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Electrostatic spraying and its use in drug delivery – cholesterol microspheres

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Abstract

Electrostatic spraying can be achieved by applying a potential difference of a few thousand volts between two electrodes and the end of a capillary supplied with liquid or melts under atmospheric pressure or controlled temperature. The system involved in this investigation consisted of two electrodes positioned 0.2 cm apart, one of which being at the tip of the capillary. The system was used in the production of excipient-free microspheres of cholesterol. The thermal stability of cholesterol (m.p. 148.5° C) allowed its electrostatic spraying at 170° C. Cholesterol congealing on spraying afforded microsphere collection with no cooling of the system. Particle size was found to be dependent upon voltage, and positioning of the two electrodes. SEM analysis of the microspheres obtained at +3000 V d.c. voltage produced a mixture of spherical particles of 150–250 μm and amorphous particles of 10–30 μm size. Particle size distribution studies using a Coulter counter showed that 65% of particles produced are in the range of 13.5 ± 3.76 μm. Investigation of the dependence of electrostatic spraying behavior of solvent systems on their physico-chemical properties suggested an inverse relationship between electrostatic spraying flow rate and polarity, viscosity, and surface tension. Liquids with high dielectric constant required higher voltages to enter into electrospraying mode. Increase in molecular symmetry improves the electrostatic spraying properties of liquids and may be correlated to molecular packing in the liquid phase. The results of this study support electrostatic spraying as a promising technique for the production of excipient-free microspheres for the delivery of macromolecules as well as molecules of lower molecular weight.

Keywords: Electrostatic spraying; Cholesterol; Melt; Voltage; Microsphere

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1. Introduction

Dispersion of liquids by various means is usually accompanied by production of charged droplets. Clouds, waterfalls and sea sprays can carry substantial amounts of electrostatic charge that can sometimes result in sparking. This natural charging of water or liquids is the result of changes in the electrical conductivity of a liquid at the liquid-air interface. Observations of natural spray electrification were recorded as early as 1890 by Elster and Geitel (1890) who detected considerable amounts of electrical charge in the vicinity of waterfalls. The first published account of monodispersion of liquid (water) off a capillary

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tip under an electrostatic field was reported by Vonnegut and Neubauer (1952). These reports suggest that production of monodisperse liquid droplets of uniform size can be achieved by applying potentials of several thousand volts d.c. or a.c. to the surface of a liquid in small capillaries. At high voltages it is possible to vaporize a liquid.

Electrostatic spraying has been applied to paint and crop spraying (Coffee, 1981), ink-jet printing (Kamphoefner, 1972), emulsion production (Hughes and Pavey, 1981) and more recently to mass spectrometry of non-volatile substances or thermally unstable lower molecular weight species (Whitehouse et al., 1985; Blades et al., 1991). Electrostatic spraying can be used as an interface to couple ion-exchange and ion-pairing chromatography to mass spectrometry (Siu et al., 1991). The electrospraying device as used in mass spectrometry delivers a continuous stream of fine droplets that carry a charge of predetermined polarity.

In spite of considerable research on electrostatic spraying, difficulties still remain in controlling the reproducibility of the spraying process including frequency, pattern, particle size of monodisperse and polydisperse systems that are usually produced. This investigation represents a study of electrostatic spraying in the context of application to drug delivery. Because of its thermal stability, cholesterol was chosen as the model compound to study the behavior of melts during the electrostatic process with the purpose of producing excipient-free microspheres.

Another part of the present investigation was devoted to the study of the diverse physical properties of liquids which directly affect their electrostatic spraying behavior. Data are presented to show the importance of dielectric constant, ionic strength, surface tension and viscosity on the electrostatic spraying behavior of liquids. The importance of intermolecular interactions is also addressed.

2. Materials and methods

Fig. 1 depicts the apparatus used in this investigation. Briefly, it consists of an infusion pump (Sage instruments, Model 355, Cambridge, MA) a 20 cm^3 glass syringe (Beckton Dickinson, Rutherford, NJ), a stainless-steel capillary (inside diameter, 0.232 cm), and a d.c. power supply (Ortec, Model 466) capable of operating in the range of 0–3000 V d.c. The electrodes are positioned 0.2 cm apart, one of them being at the tip of the capillary. The liquid to be sprayed is contained in a glass syringe and fed through the capillary. The infusion pump provides constant hydrostatic pressure and uniform liquid flow at controlled speed. The achievement of the spraying mode of the liquid was followed by the change in the flow rate on voltage application. Prior to voltage application the liquid or the melt is allowed to fall from the capillary at a rate of a few drops per min. This pre-established initial flow serves as a baseline in all experiments. + d.c. voltage is gradually applied to the tip of the capillary. Net flow rate change on voltage application was calculated as a difference between number of droplets per min at a particular voltage and baseline flow rate.

