Synthesis of *N*-vinylpyrrolidone/Acrylic acid nanoparticles for drug delivery: Method optimization

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Abstract. There are various approaches to deliver therapeutic agents to the preferred target. Polymeric nanoparticles were found to have pleasing suitability as a drug carrier. The goal of this research was to optimize the synthesis method to obtain the desirable %yield and particle properties of the new biocompatible polymer-based nanoparticles. The non-toxic polymer, *N*-vinyl pyrrolidone (NVP) and a widely used hydrophilic biocompatible acrylic acid (AA) monomer were used to form the drug nanocarriers. The synthesis method was optimized by changing the types of initiator (KPS or V50) and the monomers molar ratio (NVP:AA). It was found that by varying both the monomer molar ratio and the type of reaction initiator, did not have significant effect on the physicochemical characteristics of the nanocarriers. The FT-IR spectra of all products exhibited the peaks of carboxylic acid, carbonyl, and tertiary amine functional group vibration. The particle size of the nanocarriers was in the range of 173.6 ± 18.4 to 201.4 ± 17.1 nm with negative surface charge. However, the yield obtained increased as the initiator was altered from KPS to V50, and when the acrylic acid molar ratio was increased from 1:1 to 1:3. In conclusion, changing the initiator and monomer molar ratio may affect the physicochemical properties of the nanocarriers and the %yield of the nanocarrier product. Further investigations are essential to obtain the favorable drug nanocarriers for drug delivery.

1 Introduction

Ideal drug carriers offer several advantages such as good stability, high drug loading capacity, be able to incorporate various drugs, varies in administration route, and be capable of control drug release.[1] Recently, polymer-based nanoparticles (PNPs) are attracting lots of interest from researchers due to their marvelous characteristics.[2] These particles demonstrate very small particle size ranging between 10 – 100 nm, and they can be generated from both natural and synthetic polymers. Nevertheless, the polymers used to prepare a nanocarrier are required to be nontoxic, biocompatible, and biodegradable.[3] In the synthesis of a polymer, chain-growth polymerization reactions can be used to polymerize one or more type of monomer with the aid of an initiator.[4]

The addition polymerization technique requires decomposition of an initiator to generate active species of free radicals, cations, or anions to polymerize the unsaturated monomers.[5] Free radical initiators (such as benzoyl peroxide, potassium persulfate (KPS), and 2,2'-azobis(isobutyronitrile) (AIBN)) propagate the polymer chain with a carbon radical. Cationic initiator such as Boron trifluoride (BF_3) and 2,2'-azobis(2-methylpropionamidine) dihydrochloride (V50) generates carbocation, while alkyl lithium anionic initiator grew up the chain with carbanion. To reach the process of initiation, the initiators must be solubilized and decomposed at a certain temperature while monomers remain stable. The selection of suitable initiator brings a worthwhile synthesis.[6-9]

The molar ratio of monomers plays an important role in polymer synthesis. Different monomer ratios may lead to the difference in the polymers' properties. Also, non-reacted or exceeded monomers can be classified as synthesis impurities and needed to be removed after the reaction terminated.[10] To gain a consistence PNPs in each synthesis, the molar ratio is needed to be justified.

NVP is a safe hydrophillic monomer and is widely used as PNPs stabilizers. When formed into a polymer, it helps to prevent aggregation by having steric hindrance structure and act as polymers or NPs dispersant; moreover, it is remarkably stable and inert.[11]

AA can be classified as a hydrophilic and biocompatible monomer. With its carboxylic acid functional group, polymers containing acrylic acid can be extensively modified in adjustment of their properties to gain PNPs of plentiful advantages. [12, 13]

Therefore, this work aims to optimize the synthesis polymerization reaction between NVP and AA through

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the variation of monomer molar ratios and initiator concentrations. While considering the NVP/AA nanoparticle as the product, factors that are needed to be evaluated include %yielding, particle size, charge, and structural characteristics.

