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Investigation of the formation factors influencing the size of nanoparticles prepared by micro-emulsification method for drug delivery systems

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THE approach of using micro-emulsions chemical method has demonstrated impressive success for the formation of nanoparticles specialized for drug delivery. The purpose of this study was to investigate the influence of manipulating five distinct formation factors during the micro-emulsion preparation method on the size of nanoparticles produced. These factors constituted the stirring speed, blending time, the type of surfactant, homogenization and the Poly (ethylene-co-vinyl acetate) (PEVA) concentration. Information on the particles sizes and their distribution were obtained and analyzed using ZetaSizerNanoZS. The results revealed that small sizes and narrow/uniform particle size distributions were obtained at lower polymer (0.2 % w/v) concentrations, a reduced stirring speed (2000rpm) and with the presence of polysorbate 80 surfactant. In contrast, higher polymer (1 % w/v) concentrations and stirring speed (6000rpm), in the absence of surfactant and homogenization, yielded larger particles with a multi-modal size distribution profile (PDI:0.749). These results also clearly revealed that the particle size was significantly affected by the combination of parameters here explored, and that on-demand nanoparticles may be produced using optimized micro-emulsion parameters to meet several potential applications.

Keywords: Micro-emulsion, nanoparticles, particle size, particle size distribution, nano-zetasizer.

Introduction

Recent developments in nanotechnology bridged together in an interdisciplinary fashion the physical, chemical and biological sciences, engineering and martial science, where the technology that initially deals according to systematic functional in rang nanoscale. In particular, nanotechnology offered a wide range of applications in the field of drug delivery which advanced the research in medical sciences. In this context, researchers have designed various advanced and multifunctional nanocarrier systems that can provide targeted, sustained, and controlled delivery of drugs. These novel systems have led to the enhancement of drugs' systemic circulation, improvement of the pharmacokinetic profile of drugs, and reduction of adverse effect incidences of drugs. Some of the nanoparticulate drug delivery systems have demonstrated substantial benefits such as polymeric, lipids and metals nanoparticles (Mohsin Ali, et al, 2023& Naruthai Hongsa et al, 2022).

The national nanotechnology initiative defines nanoparticles as material particles having unique physical, chemical, mechanical, and optical properties that exist in the nanoscale, i.e., they have an approximate size of 1nm – 100nm (Kook Lee, et al, 2015). They have many applications in the medical industry particularly in the application of targeted drug delivery. Controlling the size of the nanoparticles helps in controlling the surface properties of the particle which in turn regulates the release of pharmacologically active compounds incorporated within the matrix. The stability of the drugs or proteins is also affected by the size of the nanoparticle. It is thus important to control the particle size of nanoparticles as well as the range or distribution. Creating nanoparticles with a smaller size range can be beneficial in delivering drugs to areas such as the brain in the

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case of tumor therapy (Geleperina, et al, 2010 & Saman Emami Gerami et al. 2021).

However, the small nanoparticle size often results in a strong tendency for the nanoparticles to aggregate together and clump. Larger nanoparticles are able to carry more drug particles within the matrix, but the size may impair penetration into targeted sites such as DNA. Thus, it is imperative that the size of nanoparticles can be synthesized and controlled to the range that is required for the specific drug delivery. This desired tunability and control over the nanoparticle size can be achieved during the preparation process. Certain parameters, both formation and process parameters may be manipulated in order to produce a nanoparticle product that has the desired particle size range. We will deal with process parameters such as polymer concentration, use of and type of surfactant, effect of homogenization, effect of different mixing speed and different mixing times.

Although there are a number of methods available to prepare nanoparticles, there are three main methods of preparation. The first is the dispersion of preformed polymers, which is a common method used to create biodegradable nanoparticles. The second is the polymerization of monomers where monomers are polymerized to form nanoparticles in aqueous solution. The third is the ionic gelation or coacervation of hydrophilic polymers which involves a mixture of two aqueous phases using biodegradable polymers such as chitosan, gelatin and sodium alginate (Mohanraj, Chen, 2006). Various chemical or liquid-based methods for nanoparticle preparations are widely utilized in literature, from which the micro-emulsion method stands as highly suitable for drug delivery and biomedical applications.

Therefore, in this study, we explore in detail the various parameters affecting the formation of nanoparticles prepared using the micro-emulsion method. The parameters include the polymer concentration, the type of surfactant used, the homogenization time, the mixing time and speed.

Method and Materials

Materials

Poly (ethylene-co-vinylacetate) (PEVA) with an average molar weight (MW) of MW=60000 g/mol was purchased from Sigma Aldrich (St. Louise. MO.USA). Tween 80 with a MW=1310g/mol and Tween 20 MW=1277.54g/mol, purchased from Associated Chemical Enterprises (Southdale, Johannesburg). Polyethylene Glycol (PEG) 6000 with a MW= 6000-7500 g/mol purchased from SAAR CHEM (Krugersdorp, RSA). Polysorbate 80 with a MW=1310 g/mol purchased from (St. Louise. MO.USA). Toluene with a MW=92.14 g/mol (Gauteng, South Africa). The water used was deionized water.