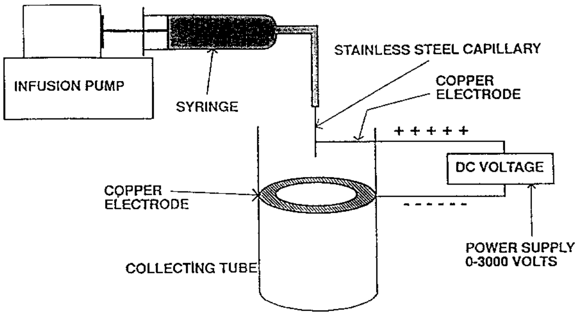

Fig. 1. Electrostatic spraying equipment.

Electrostatic spraying of cholesterol in the molten state was carried out using the same equipment. A heating mantle controlled by a thermostat was positioned around the syringe extending down to the capillary and upper electrode to maintain cholesterol in the molten state and provide uniform flow. The temperature was maintained at 170° C. Molten cholesterol was allowed to establish a baseline flow prior to voltage application. Gradual application of + d.c. voltage to the tip of the capillary initiates the spraying process. At high voltages a transition from coarse to fine cholesterol droplets occurs. The resulting spray resembled a jet of fine particles similar to an aerosol. The frequency, pattern, and shape of droplets produced with the apparatus depended on the applied voltage at the tip of the capillary and alignment of electrodes. In the spraying mode solid cholesterol microspheres were collected at

