01 Apr 2007

NANOPARTICLES FOR ENHANCED DELIVERY OF CHEMOTHERAPEUTICS

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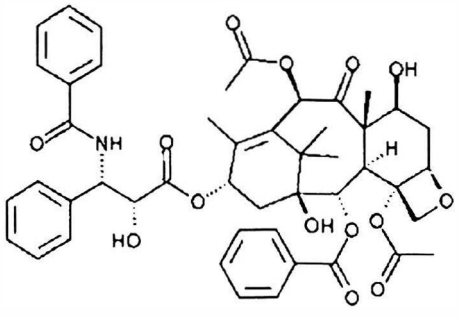
ABSTRACT

Delivery of the anticancer drug paclitaxel (commercially known as Taxol®) is difficult due to its limited solubility in aqueous media. This study proposes a novel bubble bursting technique to generate nanoparticles of the chemotherapeutic in an effort to decrease potential side effects and improve the bioavailability of hydrophobic drugs. The bubble bursting apparatus will be used to produce nanoparticles of a biodegradable polymer, poly(lactide-co-glycolide) (PLGA), as carriers for paclitaxel. The dissolved paclitaxel in this biodegradable polymer matrix will be released at a controlled rate for a more efficient delivery of the drug throughout the body.

INTRODUCTION

The design of new pharmaceuticals is constrained by the need for efficient delivery of the drug throughout the body. Typically, the solubility of a potential drug candidate must fall in a critical range – hydrophilic enough to dissolve in physiological fluids and be carried throughout the body, yet hydrophobic enough to pass through the lipid bilayer that encloses cells. Drugs such as paclitaxel (Figure 1) are promising pharmaceuticals but are difficult to administer due to their limited aqueous solubility.

Currently, hydrophobic drugs such as paclitaxel are emulsified and given intravenously. This approach, however, has several disadvantages with the main one being an allergic response to the emulsifier that occurs in some patients. This project aims to improve the bioavailability of hydrophobic drugs through the use of nanoparticulate formulations. Using a novel bubble bursting technique, we are producing nanodroplets containing the copolymer. These droplets, upon drying, are easily dispersible in aqueous media, precluding the need for an emulsifying agent.



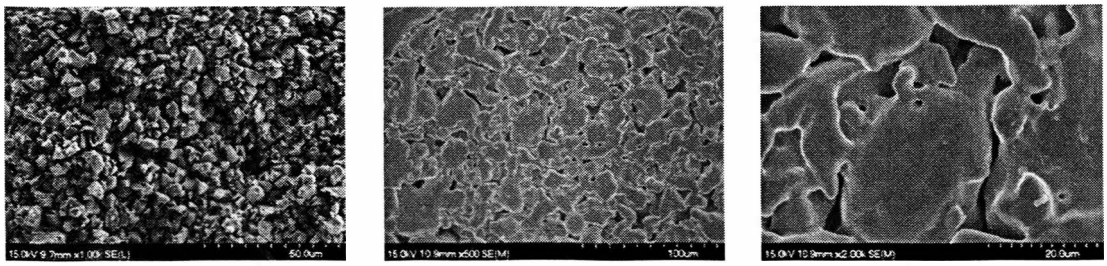
PROJECT DESCRIPTION

This project approaches delivery of paclitaxel by utilizing a bubble bursting technique. Our goal is to produce nanoparticles (particles on the scale of 10^{-9} m) to improve pharmaceutical products. Porous disks (Figure 2) with surface morphologies suitable for the formation of nanoparticles are being utilized. The schematic (Figure 3) below illustrates our method of bursting bubbles to synthesize nanoparticles.

The inlet air stream is monitored by a pressure regulator as it flows through a porous disk creating bubbles with diameters relative to the disk pores. The bubbles rise through a solution of ethyl acetate containing the desired concentrations of the copolymer carrier and drug and burst into smaller droplets at the periphery of the liquid. The droplets then rise up the drying tube and are collected in a 25mL midget impinger (from Ace Glass, Inc.) containing distilled water. Upon entering the water, the ethyl acetate diffuses from the droplet into the water leaving the copolymer particles dispersed in the water.