Method

There are a large number of methods available for the preparation of nanoparticles. Therefore, selecting the appropriate method for nanoparticles preparation will be dependent on several factors including, but not limited, the targeted potential applications, the polymer system employed and the nanoparticle size requirement (Rao & Geckeler, 2011). Some methods do use no additives such as surfactants or organic solvent and are, therefore, ideally suited for biomedical or environmental applications (Rao &Geckeler, 2011). Such methods are rapid expansion of a supercritical liquid (RESS) or rapid expansion of a supercritical solution into a liquid solvent (RESOLV). Other available methods for nanoparticle preparation include solvent evaporation, salting out, dialysis and various emulsion methods which include emulsion polymerization, micro and mini emulsion and surfactant free emulsion polymerization.

The method chosen in this work was the micro-emulsion method, as it represents one of the most easily reproducible methods available with minimal limitations and for being economically inexpensive (Mohamed M. Ashour et al 2021). Nanoparticles synthesized utilizing this method exhibit smaller particles compared to those prepared by the other emulsion preparation methods (Rao &Geckeler, 2011). A micro-emulsion method can be simply considered as being similar to an emulsion method. However, in typical emulsion methods there are three reaction phases that are seen, whereas in a micro-emulsion method two reaction phases are only seen (Rao &Geckeler, 2011). In contrast to traditional emulsion methods, particles formed following the micro-emulsion process are usually passivated with surfactant because of the high amount of surfactant used. Employing large amounts of surfactant, it is also possible to produce the desired nanoparticle size range (Gelperina, et al, 2010). A water-soluble initiator is added to an aqueous phase, whereby the aqueous phase will be a thermodynamically stable micro-emulsion containing swollen micelles. This method is preferable because it requires less shear force than

the mini-emulsion method and the experimentation can be reproducible at any laboratory.

Synthesis of nanoparticles

Nanoparticle dispersions were formed by bringing two phases into contact using micro-emulsion method. Briefly, an aqueous phase of (1% w/v) PEG was prepared in deionized water with the surfactant which made it completely clear. The oil phase consisted of different concentrations of Polyethylene co-vinyl acetate (PEVA) dissolved in Toluene (0.2, 0.4, 0.6, 0.8, 1.0% w/v). The moment that the two phases are mixed, PEVA is totally miscible in the PEG solution in the form of nano-emulsion droplets. The combined ratio of PEG, PEVA and surfactant was 10:1:0.5, respectively. Furthermore, the selected preparation parameters were controlled for the prepared emulsions and the particle size was thoroughly determined and analyzed by the nano-zetasizer.

Characterization

A zeta sizer was used to determine the particle sizes, their range and distribution as well as the dispersion of the particles and intensity. The zeta potential has been shown to be extremely relevant to assessing drug solubility enhancement (Mabrouk et al, 2015). All samples were filtered with a 0.22 micro filter and placed undiluted into the cuvettes to be measured. This ensured that larger particles were trapped in the filter, leaving smaller particles to be measured. The main characteristics that were determined were particle size, particle distribution and intensity of peaks. Then, comparing the evolution of these characteristic quantities with the preparation parameters, namely the concentration, the surfactant type, the homogenization, the mixing time and mixing speed is explored next.

Results and Discussion

Effect of Polymer Concentration

This parameter dealt with the change in the concentration of utilized polymer (i.e., PEVA) and its effect on the particle size and distribution. Five different concentrations (0.2%, 0.4%, 0.6%, 0.8% and 1%) of PEVA were tested. The samples were then analyzed with Zeta sizer to determine the particle size, particle distribution and intensity of the graphs, as shown in Fig 3.1. The samples prepared with 0.2% and 0.4% PEVA concentrations showed promising results with 100% of the particles distributed in a single well-defined peak. The particle sizes were found to be ultrasmall, ranging from 2.696nm to 7.531nm for 0.4% concentration and 2.696nm to 6.503nm for 0.2% concentration, as listed in Table 3.1. The three other concentrations exhibited distribution of particles into two peaks. At 1% concentration of polymer, it was found that particle distribution was split into two narrow peaks (50-50%) with the size range of 2.696nm - 4.186nm and 28.21nm – 37.84nm. At 0.6% polymer concentration, around 40% of nanoparticles were distributed in the size range 2.696nm – 21.04nm and 60% of particles were distributed in the 37.84nm – 220.2nm size range, while for the 0.8% concentration 40% of particle distribution was in the ranges of 3.122nm – 7.531nm and 60% particles were distributed in the size range of 18.17nm – 190.1nm. We can conclude that lower concentrations yield smaller nanoparticles with a well-defined single peak and relatively narrow size distribution. Therefore, the polymer concentration was fixed at 0.2% and the other parameters were varied in the proceeding sections.