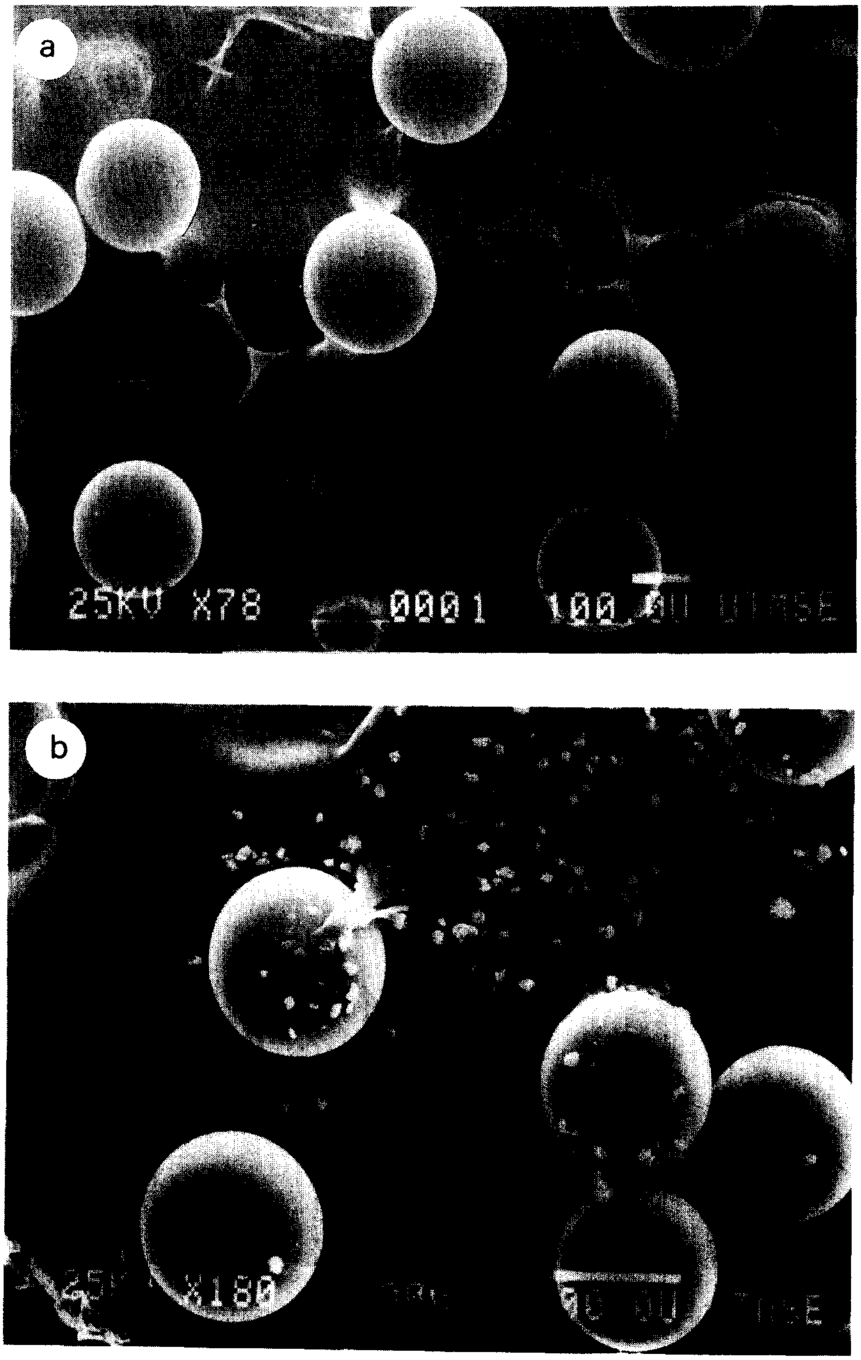

Fig. 2. (a,b) Cholesterol microspheres.

3000 V d.c. on a glass plate positioned 40 cm below the tip of the capillary. No additional cooling or handling was necessary. High voltage provides conditions for spray production, greatly enhanced evaporation and facilitated solidification of microspheres. Surface characterization of microspheres was performed by scanning electron microscopy (JEOL JSM35C). Particle size distribution was determined using a Coulter counter.

Dioxane and methanol were purchased from Mallinckrodt (Paris, KY). Glycerin, propanol and octanol were supplied by MCB Chemical Co. (Norwood, OH). Butanol isomers, pentanol, and heptanol were obtained from Sigma Chemical Co. (St. Louis, MO), hexanol from J.T. Baker Inc. (Phillipsburg, NJ) and ethanol from Midwest Grain Products (Pekin, IL). All solvents were used as received. Cholesterol was obtained from Fisher Scientific Co. (Fair Lawn, NJ) and used as received.

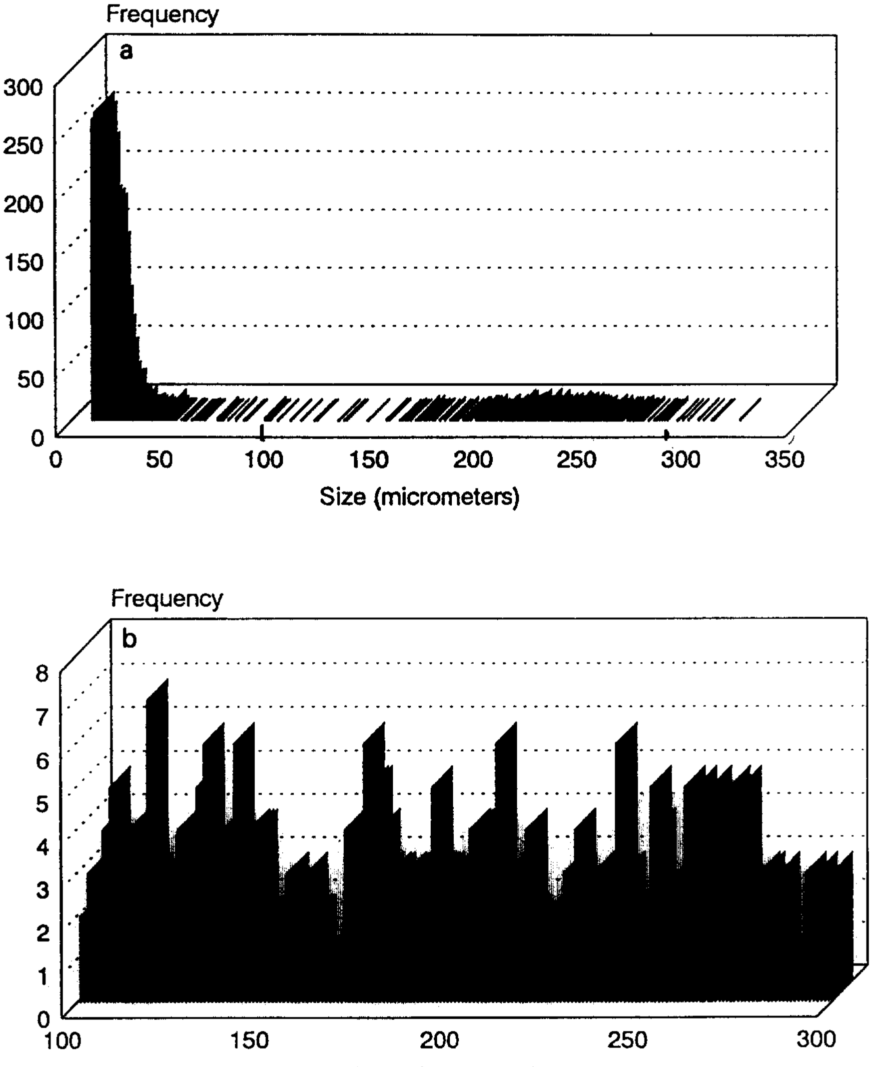

Fig. 3. (a,b) Size distribution of cholesterol microspheres.

