पेटेंट कार्यालय
शासकीय जर्नल

OFFICIAL JOURNAL
OF
THE PATENT OFFICE

निर्गमन सं. 26/2023	शुक्रवार	दिनांक: 30/06/2023
ISSUE NO. 26/2023	FRIDAY	DATE: 30/06/2023

पेटेंट कार्यालय का एक प्रकाशन
PUBLICATION OF THE PATENT OFFICE

(12) PATENT APPLICATION PUBLICATION
(19) INDIA
(22) Date of filing of Application :05/06/2023

(21) Application No.202341038503 A
(43) Publication Date : 30/06/2023

(54) Title of the invention : COMPOSITION AND METHOD FOR THE PREPARATION OF NANOPARTICLES WITH CONTROLLED RELEASE PROPERTIES FOR DRUG DELIVERY APPLICATIONS

(51) International classification :A61K 090000, A61K 091600, A61K 490000, A61P 270200, C08F 202400
(86) International Application No :PCT//
Filing Date :01/01/1900
(87) International Publication No : NA
(61) Patent of Addition to Application Number :NA
Filing Date :NA
(62) Divisional to Application Number :NA
Filing Date :NA

(71)**Name of Applicant :**
1)DR. RAMACHANDRA R K
Address of Applicant :PRINCIPAL, GOVERNMENT DEGREE COLLEGE, CHODAVARAM, ANAKAPALLE DIST 531036 ----------
2)DR. P V S S S N REDDY
3)DR. T K VISVESWARAYA RAO
4)DR. TIRUPATHI RAO
5)DR. ESUB BASHA SHAIK
Name of Applicant : NA
Address of Applicant : NA
(72)**Name of Inventor :**
1)DR. RAMACHANDRA R K
Address of Applicant :PRINCIPAL, GOVERNMENT DEGREE COLLEGE, CHODAVARAM, ANAKAPALLE DIST 531036 ----------
2)DR. P V S S S N REDDY
Address of Applicant :ASSISTANT PROFESSOR DEPARTMENT OF PHYSICS GOVERNMENT COLLEGE (AUTONOMOUS) E G DIST RAJAHMUNDRY 533105 Email: ---------- ----------
3)DR. T K VISVESWARAYA RAO
Address of Applicant :PRINCIPAL SAS GOVERNMENT DEGREE COLLEGE NARAYANAPURAM W G DIST email: ---------- ----------
4)DR. TIRUPATHI RAO
Address of Applicant :RESEARCH SCHOLAR DEPARTMENT OF PHYSICS CRYSTAL GROWTH AND NANOSCIENCE RESEARCH CENTER, GOVERNMENT COLLEGE (AUTONOMOUS) RAJAHMUNDRY E G DIST 533105 email: ---------- ----------
5)DR. ESUB BASHA SHAIK
Address of Applicant :ASSISTANT PROFESSOR DEPARTMENT OF PHYSICS GOVERNMENT COLLEGE (AUTONOMOUS) E G DIST RAJAHMUNDRY 533105 Email: ---------- ----------

(57) Abstract :
COMPOSITION AND METHOD FOR THE PREPARATION OF NANOPARTICLES WITH CONTROLLED RELEASE PROPERTIES FOR DRUG DELIVERY APPLICATIONS ABSTRACT The present invention relates to a composition and method for the preparation of nanoparticles with controlled release properties for drug delivery applications. The composition comprises biocompatible polymer matrix nanoparticles encapsulating therapeutic agents, providing a platform for efficient and targeted drug delivery. The biocompatible polymer matrix, such as poly (lactic-co-glycolic acid) (PLGA), ensures biocompatibility and controlled release of the therapeutic agents. The therapeutic agents can include small molecules, proteins, peptides, nucleic acids, or combinations thereof. The method involves dissolving the biocompatible polymer in an organic solvent to form a polymer solution, followed by adding the therapeutic agent to obtain a drug-polymer solution. This solution is then emulsified in an aqueous phase, forming an emulsion. Subsequently, the organic solvent is removed from the emulsion, resulting in the formation of nanoparticles with controlled release properties. The nanoparticles are collected, purified, and optionally modified with targeting ligands for enhanced specificity.