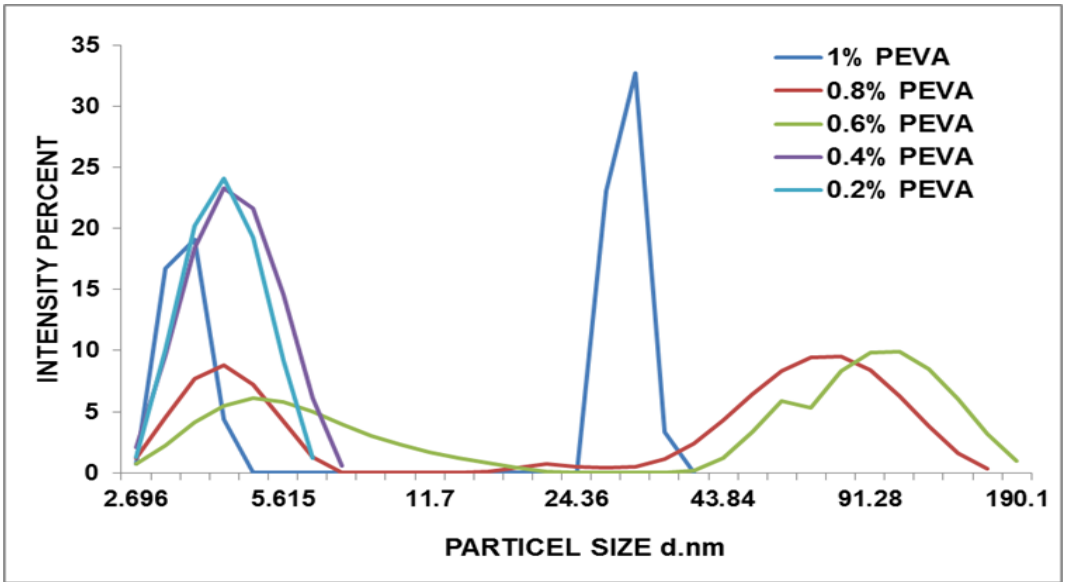

Fig 3.1. Particle size at different polymer concentrations.

TABLE3.1. Particle size range at different polymer concentrations extracted from Fig. 3.1.

PEVA	No. of peaks	Rang 1St peak (nm)	Center 1st peak (nm)	Rang 2nd peak (nm)	Center 2nd peak (nm)
0.2 %	1	2.696- 6.503	4.017	--	--
0.4 %	1	2.696- 7.531	4.687	--	--
0.6 %	2	2.696- 18.327	5.534	36.243- 215.198	145.646
0.8 %	2	2.696- 7.553	4.290	31.045-171.20	77.895
1 %	2	2.696- 4.186	3.509	25.043-36.233	36.674

Effect of Surfactant Type

It has been shown that nanoparticles synthesized using surfactants have better penetration into the blood brain barrier; particularly those produced using Polysobate 80 (Gelperina et al, 2010). Three types of surfactants were used here, those being Polysobate 80, Tween 20 and Tween 80 as well as particles without surfactant which serve as a reference for comparison. Since it was shown in the previous section that lower concentrations of polymer yielded smaller particles, we employed the 0.2% concentration throughout the surfactant effect explored here and other preparation parameters that followed. Particles produced in the absence of surfactant yielded a very broad size distribution with the biggest particles produced in the ranges of 3.615nm – 531.2nm without surfactant compared to 2.696nm – 6.503nm narrow range with the use of surfactant. Of the three surfactants used, Polysobate 80 had the most uniform and narrow distribution with 100% particles in the size ranges of 2.696nm – 6.503nm while Tween 20 and Tween 80 produced a broader distribution of particles with larger particles in the ranges 5.615 nm – 712.4 nm and 5.615 nm – 43.84 nm, respectively. We therefore concluded that using a surfactant facilitates the production of smaller particles with a well-defined and narrow particle size distribution with higher intensity, as compared to surfactant-free particles, with Polysobate 80 surfactant producing the best results.

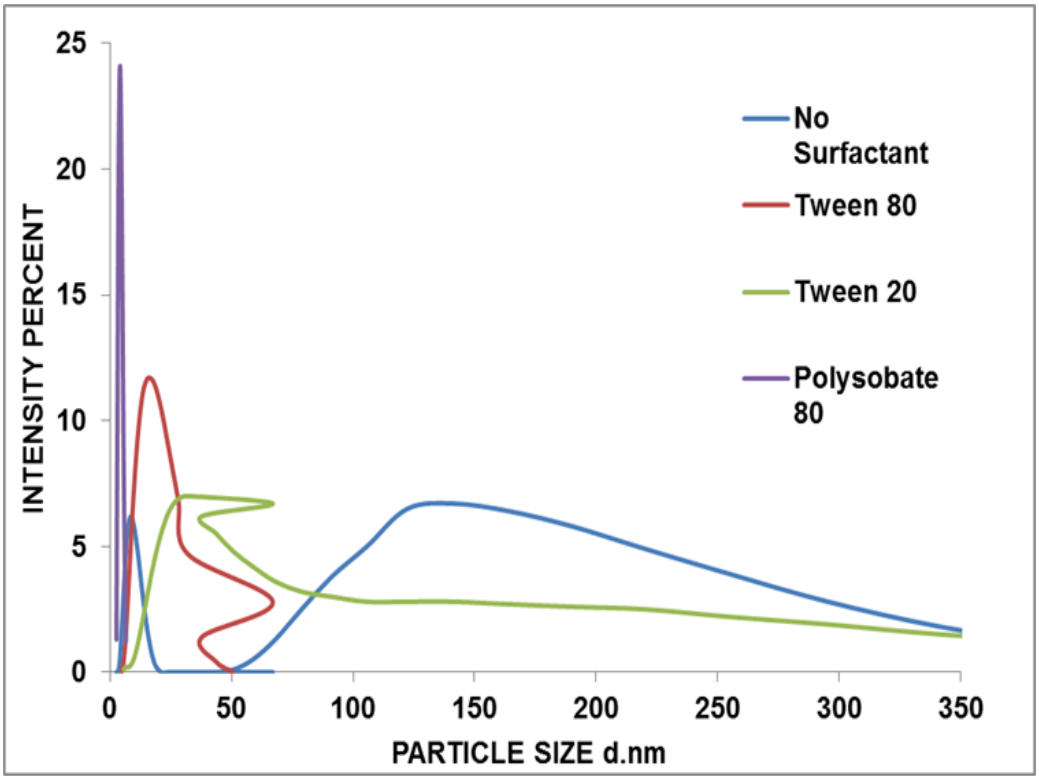

Fig. 3.2. Particle size distribution using different surfactants at 0.2% polymer concentration compared to surfactant-free particles.