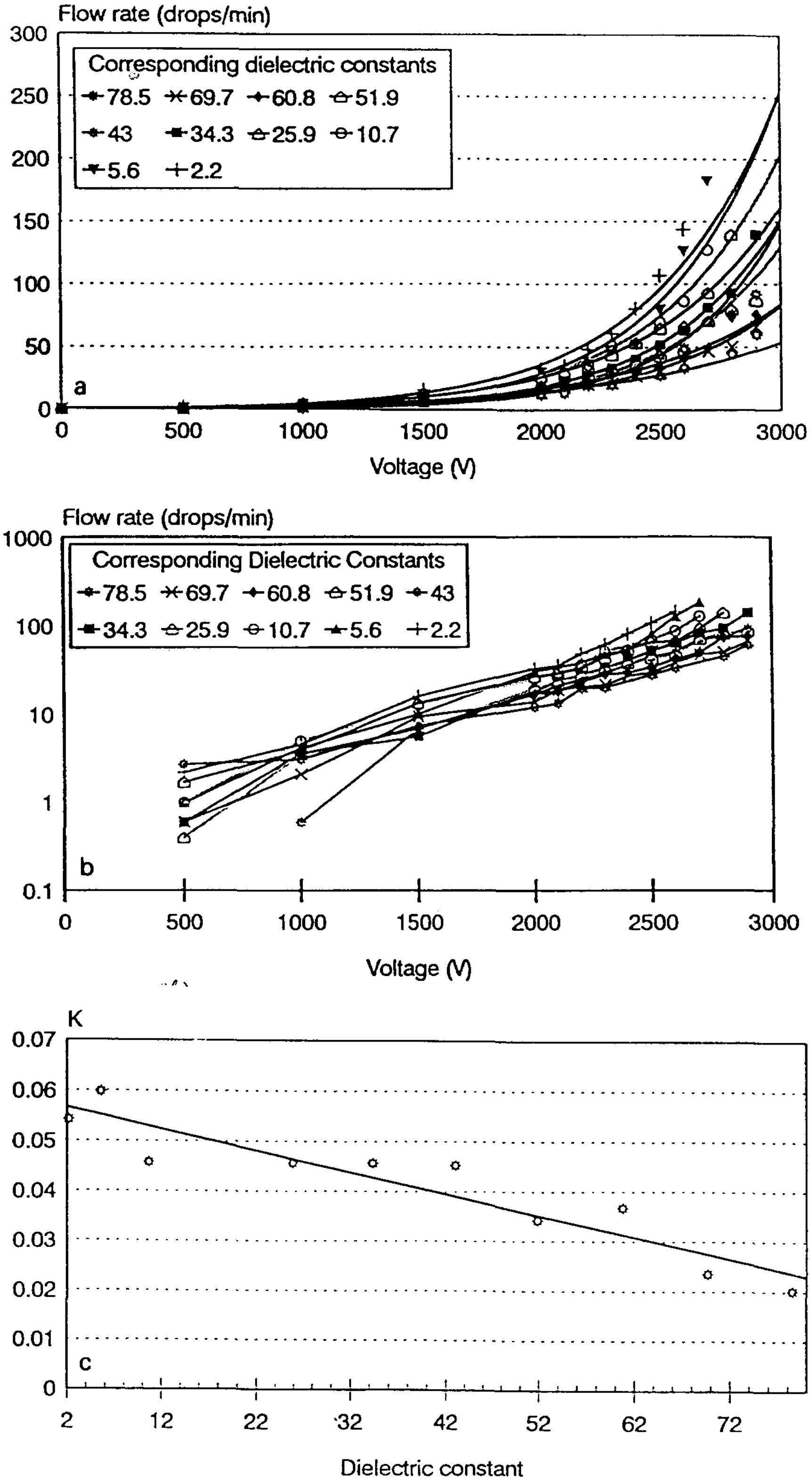

Fig. 4. (a–c) Effect of dielectric constant on electrostatic spraying: water-dioxane mixtures.

3. Results and discussion

Cholesterol microspheres were obtained by electrostatic spraying at 3000 V d.c. of molten cholesterol at 170° C.