No. of Pages : 15 No. of Claims : 9

FORM 2

THE PATENT ACT, 1970

(39 OF 1970)

&

THE PATENT RULES, 2003

COMPLETE SPECIFICATION

[SEE SECTION 10 AND RULE 13]

TITLE: COMPOSITION AND METHOD FOR THE PREPARATION OF NANOPARTICLES WITH CONTROLLED RELEASE PROPERTIES FOR DRUG DELIVERY APPLICATIONS	
APPLICANTS:	
DR. RAMACHANDRA R K	PRINCIPAL, GOVERNMENT DEGREE COLLEGE, CHODAVARAM, ANAKAPALLE DIST 531036 & HEAD, CRYSTAL GROWTH AND NANOSCIENCE RESEARCH CENTER, GOVERNMENT COLLEGE (AUTONOMOUS) RAJAHMUNDRY E G DIST 533105 Email: drkrcr@gmail.com Phone: 9440328736
DR. P V S S S N REDDY	ASSISTANT PROFESSOR DEPARTMENT OF PHYSICS GOVERNMENT COLLEGE (AUTONOMOUS) E G DIST RAJAHMUNDRY 533105 Email: satya.varam@gmail.com Phone: 9849129557
DR. T K VISVESWARAYA RAO	PRINCIPAL SAS GOVERNMENT DEGREE COLLEGE NARAYANAPURAM W G DIST email: kasitatapudi@gmail.com Phone:9440229928

DR. TIRUPATHI RAO	RESEARCH SCHOLAR DEPARTMENT OF PHYSICS CRYSTAL GROWTH AND NANOSCIENCE RESEARCH CENTER, GOVERNMENT COLLEGE (AUTONOMOUS) RAJAHMUNDRY E G DIST 533105 email: naniphysics20@gmail.com Phone:7416915808
DR. ESUB BASHA SHAIK	ASSISTANT PROFESSOR DEPARTMENT OF PHYSICS GOVERNMENT COLLEGE (AUTONOMOUS) E G DIST RAJAHMUNDRY 533105 Email: esubinau2005@gmail.com Phone:9705964213

The following specification particularly describes the invention and the manner in which it is to be performed

COMPOSITION AND METHOD FOR THE PREPARATION OF NANOPARTICLES WITH CONTROLLED RELEASE PROPERTIES FOR DRUG DELIVERY APPLICATIONS

FIELD OF THE INVENTION

The present invention generally relates to drug delivery applications. More specifically, the invention relates to composition and method for the preparation of nanoparticles with controlled release properties for drug delivery applications.

BACKGROUND OF THE INVENTION

The field of drug delivery has witnessed significant advancements aimed at enhancing therapeutic efficacy and patient compliance. One promising approach involves the use of nanoparticles as carriers for controlled release of therapeutic agents. These nanoparticles provide numerous benefits, such as improved drug stability, targeted delivery, and prolonged release kinetics.

Traditional drug delivery systems often suffer from limitations such as rapid drug degradation, non-specific distribution, and insufficient drug concentrations at the desired site of action. To overcome these challenges, researchers have explored the use of biocompatible polymers to encapsulate therapeutic agents within nanoparticles. This approach offers several advantages, including protection of the drug from enzymatic degradation, controlled release kinetics, and enhanced bioavailability.

Poly(lactic-co-glycolic acid) (PLGA) is a commonly employed biocompatible polymer in nanoparticle-based drug delivery systems. PLGA possesses desirable properties, such as biodegradability, biocompatibility, and tunable release kinetics. By adjusting the ratio of lactic acid and glycolic acid units in the polymer, the degradation rate and release profile of encapsulated drugs can be precisely controlled.

While numerous techniques for the preparation of nanoparticles have been developed, the demand for improved methods with enhanced control over particle size, drug loading, and release kinetics remains. Furthermore, the incorporation of targeting ligands onto the surface of nanoparticles enables specific interactions with target cells, enhancing therapeutic efficacy and minimizing off-target effects.