TABLE3.2. Particle sizes at different polymer concentrations and surfactant type.

Concentration	No surfactant	Tween 80	Tween 20	Polysorbate 80
0.2%	50.49nm	15.49nm	17.59nm	13.24nm
0.4%	53.12nm	18.48nm	18.12nm	15.97nm
0.6%	115.6nm	88.46nm	19.20nm	17.42nm
0.8%	117.6nm	94.02nm	21.91nm	20.08nm
1.0%	124.7nm	117.7nm	152.8nm	54.49nm

Effect of Homogenization

This parameter dealt with the homogenization of samples compared to unhomogenized samples. It is thought that by increasing the time of homogenizing the sample, smaller particles will be produced (Ali et al, 2014). To explore the homogenization effect, all three surfactants were used as well as the low polymer concentration of 0.2%. The samples were homogenized for 10 seconds and then analyzed using the zeta-sizer in terms of particle size and distribution. It is noted that Polysobate 80 produced the smallest particles in the range of 10.10nm – 342nm with particle distribution characterized by a single peak. Likewise, the particle distribution also exhibited a single peak at 100% for Tween 80 and Tween 20 with particle size in the ranges 10.10nm – 531.2nm and 58.77nm – 1718nm, respectively. For the surfactant-free sample, however, the analysis yielded two peaks with particles distributed 40% in the size range 37.84nm – 295.30nm and 60% distribution in the 458.87nm – 1718nm.

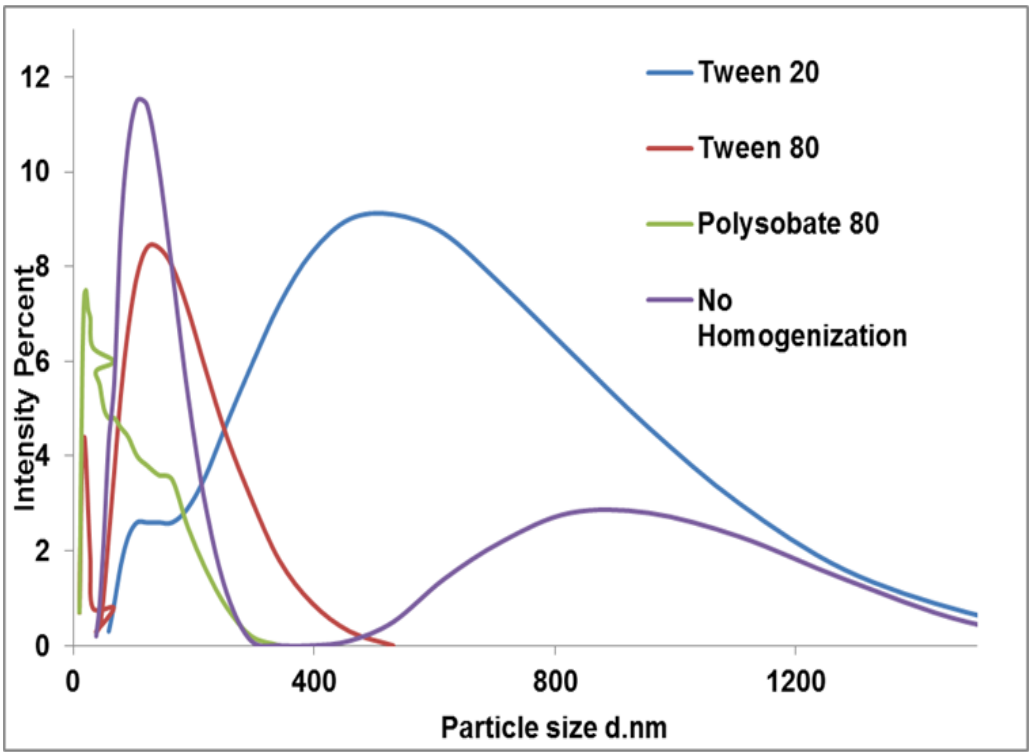

Fig. 3.3. Particle size distribution after homogenization for different surfactant at 0.2% concentration and for surfactant-free samples.

TABLE 3.3. Particle size after being homogenized with and without surfactants of different types and concentrations.