Size, shape and surface characteristics of the collected cholesterol microspheres were characterized using scanning electron microscopy (SEM) and a Coulter counter. SEM showed microspheres of perfect round shape with a very smooth surface and relatively uniform distribution in the range of 100–200 μm (Fig. 2a). Greater magnification revealed particles of uneven shape and size in the order of 10 μm (Fig. 2b). The overall particle size distribution is demonstrated in Fig. 3a. Characterization of cholesterol microspheres using the Coulter counter revealed that the particles obtained represent distributions of two particle size ranges; 10–30 and 100–300 μm.

A representative sample of the produced cholesterol microspheres was counted. Fig. 3b represents a histogram of the particles in the size range of 100–280 μm. Particles counted in this range constitute 18.3% of the total number of particles in the sample. Descriptive statistics of the data indicate a distribution with a mean of 186.7 μm and a standard deviation of 41.8 μm. Particles of the smaller size range produced in the process represent 64.7% of the counted sample with the mean of 13.5 μm and a standard deviation of 3.71. 17% of the sample accounts for the particles in the size range of 50–100 mm and above 300 μm.

The second part of the present investigation was focused on the detailed study of physical parameters that affect the electrostatic spraying behavior of liquids. These parameters include experimental setup, i.e., spatial electrode arrangement and intrinsic properties of the liquids. The physico-chemical properties of liquids studied include polarity, surface tension, viscosity, ionic strength and molecular symmetry.

Solvent mixtures of different water-to-dioxane ratios represented media with a range of dielectric constants from 2.2 to 78.5. Application of + d.c. voltage to the surface of liquid droplets induces reorientation of molecular dipoles in the bulk of the droplet. Fig. 4a shows the effect of the dielectric constant of water-dioxane mixtures on the rate of droplet formation as a function of + d.c. voltage. Direct dependence of flow rate vs the applied voltage suggested that logarithmic data transformation could result in a linear relationship. It appears that, regardless of the voltage studied, the relationship $\log F = K \cdot V$ was found to be true, where F is the flow rate, K denotes a

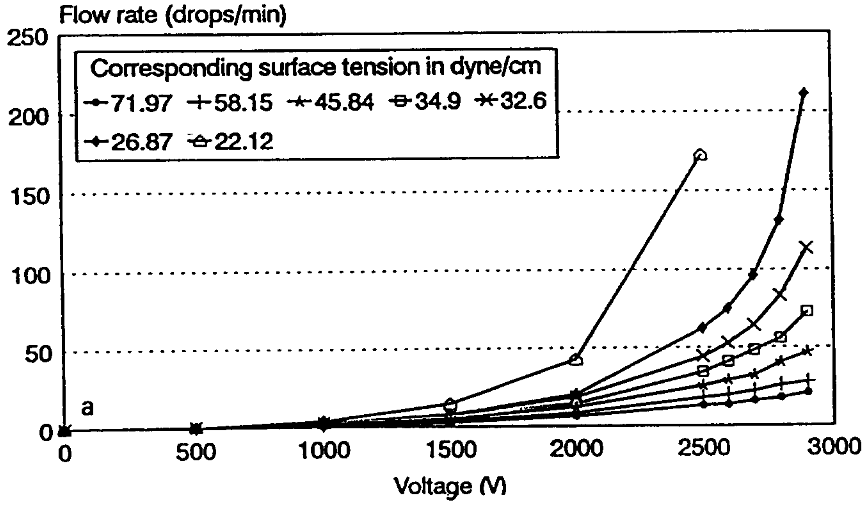

Fig. 5. Surface tension effects: methanol-water mixtures.

proportionality constant and *V* is the applied voltage. In order to obtain *K*, the data in Fig. 4a were transformed to yield Fig. 4b. Linear regression analysis of the data in Fig. 4b yields the *K* values as a function of dielectric constant. A plot of *K* values vs the dielectric constant of the medium is illustrated in Fig. 4c. Fig. 4c suggests that knowledge of the *K* may be useful in predicting the electrostatic spraying behavior of solvents which exhibit similar polarity characteristics to those of water-dioxane mixtures.

The electrostatic spraying behavior of water as a function of +d.c. voltage was investigated in the presence of potassium chloride, a strong electrolyte. Increase in the ionic strength of the solution did not affect its electrostatic spraying behavior.

Methanol-water mixtures representing liquids of a range of surface tension (22–72 dyn/cm) were used to elucidate the effect of surface tension on electrostatic spraying (Fig. 5). At constant voltage applied, higher flow rates were obtained for mixtures of lower surface tension.