2 Materials and Methods

2.1 Materials

Acrylic acid (AA), *N*-vinylpyrrolidone (NVP), Potassium persulfate (KPS), 2,2'-Azobis(2-methylpropionamidine) dihydrochloride (V50), and *N,N'*-methylenebisacrylamide (MBA) were purchased from Sigma-Chemical Co. (St. Louis, MO, USA). All chemicals were of analytical reagent grade.

2.2 Preparation of NVP/AA nanoparticles using polymerization reaction

2.2.1 Effect of initiator

Nanoparticles were synthesized using surfactant-free free radical polymerization reaction. In brief, 50 mL of deionized water in a clean round-bottom flask was heated to 65-70 ºC before the initiator (0.1 %w/w V50 or 0.2 %w/w KPS) was added. The reaction mixture was purged with nitrogen gas for 20 min to create an inert environment. In a 5 mL glass vial, NVP and AA were prepared at the weight ratio of 1:1. After that 10 wt% MBA, which was used as a crosslinking agent, was added to the glass vial and mixed. The mixture was then dispersed in chloroform (5 mL) before adding dropwise to the flask under vigorous stirring. The reaction environment was kept inert throughout 18 h of the reaction period. After that, the synthesized product was purified by dialysis against deionized water for 3 days before being freeze dried and lyophilized.

2.2.2 Effect of the NVP/AA molar ratio

The synthesis process mentioned earlier was repeated. V50 was selected to be used as the initiator, while the molar ratio of NVP/AA was varied from 1:1 to 1:3.

2.3 Nanoparticle characterizations

2.3.1 Fourier transform infrared spectroscopy (FT-IR)

The chemical structure and functional groups of the synthesized PNPs was elucidated using FT-IR (Spectrum 100, Perkin Elmer) The synthesized polymers were ground and pressed into KBr disks prior to the investigation.

2.3.2 Particle size and surface charge

The particle size and surface charge of the nanoparticles were evaluated using a Zetasizer Nano ZS (Malvern Instruments, Malvern, UK) at 25ºC. Samples were dispersed, diluted to 1:100 and place into a zeta cell (1 cm^3) prior to the measurement. The measurement was performed in triplicate.

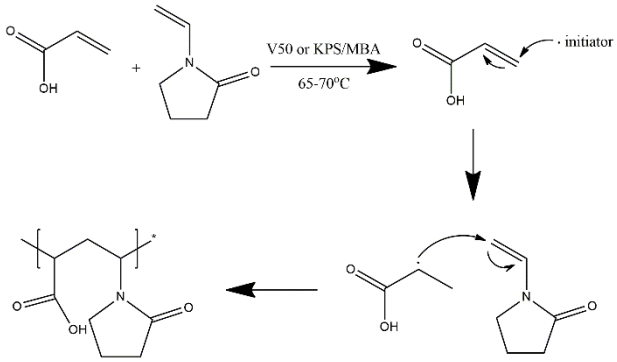

Fig. 1. Synthesis reaction of NVP/AA nanoparticle

3 Results and Discussion

3.1 NVP/AA nanoparticles: influence of initiator

The synthesis reaction was performed as shown in Fig. 1. Once the monomers were initiated with free radical, polymerization occurred while electrons transfer to one another and cross-linked to form the particle. The reaction was left for 18 h to complete the synthesis process prior to purification and drying. After the synthesis, the nanoparticles were characterized using FT-IR. The spectrum of all formulations were similar. The peaks at 3419, 1647-1725, 1174, and 1114 cm^{-1} were assigned to O–H, C=O, C–O, and C–N stretching vibration, respectively, which are the characteristics peaks of carboxylic acid (from AA) and tertiary amine (from NVP) functional groups. The appearance of these peaks are greatly suggestive of the successful polymerization of NVP and AA.

