is miscible with water. This organic solution is then poured into the anti-solvent (water with or without surfactant) under magnetic stirring to get nanoprecipitation of drug and polymer. Nanoprecipitation is based on solvent diffusion and interfacial deposition wherein diffusion of organic solvent into anti-solvent causes rapid desolvation of the polymer leading to nuclei growth that follows crystal growth, interfacial deposition and nanoprecipitation [2-4]. There are several advantages of nanoprecipitation over other techniques of preparation of nanoparticle such as its speed, cost, simplicity, ease of scalability, avoidance of high energy inputs, toxic solvents and surfactants. Moreover, prepared particles are generally submicron with narrow size distribution and are generally reproducible [5-9]. The effects of the process parameters, such as amount of drug or polymer, drug polymer ratio, types of solvent and anti-solvent, ratio of solvent to anti-solvent, the stirring rate, stirring time, reaction temperature, have great influence over size of nanoprecipitation. There are several investigations reporting such factors that may influence nanoprecipitation, however, none of them covered all of the relevant factors [10-17]. In this review, several factors that influence the nanoprecipitation are summarized and discussed.

Effect of nature and amount of drug

Nanoprecipitation was originally developed for nano-encapsulation of hydrophobic drugs [1]. Most of the available literature has reported nanoprecipitation of hydrophobic drugs as original method suffers with the drawback of unsuitability for encapsulating hydrophilic drugs [8-10, 12-14]. However, researchers have investigated encapsulation of hydrophilic drugs and proteins by modified nano-precipitation method [17-23]. Several researchers have reported the effect of drug concentration over size of the nanoparticles. In general, smaller nanoparticles were achieved at lower drug concentration. For instance, Jhang and coworkers reported that cefuroxime axetil concentration in organic phase had significant effect on the size of nanoparticles as evident from decreased particle size from ~800 to ~300 nm as the concentration of cefuroxime axetil in the acetone phase decreases from 120 to 60 mg/mL [24]. It has been reported that high drug concentrations results in larger number of nuclei at solvent/anti-solvent interface which aggregate and form larger nanoparticles. Moreover increase in viscosity due to high drug concentration decreases its diffusion form solvent to anti-solvent thus decreasing the yield of nanoparticles [25, 26].

Effect of nature and amount of polymer

Polymer type and its amount plays very crucial role on nanoparticle formation and their characteristics. Poly Lactic acid-Glycolic acid (PLGA) is found to produce smaller nanoparticles when compared with those produced by poly lactic acid (PLA) which is more hydrophobic than PLGA [18]. It has been reported that low amount of polymers generally produces smaller nanoparticles whereas high polymer concentrations results in larger nanoparticles which could be due to increased viscosity that hampered diffusion of polymer form solvent to anti-solvent [27]. It is noteworthy that high amount of polymer produces larger nanoparticles but their drug encapsulation efficiencies are generally better than the smaller nanoparticles. [11]. Molar mass of polymers are also known to affect the percent yield of nanoparticles. It has also been reported that very high molar mass or very high concentration of polymer either prevented nanoprecipitation or reduced percent yield [11, 18].

Effect of solvent

The effect of solvent on the nanoprecipitation and size of nanoparticles is not well established. Solvents are generally chosen based on solubility of drugs and polymers in question. For poorly soluble drugs, organic solvents like acetone, acetonitrile, chloroform, dichloromethane, dimethyl formamide, dimethyl sulfoxide, ethyl acetate, ethyl ether, isopropyl ether, ethanol, methanol, methylene chloride are used. It has been reported that organic solvents used for nanoprecipitation should be miscible with water (anti-solvent), as it facilitate diffusion thus affect the size of nanoparticles [1, 11]. Diffusion of the solvent in anti-solvent with or without polymer was investigated in detail and was found to control the size and size distribution of nanoparticle [28]. Solvents with high diffusion such as acetone and acetonitrile favored the formation of smaller nanoparticles with narrower distribution, whereas solvents with low diffusion such as tetra hydrofuron results in large and broad distributions of size [28]. Low boiling point of solvent is another desirable property to facilitate evaporation and formation of nanoparticles. Therefore solvent selection is generally based on its Solublization capacity for the polymer in question, its polarity (water miscibility) and its boiling point. It has been reported that affinity of the solvent for the non-solvent (dielectric constant, Hildebrand solubility

parameter) and solvent-polymer interactions play very important role in nanoprecipitation [18].