Glycerin-water mixtures having viscosity in the range of 0.9–18 cP were used to examine the influence of +d.c. voltage on the electrostatic spraying pattern of these mixtures. Fig. 6 demonstrates the relationship between the applied voltage and the viscosity of liquids. Application of higher +d.c. voltage was required for liquids with higher viscosity to enter the spraying mode.

Propanol and butanol isomers were chosen as model compounds to investigate the relationship between molecular symmetry and electrostatic spraying. Increase in molecular symmetry was correlated with higher flow rates at constant voltage applied.

The effect of intermolecular interactions was also studied using a series of aliphatic alcohols – methanol to octanol. The voltage needed to enter the spraying mode increased in the order of butanol to octanol and methanol to propanol (Fig. 7a).

The experiments presented above were designed to elucidate the effect of physico-chemical parameters on the electrostatic spraying behavior of liquids and melts. Dielectric constant, surface tension and viscosity are functions of intermolecular interactions (Table 1). Changes in one of the parameters lead to changes in the others. However, each property was studied on a solvent mixture system chosen on the basis of being the most representative of the property under consideration. Although the use of different pure solvents of a range of dielectric constant, viscosity or surface tension has an advantage of correlating

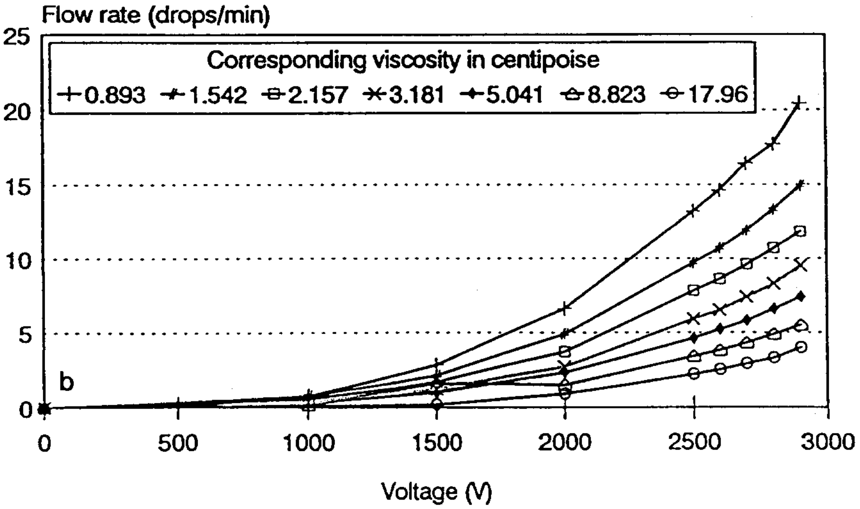

Fig. 6. Effect of viscosity: glycerin-water mixtures.

Table 1
Physico-chemical parameters of the solvents

	Dielectric constant	Surface tension (dyn/cm)	Viscosity (cP)
Water	78.70	73.05	1.00
Methanol	32.60	22.60	0.62
Glycerin	42.50	63.40	954
n-Butanol	17.80	24.60	3.40
sec-Butanol	15.80	23.47	4.20

the result of the experiment with the parameter studied, it introduces the variable chemical structure of the compounds as well as the symmetry effects which were shown to be of importance from the experiments with butanol and propanol isomers.

The data presented in Fig. 4-6 illustrated the fact that the rate of droplet formation is directly proportional to the applied voltage regardless of

