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Preparation and characterization of nanoparticles for encapsulation and delivery vehicles

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Abstract. This research creates nanoparticles that are tunable, have a high active ingredient content, and are highly encapsulated and controlled. We use model materials to determine the ethylcellulose-vanillin ratios as well as the effective processing conditions required for nanoparticle formation using ethylcellulose and vanillin as active ingredients. Nanoparticles with a mean size of 45 to 64 nm were prepared at a rate of approximately 1.3 million nanoparticles per minute using a different polymer:vanillin ratio. The encapsulation efficiency and loading of vanillin at different concentrations in nanoparticles from solutions ranged from 75 to 94 percent and 66.90 to 86.54 percent, respectively, indicating that the loading and encapsulation efficiency of the nanoparticles decreased as the amount of vanillin increased.

Introduction

Recent years have seen nanotechnology used extensively in the pharmaceutical, cosmetic, and food industries for encapsulating and releasing active ingredients under controlled conditions [1–7]. The nanoparticles used for these applications must be nontoxic, stable, have high encapsulation efficiency, and have high loading capacity, and must also be capable of being precisely tailored to meet the release kinetics of the flavour component.

There are several different types of polymer-based colloidal particles, e.g. solid lipid nanoparticles, liposomes, and micelles. A variety of different purposes can be accomplished with these capsules, including encapsulating flavor, preservatives, vitamins, and other "nutraceuticals" [8–11] Lipophilic and hydrophilic favor components can be loaded into them, and studies have demonstrated that encapsulating materials increases bioavailability as compared to unencapsulated material. Food ingredients containing liposomes have already been approved or have entered clinical trials. Liposomes are limited for use in food encapsulation, however, due to their low loading capacity, rapid release of favor components, and instability during storage [12]. Solid lipid nanoparticles are made up of solid lipids as opposed to lamellar lipid structures. There has been evidence of greater stability and more sustained release problems in the materials encasing a liquid core. In literature, three methods for flavour encapsulation have been reported: (i) homogeneous matrix; (ii) enriched shell with flavor components; and (iii) enriched core with flavour components. Matrix particles homogeneous in composition have a uniform distribution of the favour component. In this way, a long-term favor release (over weeks) may be achieved along with protection against oxidation and high encapsulation capacity. Alternatively, particle shells possessing a high proportion of favored components exhibit a rapid release rate (in minutes). Fick's law of dissolution governs the release rates of particles with enriched favour components and is affected by physicochemical properties (the partition coefficient) of the molecules and the thickness and density of the outer lipid shell. The preparation of solid lipid nanoparticles has been carried out using a variety of techniques. Hot homogenization and cold homogenisation are the two main classes . Using the latter method, the solid lipid nanoparticles will exhibit poor control over their chemical and physical properties, resulting in the release of the active ingredient to the

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surrounding medium or to recrystallization. In contrast, cold homogenisation promotes the formation of particles with enriched shells containing favor components. In order to overcome these drawbacks, alternative methods of fabricating solid lipid nanoparticles are desirable. In this study, electrohydrodynamic techniques are examined for use in this application. Electrohydrodynamic atomisation or electrospraying involves an electrically induced focus and breakup of a liquid jet in order to produce droplets of micrometers to nanometres in diameter. As far as particle size and uniformity are concerned, physical properties of the materials being processed, their low rate(s), and the applied electrical potential difference play the largest roles. A wide range of nano-, micro-, and electrohydrodynamic structures have been produced using electrohydrodynamic techniques. It is easier to control particle size, shape, and uniformity, and it does not require multiple processing steps or high temperatures or pressure. The production of multilayer particles has also been shown to be feasible by single and coaxial spraying devices. An electrohydrodynamic process was used in this study to produce nanoparticles of ethylcellulose encapsulating vanillin. In the food industry, both materials have a wide range of applications and are typical hydrophobic coatings and hydrophilic favor components respectively [13]. The purpose of this study is to analyze the rate of release of active ingredients so that particle characteristics can be tailored to a particular application. In addition to demonstrating that electrohydrodynamic techniques [14] can be applied to many combinations of materials, our kinetic analysis has been significantly improved.