The initial apparatus (Figure 4) involved the collection of particles on filter paper at the top of the drying tube, which could be dried more thoroughly in a vacuum oven.

However, this previous design was modified to improve the method of particle collection.



SEM (1000x): Glass disk, SEM (500x): Stainless Steel SEM (2000x): Stainless Steel

Figure 2. Scanning Electron Micrographs of Porous Disks

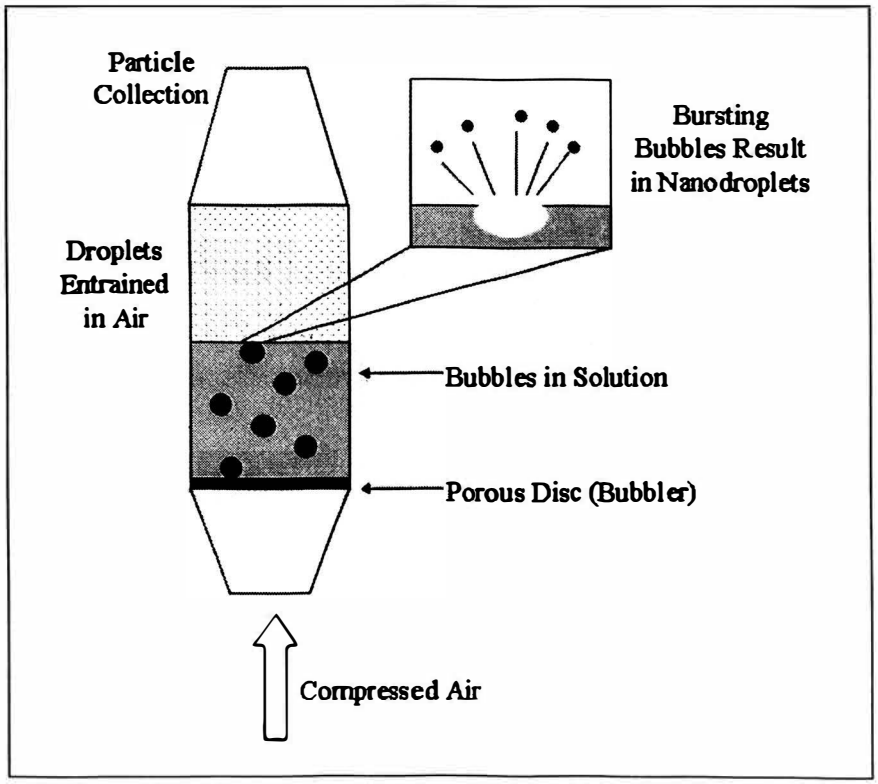


Figure 3. Schematic of Bubbler

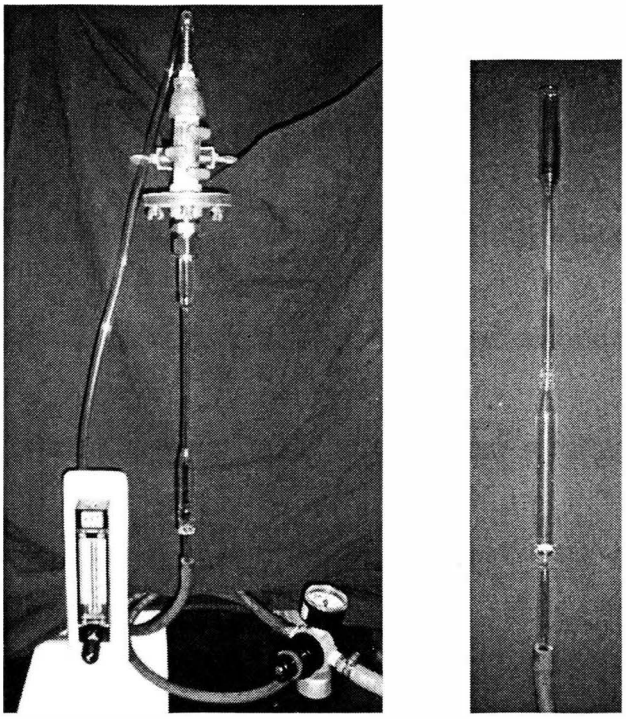


Figure 4. Bubble Bursting Apparatus

METHODS

Nanoparticles of biodegradable polymers will be synthesized as carriers for paclitaxel by bursting bubbles through a solution of poly(lactide-co-glycolide) (PLGA) copolymer dissolved in ethyl acetate. PLGA (Figure 5) was chosen because of its medical applications. This copolymer is both biodegradable and biocompatible. The percentage of polylactide and polyglycolide can be varied in order to control the rate at which it biodegrades. Degradation of the copolymer matrix would permit the process of sustained drug release (Figure 6). Paclitaxel contained within a biodegradable polymer matrix of PLGA would maintain a constant release of the drug after being given to the patient without a negative immune response. Ethyl acetate was chosen because of its low surface tension, its ability to dissolve PLGA, and the relative ease of removing it from the copolymer matrix. Inert nitrogen gas is used for the inlet air stream due to the flammable limits of ethyl acetate.