The controlled-release of drugs, their targeting to specific sites in the human body and the protection of delicate bioactive agents is desirable for efficient drug delivery. One approach towards achieving these ends involves encapsulating bioactive agents in biocompatible nanoparticle matrices. Control is needed over particle size and size distribution, substructure, crystallinity and thickness of encapsulating shell. Among matrix materials, polymers are not approved by the US-FDA for intravenous or pulmonary applications, because of toxic or allergenic end products from their metabolism, while liposomes are limited by low physical stability and high cost. Lipid nanoparticles, made from physiological lipids, like fatty acids and triglycerides, have shown promise in cellular/tissue targeting, sustained/controlled-release, enhancing solubility of poorly water-soluble drugs, and protection of susceptible therapeutic agents for example: Proteins, peptides, and nucleic acid. Their longer circulation time, in the human system, and higher drug payload have been exploited for treating diseases like cancer and brain disorders.

Preparation of nanoparticle drug matrices from processing of delicate, thermolabile materials, like lipids, including fatty acids and triglycerides, and other materials, including waxes and polymers (polylactides, polycyanoacrylates alginates, chitosan and gelatin), needs to address thermal and shear stress imposed, in addition to complexity (multiple steps, use of high or reduced pressure, cryogenic conditions) and cost. For example, current methods of production of lipid nanoparticles can be categorized as top-down methods such as emulsion based techniques (emulsification-solvent-evaporation; solvent emulsification-diffusion; warm w/o/w microemulsion-based techniques), and high pressure homogenization (hot/cold); and bottom-up methods based on supercritical fluids. Spray-drying and an aerosol reactor method are emerging bottom-up techniques, used at temperature of 100-250° C. to process crystalline drugs, polymers and proteins with high melting points.

Therefore, there is a need for a composition and method that allow for the preparation of nanoparticles with controlled release properties for drug delivery applications. Such a system

would offer precise control over the release kinetics, enable targeted delivery to specific cells or tissues, and improve therapeutic outcomes.

In light of these considerations, the present invention provides a novel composition and method for the preparation of nanoparticles with controlled release properties. The invention addresses the limitations of existing drug delivery systems, offering an innovative approach to optimize drug delivery for various applications, including oral, intravenous, transdermal, and inhalation routes.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1: Schematic diagram of the pulse-heat aerosol reactor (PHAR) system used for synthesis of nanoparticle matrices with controlled properties comprised a pulse-heating zone followed by a perforated diluter and an isoaxial sampler. The key variables in aerosol reactor design were maintaining laminar flow of the aerosol and minimizing particle losses by diffusion and sedimentation and provision for imposing pulse-heat with alternate heating and quenching by dilution air.

FIG. 2: Number particle size distributions of nanoparticle aerosol lipid matrices synthesized using stearic acid in cyclohexane solutions at gas temperature of 298 K and 383 K (pulse), of varying concentrations, (a) 0.01 mg·cm−3, (b) 0.1 mg·cm−3, (c) 1 mg·cm−3 and (d) 10 mg·cm−3, measured using scanning mobility particle sizer. The mobility diameters ranged from 47-183 nm with a unimodal distribution and geometric standard deviation of 1.5-1.8.

DETAILED DESCRIPTION OF THE INVENTION

The present invention discloses a composition and method for the preparation of nanoparticles with controlled release properties for drug delivery applications. The composition comprises biocompatible polymer matrix nanoparticles encapsulating therapeutic agents, while the method involves a series of steps to achieve efficient and targeted drug delivery.

The nanoparticles in the composition are constructed using a biocompatible polymer matrix, with poly(lactic-co-glycolic acid) (PLGA) being a preferred choice. PLGA offers excellent biocompatibility, biodegradability, and versatility in controlling the release kinetics of encapsulated therapeutic agents. Other biocompatible polymers may also be used in combination with or as alternatives to PLGA, depending on the specific requirements of the drug delivery system.

The therapeutic agents encapsulated within the nanoparticles can include a wide range of substances, such as small molecules, proteins, peptides, nucleic acids, or combinations thereof. The selection of the therapeutic agent depends on the desired application and targeted disease or condition.