Materials and methods

Materials

All the consumables were purchased from Sigma-Aldrich (Poole, Dorset, UK), including ethylcellulose, vanillin (3-ethoxy-4-hydroxybenzaldehyde), and 95% (v) ethanol. All experiments used double distilled (DD) water as the release medium.

Preparation and characterisation of spraying solutions

Various concentrations of ethylcellulose and vanillin were dissolved in ethanol (Table 1) (from 1 to 4 weight%).

Table 1: Characteristics of ethylcellulose only (mean ± S.D., n = 5).

Solutions	Polymer concentration (wt %)	Density (kg/m^{-3})	Surface tension ($mN\ m^{-1}$)	Viscosity (mPa s)	Electrical conductivity ($mS\ m^{-1}$)
S1	0.25	759	22.2	4.4	2.97
S2	0.50	761	22.1	3.7	3.5
S3	0.75	763	22.1	3.2	5.16
S4	1.00	765	21.9	2.8	6.3
S5	1.25	767	21.8	2.7	6.91
S6	1.50	769	21.7	2.5	7.57
S7	1.75	771	21.5	2.3	8.33
S8	2	773	21.3	2	8.56
S9	2.25	777	20.1	1.6	8.78
S10	2.5	779	20	1.5	9.3

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Table 2: Characteristics of ethylcellulose and vanillin (mean ± S.D., n = 5).

Solutions	Polymer concentration (wt %)	Density (kg/m^{-3})	Surface tension (mN m^{-1})	Viscosity (mPa s)	Electrical conductivity (mS m^{-1})
S1	0.25	764	22.1	4.2	3.1
S2	0.50	768	22	3.6	4.35
S3	0.75	770	21.9	3.1	5.24
S4	1.00	772	21.7	2.8	7.01
S5	1.25	774	21.6	2.6	7.21
S6	1.50	776	21.5	2.3	7.93
S7	1.75	779	21.4	2.1	8.39
S8	2	781	21.2	1.6	9.17
S9	2.25	784	20	1.5	9.49
S10	2.5	786	19.9	1.3	10.13

A magnetic stirrer was used to mix the solutions until they became optically transparent at ambient temperature (25C): this took around 10 minutes. From three repeat measurements of each solution, surface tension and viscosity were determined by a Kruss tension meter (Model-K9, Kruss GmbH, Germany) and a U-tube viscometer (75 mlnCannon-Fenske Routine Viscometer, Cannon Instruments, USA).

Electrohydrodynamic processing

Silicon tubing was used to feed the solution into a stainless steel needle with internal diameter 450 m from a 10 ml plastic syringe driven by Harvard PHD 4400 syringe pump (Edenbridge, UK) at a rate of 15 l min. In the experiment, a high voltage power supply was used to apply a potential difference between a needle electrode and a ground electrode between 13 and 15 kV (Glassman Europe Ltd., Tadley, UK). After an optimal cone jet voltage of 14:5 kV was achieved, nanoparticles were collected on glass microscope slides or in vials containing DD water for the release studies. Both vials were maintained at a distance of 100mm from the needle tip. A video camera (Leica S6D JVC-color) was used to observe the jet created at the tip of the needle when nanoparticles were produced. Before the current study, a study was carried out to determine how operating parameters and formulation could affect nanoparticle physical properties and vanillin release rate [50, 56]. In the present study, operating parameters (i.e. polymer concentration, low solution rate, distance between needle tip and collector) were selected to produce an effective cone jet and control the nanoparticle formation process [50, 56].