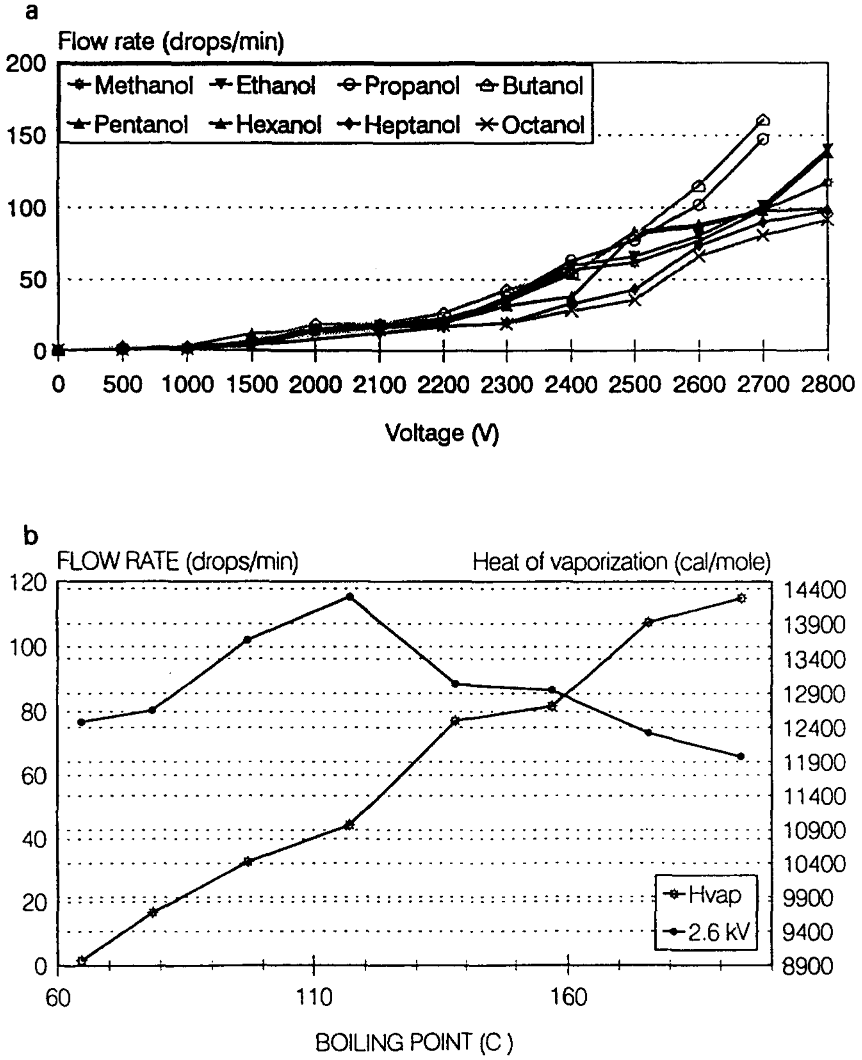

Fig. 7. (a) Effect of voltage on flow water: alcohols. (b) Intermolecular interactions: aliphatic alcohols.

the solvent system used in the study. The rate at which droplets are formed is slow at voltages between 500 and 2000 V. However, as the voltage increases above 2000 V, the rate of droplet formation increases in almost an exponential fashion. The change of rate of droplet formation as a function of applied voltage showed that the solvent polarity, surface tension, viscosity and molecular symmetry are of the utmost importance in determining liquid spray under experimental conditions. Fine aerosol-like sprays were obtained for pure dioxane (dielectric constant, 2.2) at 2500 V, whereas spraying was still not observed for water (dielectric constant, 78.5) at 3000 V. Therefore, liquids with high dielectric constant will require higher voltages to establish spraying mode.

The data indicate that the flow rate is inversely proportional to the dielectric constant of the medium, regardless of the applied voltage.

In addition, changes in the conductivity of the liquid, and surface tension, by addition of an ionic salt such as potassium chloride did not affect the electrostatic spraying of the solution.

Surface tension and viscosity are functions of intermolecular interactions in the bulk and on the surface of the liquid. Stronger intermolecular interactions result in an increase in the surface tension of the liquid. When voltage is applied to the liquid, large electrostatic charge is concentrated on the surface of the droplet. Repulsion of the like charges on the droplet surface that pull the droplet apart is counterbalanced by intermolecular forces holding it intact. At a critical charge strength coloumbic forces prevail and the droplet is split into numerous satellites that move away from the tip of the capillary and each other due to gravitational and repulsion forces, respectively. Thus, the strength of the intermolecular interactions will dictate the magnitude of the applied force needed for spray production. Lower viscosity and surface tension were beneficial for the production of sprays with minimal voltage input requirement.

In the series of methanol-water mixtures dielectric constant, surface tension, and viscosity decrease with the increase in the methanol content. These changes result in the increased flow rate at the constant voltage applied. Increase in the viscosity in the series of glycerin-water mixtures is accompanied by a decrease in the surface tension (from 73.05 to 63.4 dyn/cm) as well as dielectric constant values (78.7 to 42.5). Thus the decrease in the flow rate can be attributed mainly to the viscosity effects. In the series of *n*-, *sec*-, *tert*-butanol and *n*-, 2-propanol the same pattern of property changes occurs. Surface tension changes from 24.60 to 19.56, and 23.78 to 21.35 dyn/cm for butanol and propanol isomers, respectively. The values indicate that as the symmetry of the molecules increases, the surface tension of the alcohols decreases. However, this results in an increase rather than a decrease in the flow rate on voltage application. It can be seen that the differences in dipole moments cannot explain the significant differences observed in the flow rate of droplet formation as a function of applied voltage. Consequently, it can be postulated that molecular packing in addition to polarity may influence the electrostatic spraying. This may explain the significant differences in the electrostatic spraying behavior of the isomers of *n*-butanol as well as *n*-propanol.