The method for preparing the nanoparticles with controlled release properties involves several key steps. First, a biocompatible polymer, such as PLGA, is dissolved in an organic solvent, which can be dichloromethane, chloroform, ethyl acetate, or a combination thereof. The dissolution process results in the formation of a polymer solution.

Next, the therapeutic agent is added to the polymer solution, forming a drug-polymer solution. The therapeutic agent can be dissolved or dispersed within the solution, depending on its solubility and desired release profile. The drug-polymer solution is then mixed thoroughly to ensure uniform distribution of the therapeutic agent within the polymer matrix.

To form nanoparticles, the drug-polymer solution is emulsified in an aqueous phase. The aqueous phase may contain a surfactant or emulsifying agent to stabilize the emulsion. Emulsification can be achieved by various methods, such as sonication, homogenization, or microfluidization. The emulsification process generates a dispersion of droplets containing the drug-polymer solution within the aqueous phase, resulting in an emulsion.

Subsequently, the organic solvent is removed from the emulsion to obtain solid nanoparticles with controlled release properties. This removal process can be accomplished through evaporation, extraction, or a combination of methods. The choice of solvent removal technique depends on factors such as the nature of the solvent, desired particle size, and scalability.

After the removal of the organic solvent, the nanoparticles are collected and purified to eliminate any residual solvent or impurities. Purification can be performed using techniques such as

centrifugation, filtration, or dialysis, ensuring the production of high-quality nanoparticles suitable for drug delivery applications.

In addition to the core steps, the method can also involve optional modifications to the surface of the nanoparticles. This can be achieved by attaching targeting ligands to enhance the specificity of drug delivery. Targeting ligands can include antibodies, peptides, aptamers, or other molecules that recognize specific receptors or markers expressed on target cells or tissues.

The resulting nanoparticles exhibit controlled release properties, allowing for sustained drug delivery over a predetermined period of time. The release kinetics can be precisely controlled by adjusting the properties of the polymer matrix, including its molecular weight, composition, and degradation rate. The composition and method provide versatility in tailoring the release profile to match the therapeutic needs of different drugs and diseases.

The nanoparticles prepared using this composition and method can be formulated into a drug delivery system by incorporating them into a pharmaceutically acceptable carrier. Such carriers can include gels, creams, or injectable formulations, depending on the intended route of administration and desired application.

The following specific example is not intended to be limitive but only illustrative.

FIG. 1, a prototype pulse-heat aerosol reactor (PHAR) was designed and fabricated for control of particle properties through aerosol dynamics. The pulse-heating zone has an internal diameter and heated length of 38 mm and 80 mm, respectively. The aerosol flow rate was fixed at 3 L·min-1, with a flow Reynolds number of ˜109 and a pulse time of one second. Stokes number for atomized droplets (mean diameter 300 nm) flowing in the reactor is in the order of 10−5, implying that droplets follow gas streamlines and do not undergo impaction. Evaporating droplets flowing along with the gas streamlines are expected to undergo negligible drop breakup, internal solute circulation/motion and asymmetric solute concentration distribution. Thus the droplet evaporation process is expected to be uniform leading to isotropic particle properties. In the prototype PHAR, heating was provided to the pulse-heat zone to attain a gas temperature of (low and high 383±1 K) using heating tape of 250 W. Gas temperature in the pulse-heat zone was measured using a platinum resistance temperature detector (RTD, PT100) interfaced with a digital controller. The magnitude of temperature was fixed based on the required evaporation rate to produce particles of

different morphology and size, as described in a following section. In order to quench the aerosol, rapid cooling was applied following the pulse-heat zone, by diluting with dry nitrogen (298 K), with the ratio of 1:11, in a perforated-wall diluter of stainless steel (inner diameter 38 mm and length 250 mm). To ensure uniform and complete mixing of aerosols with dilution gas, the perforated-wall diluter comprised of 400 holes of 2 mm diameter each drilled at regular intervals upto a length of 100 mm. The diluted aerosol flow rate is 33 L·min−1, with a flow Reynolds number of ˜1199. The total loss of particles due to diffusion and sedimentation, in the PHAR, is estimated to be less than 1%.