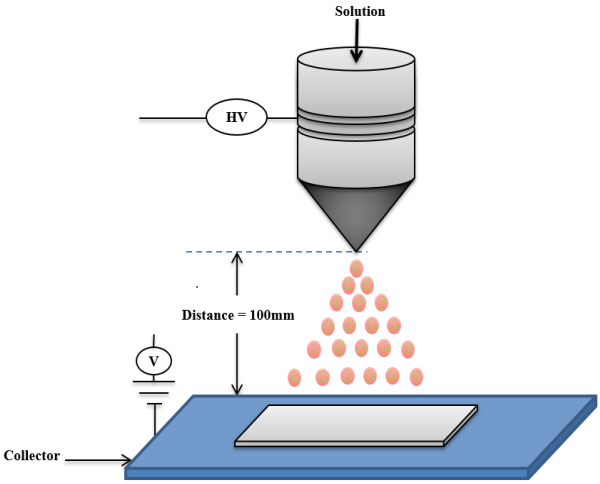

Figure 1: An illustration of an EHD spraying setup used for nanoparticle preparation.

Scanning electron microscopy (SEM)

By using SEM (Model JEOL JSM 3600, UK), the polymer nanoparticles were characterised in terms of size and morphology. After vacuum sputter coating dried polymer nanoparticles with gold for 2 min, with 40 mA, and mounting them on aluminium stubs with double-sided carbon tape, they were subjected to high voltage SEM examination (5 kV). The standard deviation and mean of the nanoparticle diameter were calculated using ImageJ (National Institutes of Health, NIH, Maryland, USA). For each set of processing conditions, approximately 300 nanoparticles were measured.

Table 3: Nanoparticle mean sizes, standard deviations (nm) and polydispersivity index.

Solutions	nanoparticle mean size (nm)	polydispersivity index	SD	Min	Max	PDI
S1	64.39	20.74	13.36	39.98	97.15	0.21
S2	62.51	17.31	10.82	35.85	81.98	0.17
S3	61.11	30.64	12.11	35.94	82.81	0.22
S4	57.66	16.50	17.67	38.89	92.05	0.31
S5	56.57	21.02	11.89	40.54	78.43	0.21
S6	55.00	22.91	12.60	34.48	83.05	0.23
S7	53.54	31.45	15.08	30.76	89.75	0.28
S8	51.86	23.89	16.31	29.73	91.89	0.31
S9	46.96	31.12	14.61	24.36	73.12	0.31
S10	45.31	33.82	10.82	24.47	70.27	0.24

Determination of encapsulation efficiency, loading capacity and release profile

Determination of vanillin encapsulation efficiency, loading capacity and release profile. A total of 3 ml of the collected suspensions were divided equally among three tubes for evaluation of vanillin encapsulation efficiency, loading capacity, and release rate of vanillin. The tubes were filtered using 200nm syringe filters in 10 ml of DD water at ambient temperature (25C). Each tube of polymer nanoparticles was mixed with equal amounts of DD water to disperse the polymer nanoparticles. A UV spectrophotometer (Perkin Elmer, Lambda 35, UV/Vis spectrophotometer, Waltham, USA) was used to determine the free vanillin content in each tube. Vanillin's absorbance at 278 nm was measured using a UV spectrophotometer. To calculate vanillin encapsulated in the

polymer nanoparticles, we subtracted the amount in the DD water from the total amount in the polymer nanoparticle solution. Equations 1 and 2 were used to determine encapsulation efficiency and loading capacity:

$$\% \text{ Encapsulation efficiency} = \frac{\text{Amount of dried nanoparticles}}{\text{Total active ingredient used}} \quad (1)$$

$$\% \text{ loading capacity}$$

$$= \frac{\text{weight of dry nanoparticles}}{\text{weight of dried ethylcellulose and vanillin}} \times 100 \quad (2)$$

This equation expresses the weight of vanillin in nanoparticles, the weight of vanillin in supernatants, the total weight of polymer nanoparticles as NP, and the total weight of electrosprayed nanoparticles as DNP. Each set of polymer nanoparticles was released three times over 240 minutes, with the cumulative vanillin release rate plotted as a function of time.

Table 4: Nanoparticle loading capacity and entrapment efficiency obtained by electrohydrodynamic flow at 10, 25 and 50µl/min.