The %yield and nanoparticle characteristics of the nanoparticles obtained from the synthesis reaction using different initiators and monomer ratios are listed in Table 1. As it can be seen from the results, the %yield of the synthesized product increased as the initiator was changed to V50. However, this did not affect the size and surface charge of the obtained nanoparticles. The increase in the %yield may be because the different decomposition rate (k_d) of the initiators. The k_d of KPS at 70 ºC is $2.83x10^{-5}$ sec^{-1}, while the rate of V50 is $1.21x10^{-4}$ sec^{-1}[14]. Therefore, it is obvious that at a higher rate of initiator decomposition, V50 may propagate the chain at a greater rate compared to KPS. Due to the increment of %yield and the smaller size of the particles, V50 was selected as the initiator for the molar ratio variation.

Table 1. Summary of method optimization results.

Initiator	Molar ratio	%yield	Size (nm)	Zeta Potential (mV)
KPS	1:1	12.3	201.4 ± 17.1	-42.7 ± 0.8
V50	1:1	24.0	173.6 ± 18.4	-40.0 ± 3.2
V50	1:3	42.3	178.9 ± 9.5	-22.3 ± 1.0

3.2 NVP/AA nanoparticles: influence of monomer molar ratio

To investigate the effect of monomer ratios on the %yield and the properties of the nanoparticles, V50 was selected as an initiator. The NVP:AA ratio was varied from 1:1 to 1:3. The FT-IR spectra of the nanoparticles prepared from different monomer ratios are presented in Fig. 2. The FT-IR spectra of the nanoparticles synthesized from different monomer ratios showed identical characteristic peaks of carboxylic acid and tertiary amine. As it can be observed from Table 1, at the monomer ratio of 1:3, the % yield was almost twice greater compared that obtained at the monomer ratio of 1:1 (42.29 vs 23.95%). In addition, changing the monomer molar ratio (NVP:AA) from 1:1 to 1:3 led to the more negative surface charge of the particles. This may be because the greater amount of acrylic acid was used to form the nanoparticles. However, this did not affect the particle size.

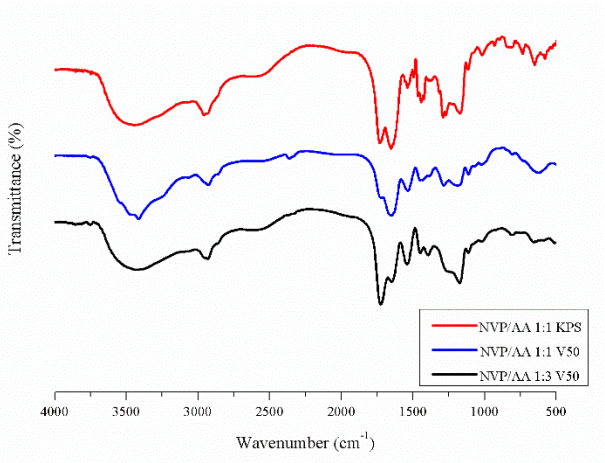

Fig 2. FT-IR spectra of the synthesized nanoparticles

4 Conclusions

There are various factors affecting polymer synthesis, including type of initiator and monomers molar ratio. This study demonstrated the influence of these elements on the final product obtained. It was found that while other reaction factors including monomer stoichiometry remains unchanged, percent yielding obtain form the reaction using KPS as reaction initiator was not comparable to V50. However, the PNPs obtained from the both reaction exhibited similar FT-IR peak characteristics, particle size and charge. Although the yield might differ, type of initiator did not affect the PNPs attributes. The molar ratio of the monomers also has an impact on the product yield. Stoichiometric equivalent ratio may not practically bring about the highest amount of product. Excess monomer input can cause greater product impurities, but also generates a more promising productive synthesis. Altering the monomer ratio could lead to the alteration in the product yield and particle attributes. Nevertheless, other synthesis reaction factors such as synthesis method, time, temperature, initiator concentration and cross-linker ratio may also affect the properties of the synthesis products.

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