Solutions of encapsulating agents like lipids (e.g. but not limited to stearic acid, palmitic acid, trimyristin), biopolymers (e.g. but not limited to poly-lactic-co-glycolic acid (PLGA), polymethacrylic copolymers), with surface active additives like sodium cholate, phosphatidylcholine and selected drug/s in organic solvents (e.g. but not limited to cyclohexane, chloroform and dichloromethane).

The disclosure can be employed as a single-step method for production of nanoparticle matrices, with controlled diameter (50-200 nm), morphology or structure (solid versus shell), crystallinity and controlled-release properties. To fix operating conditions for evaporation rate control in the PHAR, a stationary drop model was developed (Shetty et al. 2011). The difference in required evaporation rate to achieve solid versus shell morphology was estimated to be around a factor of five. Compute evaporation rates of stearic acid in cyclohexane solution drops (300 nm mean droplet diameter) of varying concentrations (0.01-10 mg·cm−3) led to at gas temperature control at 298 K and 383 K (pulse).

Applications Include the Following:

Production of nanoparticle lipid matrices containing anticancer drugs for intravenous cancer chemotherapy for enhanced penetration and retention effects in tumor tissues, leading to improved efficacy of treatment.

Production of nanoparticle lipid matrices for controlled-release and pulmonary targeting applications. Drugs of interest may include anti-cancer drugs (e.g. Gefitinib), anti-diabetics (e.g. insulin), anti-tubercular drugs, therapeutics based on biotechnology derived products (like

proteins, peptides, nucleic acids, vaccines, antibiotics) for treatment of various diseases and disorders.

Example Illustrating the Disclosure

Experiments were done to produce stearic acid nanoparticles, in PHAR, with controlled size and morphology at varying evaporation rates. The pulse-heat aerosol reactor (PHAR) system used to study effect of pulse-heat on synthesis of nanoparticle matrices (FIG. 4) comprises of a collision-type air jet atomizer. The atomization device could also comprise of any device based on ultrasonic, electro spray, evaporation-condensation or FEAG principle of aerosol generation. The PHAR is designed with a pulse-heat zone, wherein a heat pulse of controlled temperature (heating element) and duration (flowrate of gas) is applied to the droplet aerosol to control the rate of evaporation. A perforated-wall aerosol diluter is provided to quench the temperature and aerosol dynamics mechanisms immediately after the pulse-heating. A scanning mobility particle sizer was placed downstream for measurement of mobility diameter. Any other nanoparticle size distribution measurement device including, ELPI, hypersonic impactor can be used in-lieu of or in addition to the SMPS. The standard upstream pressure of the atomizer was 35 psig. The solution, of lipid in a selected organic solvent (stearic acid in cyclohexane of varying concentrations, 0.01 mg·cm−3, 0.1 mg·cm−3, 1 mg·cm−3 and 10 mg·cm−3), was fed with a syringe pump at a flow rate of 0.6 mL/min. The resulting atomized droplets were suspended in a nitrogen flow through the PHAR, where droplet evaporation at a controlled rate, followed by quenching of aerosol dynamics was used to produce nanoparticles with controlled size, morphology and crystallinity.

Stearic acid nanoparticle matrices of mobility diameters of 47-183 nm, with a unimodal size distribution of geometric standard deviations (GSD) (1.5-1.8), were obtained in PHAR by fixing the gas temperatures, at 298 K and 383 K (pulse), to obtain the varying evaporation rates. For a given concentration, stearic acid nanoparticles of smaller mobility diameters were synthesized at lower evaporation rates, while nanoparticles with larger mobility diameters were synthesized at higher evaporation rates. The differences in the mean mobility diameters of stearic acid nanoparticles synthesized at higher evaporation rates, using larger concentrations (1 mg·cm −3 and 10 mg·cm−3), were statistically significant (at the 95% confidence level; P=0.002, by t-test) than those synthesized at lower evaporation rates (Table 1). TEM images of nanoparticle matrices (FIG. 3 a), synthesized at 298 K using stearic acid in cyclohexane solution of 10 mg·cm−3, showed

solid particles of ˜150 nm diameters with smooth spherical shape. On contrary, TEM images of nanoparticle matrices.