Effect of anti-solvent

Water is the most common anti-solvent used in nanoprecipitation techniques. It is required that the drug and polymer must be insoluble in the anti-solvent to prevent ant diffusion of drug during nanoparticle preparation. Several researchers have employed aqueous phase / buffer with different pH, with observation that pH affected entrapment efficiency of nanoparticles. This could be due to the fact that ionizable drugs have different solubility at different pH conditions and hence the pH at which it is ionized maximum will cause minimum Solublization of drug leading to improved entrapment efficiency of nanoparticles [3, 29]. Ratio of solvent to anti-solvent has also been reported by several researchers and it was observed that increase in proportion of anti-solvent with respect to solvent (1:2-1:20) generally produces smaller nanoparticles [3, 24]. Stabilizing agent such as polyvinyl alcohol, or other hydrophyllic surfactants such as Tweens, poloxamers and pluronics are added in the water to stabilize the nanoparticles. Concentration of stabilizers in anti-solvent is known to influence size of the nanoparticles formed along with their entrapment efficiency and stability [30-34]. Generally a concentration range between 0.1-1% 7% w/v of stabilizer is found sufficient to stabilize the nanoparticles, however, sometimes concentrations as high as 7% w/v is required depending upon type of stabilizer and dispersion medium [35]. Moreover, nature or physical state of the nanoparticles is known to be significantly influenced by the nature of anti-solvent. For instance, cefuroxime axetil in acetone lead to development of amorphous nanoparticles when organic solvent like isopropyl ether used as anti-solvent however end product was gel or crystalline when water was used as anti-solvent [24].

Effect of addition of organic phase

Effect of addition of organic phase to the aqueous phase has been reported in very few number of studies. Most of the available data reported dropwise addition of organic phase to the aqueous phase. However some researches have investigated the effect of addition of organic phase by using slow or fast injection rate (2-2000 μL min−1), by using different needle gauze sizes (14,16, 20, 23, 27). It was observed that both organic phase injection rate and gauge size of the needles did not affected the size of nanoparticles significantly as these parameters have no effect over diffusion rather they only affect the rate of mass transport [28].

Effect of stirring

In the original nanoprecipitation method, researchers used moderate stirring to emphasize on low external energy requirement which is generally very high for emulsion-evaporation methods. However, it has been reported that size of nanoparticles developed in nanoprecipitation techniques is significantly influenced by rate of stirring. Generally speaking higher stirring rates result in smaller nanoparticles [23, 36]. For instance a reduction in particle size from 800 to 300 nm was observed with increase in stirring rate from 300 to 1200 rpm [24]. The decrease in particle size may be due to enhanced mass transfer and rate of diffusion leading to rapid nucleation and precipitation. However, in one of the report, effect of stirring rate (1200, 1100, 700, 350, 125, and 0 rpm) over size of nanoparticles was found to be insignificant [28].

Effect of temperature

Nanoprecipitation process are generally reported to be carried out at ambient or room temperature, thus there are limited reports only that investigate the effect of temperature over nanoprecipitation. For instance, Zhang and coworkers investigated effect of temperature (10, 20, 30 and 40 °C) on particle size produced by nanoprecipitation [24]. They observed reduction in particle size from about 800 to 300 nm with reduction in temperature from 40 to 10 °C. They suggested that low solubility thus high supersaturation and faster nucleating rate at low temperature could be reason of smaller particles. However, in another investigation, opposite trend was observed [28]. They reported an approximate 10 nm decrease of particle size with every 10 degree increase of temperature with overall decrease of about 100 nm when the temperature was increased from 0 to 80 °C. They suggested that increased solubility of polymer at higher temperatures inhibits precipitation [28].

CONCLUSION:

Nanoprecipitation is a rapid, simple and economical method for preparation nano-capsules which produces monodisperse nanoparticles of sizes generally smaller than those produced by using other available methods such as emulsification-solvent evaporation (single or double emulsion produced by high shear or ultra-sonication, solvent evaporated by stirring at room temperature or under reduced pressure), supercritical fluid technology, salting-out and dialysis etc. Moreover, nanoprecipitation is scalable and parameters involved in nanoprecipitation can easily be tuned to control the size of nanoparticles produced with reproducible results. Several researchers have investigated influencing

parameters such as drug load, amount of polymer, drug: polymer ratio, organic solvents, mode and rate of addition of solvent into anti-solvent, nature of anti-solvent, stabilizers in anti-solvent, pH of anti-solvent, ratio of solvent : anti-solvent, stirring rate and temperature etc. Of all investigated parameters, nature and amount of polymer, solvent and anti-solvent were found to affect the size of nanoparticles significantly.

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