Concentration	No surfactant	Tween 80	Tween 20	Polysorbate 80
0.2%	50.65nm	59.10nm	321.5nm	34.31nm
0.4%	141.9nm	24.85nm	59.48nm	28.73nm
0.6%	150.5nm	26.74nm	62.50nm	30.42nm
0.8%	398.6nm	108.8nm	166.5nm	27.42nm
1.0%	1046nm	52.49nm	181.7nm	24.72nm

*Effect of Mixing Time*_

In this section, the polymer concentration was kept fixed at 0.2% and all other three preparation parameters were varied to test the effect of different mixing time. All combinations of parameters produced 100% particles distributed in into single peak but having different intensity. At the lower mixing time of 5 minutes, the smallest particle sizes were noted, while larger particles were produced for a prolonged mixing time up to 25 minutes. The particle size range when using Tween 20 surfactant is 10.1nm -712.4nm at 5 minutes mixing time, whereas for higher mixing times such as at 10 minutes the particle sizes are in the range 10-13.54 nm, 15-11.7nm - 1990.06nm, at 20 minutes 11.7nm - 712.40nm and at 78.82nm - 171.8nm for 25 minutes where 70% of the particles distributed in the widest intensity. From Fig. 3.4 it is seen clearly that at the shortest mixing time, i.e., 5 minutes, the particles maintained a uniform size distribution with the smallest nanoparticles produced. The single peak obtained is of high intensity and very narrow width where 100% of the products are small nanoparticles. When the mixing time was increased, the peak intensity decreased progressively and broad peaks with wide size distribution developed. The use of 20% concentration of Tween 80 surfactant produced particle sizes between 10.1nm - 13.84nm at 5 minutes, 6.503nm - 68.2nm at 10 minutes, 6.53nm - 78.82nm at 15 minutes, 6.503nm - 78.82nm at 20 minutes and 47.84nm - 342nm for the longest mixing time, i.e., at 25 minutes. Likewise, for Polysobate 80 surfactant at 5 minutes, a narrow and high intensity peak with a 100% uniform particle distribution of small particles is produced. Increasing mixing time led to profiles that had two peaks with low intensity and broader particle distribution. The particle size distribution is not uniform with 20% of the particles being small and 80% of the particle are larger. In this case, the particle size ranges at 5 minutes are between 13.54nm-18.17nm, at 10 minutes particle size is at 6.503nm –396.1nm, at 15 minutes particle size is at 8.721nm – 105.7nm, at 20 minutes particle size is at 8.721nm - 396.1nm and at 25 minutes particle size is at 11.7nm - 458.7nm. Thus, we state that the particles size distribution is irregular and non-uniform with increased particle size when performing the mixing at longer times. Lower mixing time will, therefore, produce the smallest particles with uniform distribution. The analysis is given in Tables 3.4.1, 3.4.2, and 3.4.3 for the three surfactants used.

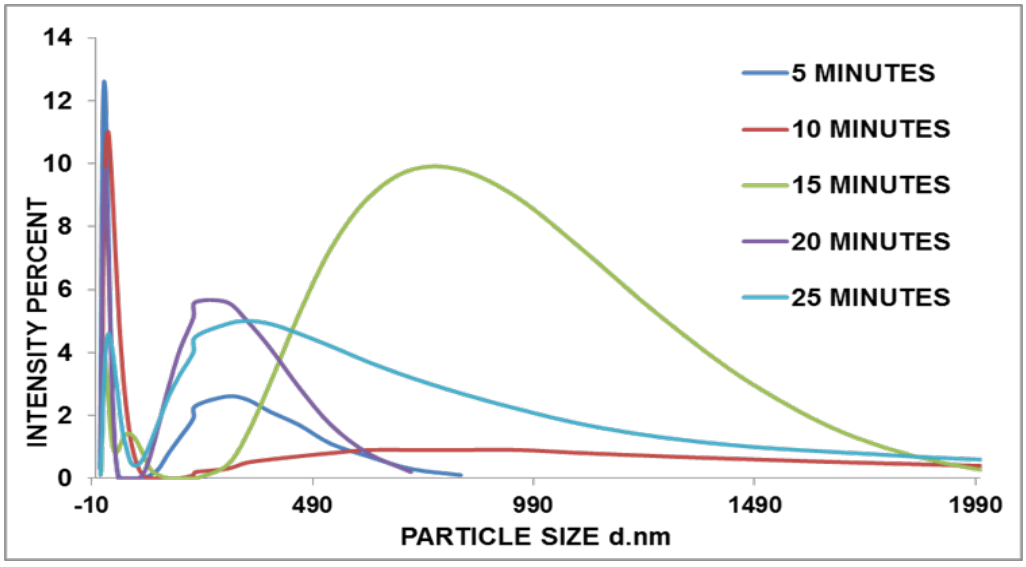

Fig. 3.4. Particle size distribution after different mixing times using Tween 20 at 0.2% polymer concentration.

TABLE 3.4.1. Particle size with changing stirring time with Polysorbate 80.

Time	Particle size at 0.2% concentration	Particle size at 0.4% concentration	Particle size at 0.6% concentration	Particle size at 0.8% concentration	Particle size at 1% concentration
5minutes	19.63nm	420.0nm	29.30nm	34.30nm	43.40nm
10minutes	21.77nm	328.3nm	42.01nm	37.19nm	164.3nm
15minutes	30.55nm	68.79nm	49.03nm	60.41nm	33.91nm
20minutes	76.28nm	35.33nm	54.3nm	59.76nm	51.87nm
25minutes	455.6nm	18.44nm	265.8nm	22.50nm	88.32nm

TABLE 3.4.2. Particle size changing with stirring/mixing time using Tween 20.