This disclosure therefore relates to a single step method for producing thermolabile nanoparticles of lipids and biopolymers with controlled diameter ranging from 50 to 500 nm which comprises the steps of pumping as aerosol of a precursor solution of lipid/biopolymers in an organic solvent, through a pulse-heat aerosol reactor to control droplet evaporation followed by quenching to produce nanoparticles of controlled size, morphology and crystallinity.

Mean mobility diameter of nanoparticles thus produced will be directly proportional to the rate of evaporation and concentration of the lipid in solution. Higher evaporation and higher concentration result in larger mobility particle size and crystallinity.

This disclosure also relates to a system for carrying out the above method which comprises a pulse-heating zone, connected to a perforated diluter and isoaxial sampler, said system maintaining laminar flow of aerosol introduced there into through an atomizer and said perforated diluter having means to supply a gas there into in a regulated manner.

I/WE CLAIM:

1. A composition for drug delivery comprising:
    - Nanoparticles comprising a biocompatible polymer matrix; and
    - A therapeutic agent encapsulated within said nanoparticles.

2. The composition of claim 1, wherein said biocompatible polymer matrix comprises poly (lactic-co-glycolic acid) (PLGA).

3. The composition of claim 1, wherein said therapeutic agent is selected from the group consisting of small molecules, proteins, peptides, nucleic acids, and combinations thereof.

4. A method for preparing nanoparticles with controlled release properties, comprising the steps of: a. Dissolving a biocompatible polymer in an organic solvent to form a polymer solution; b. Adding a therapeutic agent to said polymer solution to form a drug-polymer solution; c. Emulsifying said drug-polymer solution in an aqueous phase to form an emulsion; d. Removing the organic solvent from said emulsion to obtain nanoparticles with controlled release properties; and e. Collecting and purifying said nanoparticles.

5. The method of claim 4, wherein said organic solvent is selected from the group consisting of dichloromethane, chloroform, ethyl acetate, and combinations thereof.

6. The method of claim 4, wherein said aqueous phase comprises a surfactant to stabilize the emulsion.

7. The method of claim 4, further comprising the step of modifying the surface of said nanoparticles with a targeting ligand.

8. The method of claim 4, wherein said removing of the organic solvent is achieved by evaporation, extraction, or a combination thereof.

9. The method of claim 4, wherein said nanoparticles exhibit a controlled release profile of said therapeutic agent over a predetermined period of time.

COMPOSITION AND METHOD FOR THE PREPARATION OF NANOPARTICLES WITH CONTROLLED RELEASE PROPERTIES FOR DRUG DELIVERY APPLICATIONS

ABSTRACT

The present invention relates to a composition and method for the preparation of nanoparticles with controlled release properties for drug delivery applications. The composition comprises biocompatible polymer matrix nanoparticles encapsulating therapeutic agents, providing a platform for efficient and targeted drug delivery. The biocompatible polymer matrix, such as poly (lactic-co-glycolic acid) (PLGA), ensures biocompatibility and controlled release of the therapeutic agents. The therapeutic agents can include small molecules, proteins, peptides, nucleic acids, or combinations thereof. The method involves dissolving the biocompatible polymer in an organic solvent to form a polymer solution, followed by adding the therapeutic agent to obtain a drug-polymer solution. This solution is then emulsified in an aqueous phase, forming an emulsion. Subsequently, the organic solvent is removed from the emulsion, resulting in the formation of nanoparticles with controlled release properties. The nanoparticles are collected, purified, and optionally modified with targeting ligands for enhanced specificity.