A measure of intermolecular interactions can be given by the heat of vaporization. Increase in the symmetry of alcohols is reflected by a decrease in the heat of vaporization. This is also reflected by a decrease in the boiling point of the alcohols. Fig. 7b represents an attempt to correlate the heat of vaporization, boiling point and flow rate of droplet formation of a series of aliphatic alcohols at a fixed +d.c. voltage of 2.6 kV.

The correlation of the heat of vaporization to the free energy change can be made assuming that the surface tension is directly proportional to the free energy change and the entropy of the alcohols used in this investigation remains constant. Thus, the free energy change in combination with the surface tension may be used as predictors of the electrostatic spraying behavior of liquids. The results from butanol to octanol depicted in Fig. 7b suggest a relationship between surface tension, the heat of vaporization and the electrostatic spraying behavior of liquids. Thus, as the heat of vaporization decreases or the surface tension decreases, the flow rate of droplet formation will increase. However, a deviation from this concept occurs when one examines methanol, ethanol, and propanol. Further investigation is needed to fully understand the behavior of these alcohols as a function of + d.c. voltage. Nevertheless, the data clearly indicate that there is a strong trend suggesting that surface tension, heat of vaporization, and free energy changes, as well as the packing of the molecules in the liquid phase, are significant factors affecting electrostatic spraying behavior of liquids.

The effect of experimental setup on electrostatic spraying of liquids was investigated by varying the distance between the two electrodes (Fig. 8). Experiments were conducted using dioxane as a model compound. The distance between the electrodes was varied from 0.5 to 1.5 cm. An increase in the distance between the lower negative electrode and the one at the tip is accompanied by a decrease in the rate of formation of droplets as a function of applied voltage. Larger interelectrode distances hindered the electrostatic spraying at voltages as high as 3000 V. The positioning of the electrodes in the experimental equipment is an important factor in electrostatic spraying behavior of liquids. It affects the critical voltage of spray onset, droplet size distribution, reproducibility and spraying mode pattern. Careful positioning of the electrodes is essential for obtaining reproducible spraying patterns.

4. Conclusions

The results of this investigation support the potential use of electrostatic spraying of liquids and melts for the production of microspheres of uniform size. In the case of electrostatic spraying of melts careful consideration should be given to the thermal stability of drugs and the potential polymorphic changes as well as moisture entrapment during the solidification process. The choice of cholesterol as a model compound for the investigation was based on its thermal stability and lack of polymorphic transformations during the solidification process. In addition, the chemical structure of cholesterol is analogous to diverse steroids suggesting the use of this technique for the production of microspheres of water insoluble steroids which may act as a sustained release formulations upon intramuscular or intradermal administration. Electrostatic spraying was carried out in a closed system which results in high production yields and does not include a detrimental external phase which is usually required

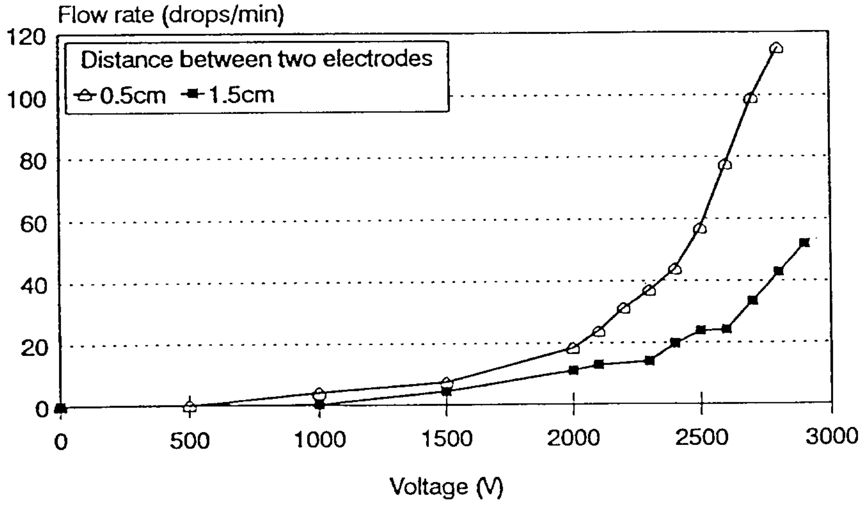

Fig. 8. Effect of distance between the capillary tip and negative electrode.

for most microencapsulation processes. Finally, the equipment required for electrostatic spraying is relatively inexpensive and easily transportable.

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