Time	Particle size at 0.2% concentration	Particle size at 0.4% concentration	Particle size at 0.6% concentration	Particle size at 0.8% concentration	Particle size at 1% concentration
5minutes	22.94nm	25.24nm	19.57nm	17.05nm	27.31nm
10minutes	29.63nm	25.70nm	27.00nm	29.55nm	28.59nm
15minutes	33.76nm	88.99nm	30.1nm	31.41nm	31.00nm
20minutes	69.00nm	29.96nm	35.4nm	33.21nm	36.01nm
25minutes	110.7nm	1472nm	1301nm	1501nm	117.00nm

TABLE 3.4.3. Particle size changing with mixing time using Tween 80.

Time	Particle size at 0.2% concentration	Particle size at 0.4% concentration	Particle size at 0.6% concentration	Particle size at 0.8% concentration	Particle size at 1% concentration
5minutes	6897.00nm	449.0nm	415nm	150.3nm	13.46nm
10minutes	26.15nm	30.05nm	140.1nm	75.91nm	149.8nm
15minutes	14.65nm	21.67nm	24.19nm	30.27nm	13.91nm
20minutes	18.85nm	19.06nm	15.31nm	14.72nm	17.54nm
25minutes	17.57nm	15.55nm	18.50nm	18.99nm	35.13nm

Effect of Mixing Speed

Three different speeds were dealt with in this section, those being low speed at 2000rpm, medium speed at 4000rmp and high speed at 6000rpm. We used 0.2% polymer concentrations and all three types of surfactants. The particle size distribution profiles for these cases are displayed in Figs. 3.5.1, 3.5.2 and 3.5.3. With the mixing speed parameter, it is noted that the smallest particles are produced at low speed, while higher speed produced a broader range of particle size and distribution. The size distribution for all the surfactants that were used varied immensely, with Tween 20 producing 100% particle distributed in one peak for all speeds. Polysobate 80 and Tween 80 produced a varied particle distribution with irregularly shaped peaks for Polysobate 80 and multiple peaks for Tween 80. For Tween 20 100% particle distribution was noted with low speed producing the smallest particle size at 10.10nm – 712.4nm, while medium speed produced particles in the size range of 68.06nm – 2305nm and high speed produced particles in the size range of 91.28nm – 1990nm. At high and medium speeds, Tween 80 had 90% particle distribution in the size range of 105.7nm – 342nm for high speed and 58.77nm – 342nm for medium speed in addition to 10% particle distribution at 6.503nm – 68.06nm for high speed and 6.503nm – 32.67nm for medium speed. For Polysobate 80 surfactant, low and medium mixing speed yielded smaller particle sizes although the size distribution was broad with sizes ranged from 15.69nm – 1106nm for both low and medium speeds, while high speed had 10% particle distribution in 13.54nm – 78.82nm and 90% particle distribution in the 122.4nm – 955.4nm. From this we can note that lower mixing speed of 2000rpm produced smaller particles with the most uniform distribution.

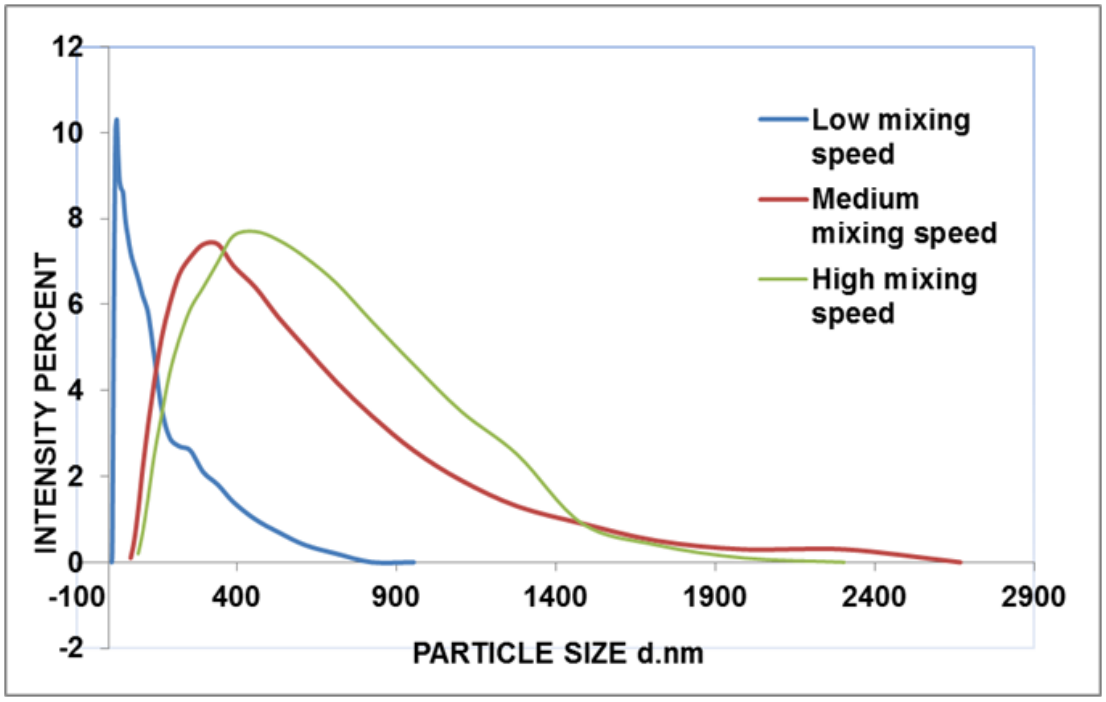

Fig. 3.5.1. Particle size distribution at different mixing speeds using Tween 20 at 0.2% polymer concentration.