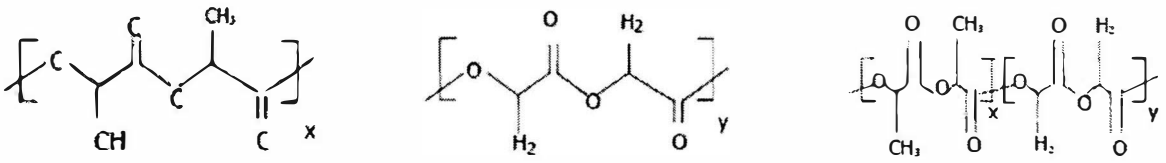


Figure 5. Chemical Structures of Biodegradable Polymers

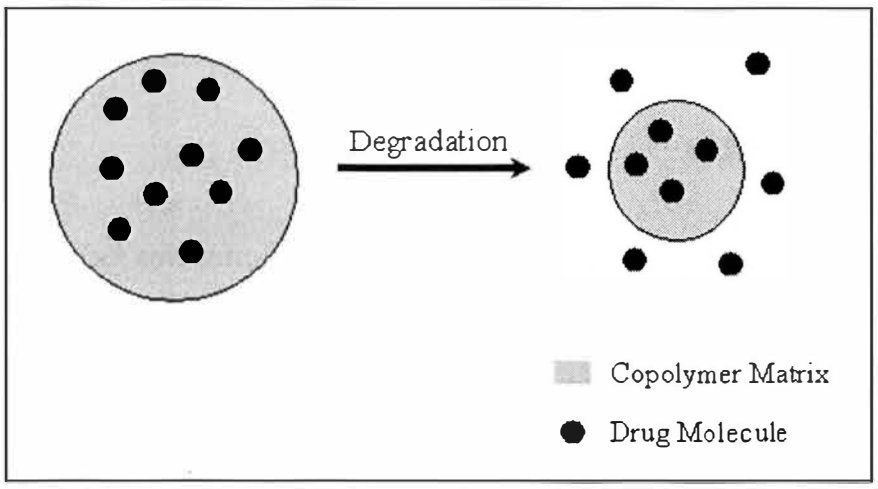


Figure 6. Degradation of Copolymer Matrix

CONCLUSION

Currently, tests are being run with the bubble bursting apparatus by utilizing the method described above. Once we are able to generate nanoparticles of the biodegradable copolymer reproducibly, we will encapsulate nanoparticles of a model drug in the copolymer matrix before testing with paclitaxel. The current method of delivering paclitaxel to the body is inefficient and has adverse effects on the patient because of the emulsifier that must be used. The method being proposed in this research would eliminate the use of an emulsifying agent and deliver the anticancer drug more effectively by sustained release.

ACKNOWLEDGEMENTS

Support for this research was provided by the UMR Opportunities for Undergraduate Research Experiences (OURE) Program. I would also like to thank my advisor, Dr. David Henthorn, and co-advisor, Dr. Judy Raper, for their guidance and encouragement throughout the project.

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