COMPLETE SPECIFICATION - DRAWINGS

Sheet No. 1

Total No. of Sheets. 2

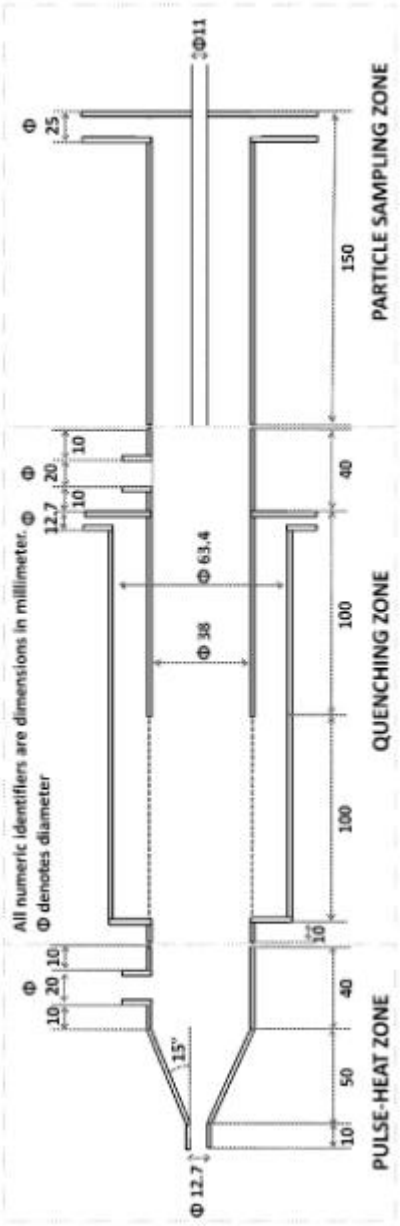

FIG. 1

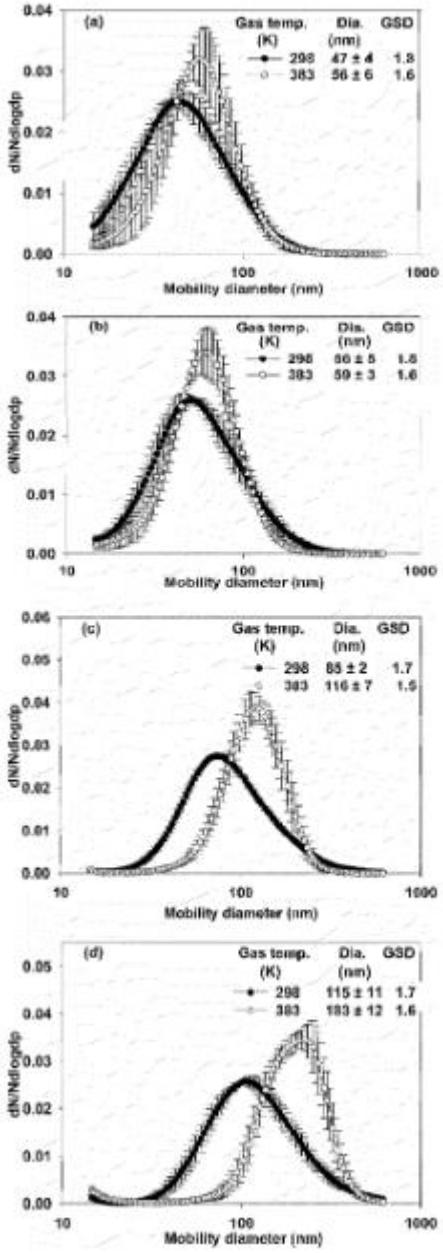
(a)
Gas temp. (K)
Dia. (nm)
GSD
298 47 ± 4 1.8
383 56 ± 6 1.6
dN/dlogdp
Mobility diameter (nm)
(b)
Gas temp. (K)
Dia. (nm)
GSD
298 56 ± 5 1.8
383 59 ± 3 1.6
dN/dlogdp
Mobility diameter (nm)
(c)
Gas temp. (K)
Dia. (nm)
GSD
298 85 ± 2 1.7
383 116 ± 7 1.5
dN/dlogdp
Mobility diameter (nm)
(d)
Gas temp. (K)
Dia. (nm)
GSD
298 115 ± 11 1.7
383 183 ± 12 1.6
dN/dlogdp
Mobility diameter (nm)

FIG. 2