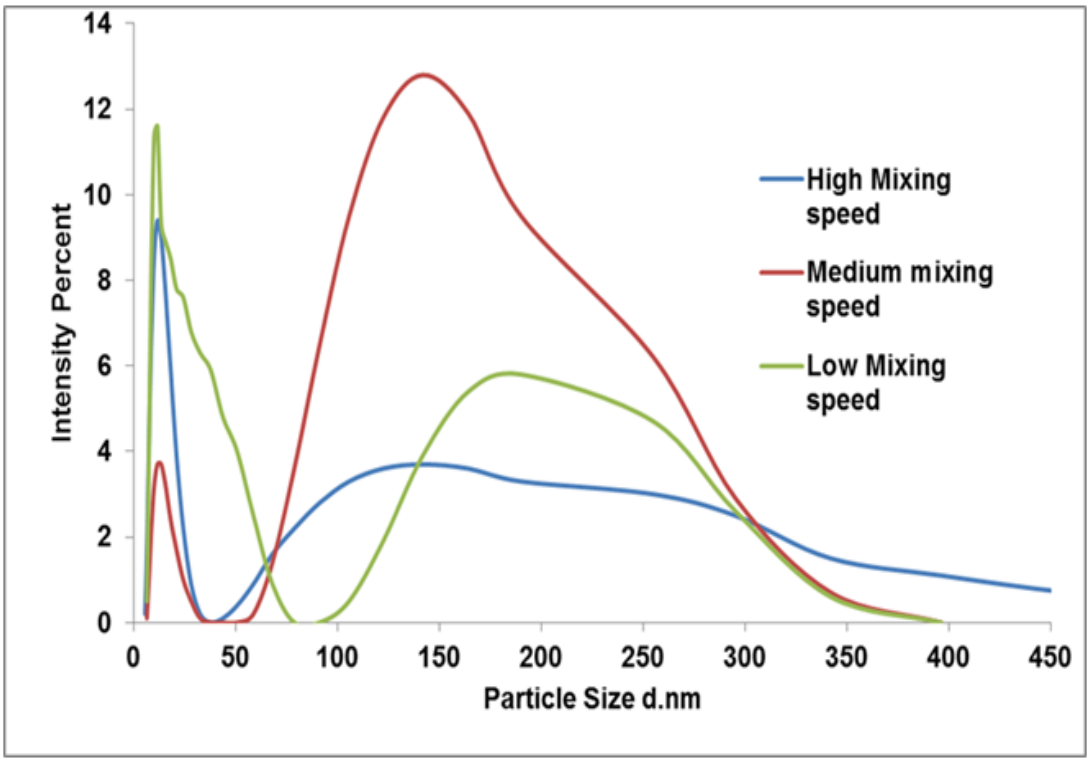

Fig. 3.5.2. Particle size distribution at different mixing speeds using Tween 80 at 0.2% polymer concentration.

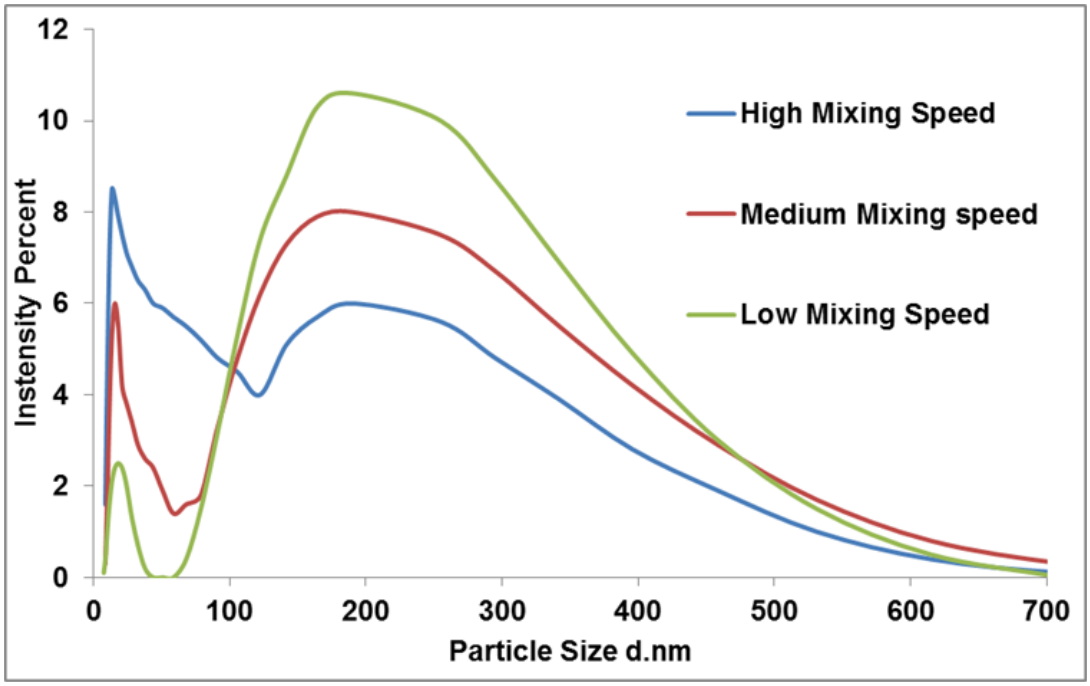

Fig. 3.5.3. Particle size distribution at different mixing speeds using Polysobate 80 at 0.2% polymer concentration.