Solutions	Polymer concentration (w%)	Active component loading (%)	Flow rate (µl/min)	Loading capacity (%)	Entrapment efficiency (%)	Burst (%)
S1	10.0	10	25	86.54	0.94	5.57
S2	10.0	10	20	88.57	0.95	4.33
S3	10.0	10	15	90.51	0.97	2.80
S4	10.0	25	15	86.98	0.94	5.83
S5	10.0	50	15	64.61	0.70	27.39
S6	7.5	10	15	79.21	0.88	10.59
S7	7.5	25	15	74.54	0.83	15.56
S8	5.0	10	15	73.71	0.81	16.89
S9	7.5	50	15	70.96	0.80	18.24
S10	2.5	10	15	66.90	0.75	22.00

This equation expresses the weight of vanillin in nanoparticles, the weight of vanillin in supernatants, the total weight of polymer nanoparticles as NP, and the total weight of electrosprayed nanoparticles as DNP. Each set of polymer nanoparticles was released three times over 240 minutes, with the cumulative vanillin release rate plotted as a function of time.

Results and Discussion

This study was conducted at a variety of solution flow rates ranging from 10 to 25 l min1. This was discovered to be necessary for the formation of uniform nanoparticles. The voltage required to generate nanoparticles increased as polymer concentration increased, and the jet eventually became unstable [15]. The polymer concentration is known to affect the surface tension, viscosity, and electrical conductivity of the liquid phase, all of which affect the EHD process [15]. Initial research was conducted to optimize the polymer concentration, and it was discovered that the viscosity and surface tension of the solution increased with polymer concentration Table 3 and

Table 2), resulting in an increase in mean nanoparticle size (Table 3). Furthermore, as the polymer concentration increased, the electrical conductivity of the solutions decreased noticeably (table 1), increasing nanoparticle size. Depending on the operating conditions, the diameter of the polymer nanoparticles ranged between 45.31 and 64.39 nm. With a polydispersity index ranging between 16.50 and 33.82 percent, the corresponding size distributions were relatively narrow (see Table 3). Table 3 shows how the size of the nanoparticles varied with polymer concentration and operating conditions. When the flow rate was increased from 10 to 25, the mean size of the nanoparticles increased by 19%, as did the polydispersity index. This finding is consistent with previous research [16]. The size of nanoparticles increased with polymer concentration (Table 3), which is most likely due to an increase in viscosity. Increasing the vanillin concentration reduced the mean size of the nanoparticles. This could be explained by a decrease in the liquid's electrical conductivity. However, the effect was less pronounced than for the corresponding polymer concentration, which is consistent with previous work by the authors [17]. Table 2 shows that the encapsulation efficiency and loading of vanillin at different concentrations in nanoparticles from solutions P1 - P10 ranged from 75 percent and 94 percent and 66.90 percent to 86.54 percent respectively, indicating that the nanoparticles' loading and encapsulation efficiency decreased as the amount of vanillin increased. 1wt% vanillin was encapsulated in nanoparticles with high encapsulation efficiency. The effect of vanillin loading capacity is consistent with previous studies [18] and can be explained by the fact that the decreased active component loading increases the relative amount of ethylcellulose acting as a diffusional barrier. By changing the polymer concentration of the polymer solution, the vanillin loading had a similar but smaller influence on nanoparticle mean size, with a large amount of active component loading causing an increase in mean particle size. As expected, flow rate has an effect on nanoparticle size. This is not surprising given that ethylcellulose is nearly insoluble in water.

Conclusions

Electrospraying has been shown to produce polymer nanoparticles containing vanillin. The diameter and size distribution of the nanoparticles were controlled by varying the polymer:vanillin concentration ratio in the sprayed solution. The thickness of the outer polymer layer of the nanoparticles was influenced by the concentration of polymer in the processed solution. Similarly, encapsulation efficiency and loading capacity were both affected by the polymer-vanillin ratio, though there was a limit beyond which both began to decline. A polymer-based nanoparticle that can be separated electrohydrodynamically in one step may be of considerable use for mass production of polymer based nanoparticles with different characteristics for food or medical applications.

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