TABLE 3.5.1. Particle size with changing speed using Tween 20

Concentration	Low speed (2)	Medium speed (4)	High speed (6)
0.2%	32.60nm	276.2nm	368.6nm
0.4%	30.25nm	347.6nm	212.4nm
0.6%	25.13nm	558.8nm	566.3nm
0.8%	52.54nm	474.7nm	27.70nm
1%	348.1nm	24.95nm	30.83nm

TABLE 3.5.2. Particle size with changing speed using Tween 80

Concentration	Low speed (2)	Medium speed (4)	High speed (6)
0.2%	19.56nm	90.11nm	224.6nm
0.4%	38.97nm	249.4nm	18.58nm
0.6%	51.27nm	14.21nm	14.03nm
0.8%	97.76nm	34.64nm	19.95nm
1%	113.3nm	18.87nm	84.38nm

From the detailed investigation of the effect of each individual preparation parameter it can be states that smaller particle suitable for drug delivery applications are best obtained for Polysobate 80 surfactant at concentration of 0.2% and at low mixing time and speed of 5 minutes and 2000rpm, respectively.

Conclusion

The micro-emulsion method represents one of the easiest methods to produce the smallest nanoparticles with the least limitations. A few challenges were encountered when trying to obtain a particular size with a well-defined distribution, however a general trend can be seen from all the formation parameters investigated. Lower polymer concentrations yield smaller nanoparticles ranging from 2.696nm – 6.503nm with uniform size distribution and sharp intensity. The use of a surfactant produced smaller particles as compared with surfactant-free samples. Furthermore, among the different types of surfactants used, Polysobate 80 surfactant produced the smallest particles of all three surfactants used in the size range of 2.696nm – 6.503nm with uniform particle distribution and good intensity. Homogenization of samples also facilitates the production of small particles with the smallest nanoparticles produced using Polysobate 80 in the range of 10.10nm – 342nm. Low mixing time produced smaller particles with the100% particles distributed in one intense peak with the smallest range at 6.503nm – 24.28nm also produced using Polysobate 80 surfactant. With mixing speed, lower mixing speed at 2000rpm yielded smaller particles with 100% particle distribution in one peak with sharp intensity at 15.69nm – 1106nm. Throughout the process Polysobate 80 maintained its consistency in producing smaller particles as compared to the Tween 20 and Tween 80. Each tested parameter showed promising results when it was manipulated to produce smaller nanoparticles. However, it is thus important to note that particle size and distribution is influenced by more than one factor and the combination of multiple manipulations of these factors would lead to the ideal particle size and distribution to obtain optimized results.

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عنوان المخطوطه: فحص العوامل المؤثره فى تكوين وحجم الجزيئات النانويه المحضرة بطريقة الاستحلاب الدقيقه والتى تستخدم لأنظمة توصيل الدواء

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لقد أثبتت استخدام الطريقة الكيميائية للمستحلبات الدقيقة نجاحاً باهرا في تكوين الجسيمات النانوية والتحكم فى حجم تلك الجسيمات والمستخدمه في انظمة توصيل الدواء.

الغرض من هذه الدراسة:
هو دراسة تأثير خمسة عوامل اساسيهفي طريقة تحضير المستحلب الدقيق على حجم الجسيمات النانوية المنتجة والتى تكون مثالية فى استخدامها فى انظمة توصيل الادويه داخل الكائنات الحيه. وحيث ان هذه العوامل هي سرعة التقليب، وزمن المزج، ونوع المادة الخافضة للتوتر السطحي، والتجانس، وتركيز البوليمر (خلات الإيثيلين المشترك فينيل) (PEVA). تم الحصول على معلومات حول أحجام الجسيمات وتوزيعها وتحليلها باستخدام ZetaSizerNanoZS.

لقد أظهرت النتائج أنه تم الحصول على أحجام صغيرة وتوزيعات ضيقة/موحدة لحجم الجسيمات عند استخدام تركيز أقل من البوليمر (0.2% وزن/حجم)، وسرعة تقليب منخفضة (2000 دورة في الدقيقة) ومع وجود بوليسوربات 80 كماده خافضه للتوتر السطحي. في المقابل، فإن تركيزات البوليمر الأعلى (1% وزن/حجم) وسرعة التحريك (6000 دورة في الدقيقة)، في غياب المادة الخافضة للتوتر السطحي والتجانس، أسفرت عن جزيئات كبيره والتى تكون نسبيا غير ملائمة فى عملية توصيل الدواء

وكشفت هذه النتائج أيضًا بوضوح أن حجم الجسيمات تتأثر بشكل كبير بمزيج عدد من العوامل المستخدمة فى هذه المخطوطة معاوالتي اثبتت الدراسه فاعليتها ، وأنه يمكن إنتاج الجسيمات النانوية عند طلبها باستخدام هذه العواملفى انتاج جزيئات نانونيه صغيره محسنة لتلبية العديد من التطبيقات المحتملة والمستخدمة فى العديد من التطبيقات الحيوية الهامه ومنها انظمة توصيل الدواء.