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DRUG DELIVERY WITH POLYMERS AND POLYMERIC NANOPARTICLES: SYNTHESIS AND CHARACTERISATION

Dwivedi Bandana
Deptt of Chemistry T.D.P.G.College Jaunpur (U.P)

ABSTRACT

Introduction: To treat, image, diagnose, or prevent illness in humans, drug delivery is the administration of a therapeutically active chemical.

Aim of the study: the main aim of the study is Drug delivery with polymers and polymeric nanoparticles: synthesis and characterisation

Material and method: Acros Organics Belgium were contacted for the acquisition of N-isopropylacrylamide, which was then recrystallized from n-hexane and kept at 4 degrees Celsius until usage.

Conclusion: For the purpose of transporting proteins, NIPAM-VP microgel nanoparticles were produced and purified.

INTRODUCTION

1.1 OVERVIEW

To treat, image, diagnose, or prevent illness in humans, drug delivery is the administration of a therapeutically active chemical. Multiple methods, including both traditional and cutting-edge controlled systems, exist for accomplishing this therapeutic objective. Newer controlled release technologies are more effective than older methods of dosing the same substance. New delivery methods are being developed to keep the medicine inside its therapeutic window while still delivering the therapeutic component to the site of action at the desired pace. Polymeric carriers, which may protect the medication until it reaches the site of action and then adjust its release to achieve a desired release profile, are often used as delivery agents for this purpose. It is possible to program these delivery systems to react intelligently to certain physiological or biological cues. Chapter 4 of the present thesis details the fabrication of a temperature-dependent polymer carrier, and from this work, an effort has been made to assess the viability of the produced and optimized delivery carrier for pharmaceutical usage. In this section, we analyze the kinetic release of the entrapped drug moiety from the formulation by conducting dissolving studies. To this end, we have chosen to conduct a kinetic release research using Bovine Serum Albumin (BSA) as a model medication.

LITERATURE REVIEW

Kendre, Prakash & Kayande (2022) The injection of drugs via the nasal passages to the brain is gaining popularity as a means of treating neurological disorders. The blood-brain barrier (BBB) prevents the entry of most substances into the brain via more conventional routes. This prevents reaching the necessary therapeutic concentration in the brain, resulting in a suboptimal response. Intranasal drug administration is an attractive method since it avoids first-pass metabolism and crosses the blood-brain barrier. It lessens the medicine's systemic effects while decreasing the dosage. A nanoparticulate medication delivery approach improves nasal penetration in comparison to standard drug delivery platforms. Using a high-quality carrier (polymers) makes it easier to create nanoparticles

for nasal-to-cerebral delivery. This article discusses the many methods for producing polymeric nanoparticles, as well as techniques and tactics for enhancing the efficacy of medication transport from the nasal cavity to the brain. Researchers are testing a number of nanoparticles designed specifically for the treatment of neurological disorders by delivering them via the nasal passages and into the brain.

Zielińska, Aleksandra & Carreiró (2020) Sized between 1 to 1 000 nm, polymeric nanoparticles (NPs) may have active chemicals encapsulated inside or surface-adsorbed onto the polymeric core. In this context, "nanoparticle" refers to both nanocapsules and nanospheres, the two most common types of nanoparticles. Targeted medication delivery using polymeric NPs for the treatment of several disorders has shown promising results. Methods for producing and characterizing polymeric NPs, as well as the association efficiency of the active ingredient to the polymeric core, and in vitro release processes, are discussed in this study. We also talk about the toxicity and ecotoxicology of nanoparticles, since the safety of nanoparticles is a major concern.

Acar, Serap & Katmıs, Aslı & Fide (2018) In this article, we take a close look at the various strategies for creating and characterizing polymeric nanoparticles. Particles of macromolecular compounds that are less than 100 nm in size are considered nanoparticles. Nanoparticles are employed for a wide variety of biological purposes (bio-sensing, biological separation, molecular imaging, anticancer treatment, etc.). Nanoscale modifications provide significantly different properties and capabilities than their bulk counterparts. These materials obtain a plethora of new properties because to their high volume/surface ratio, enhanced resolution, and capacity for many uses.

Amgoth, Chander & Dharmapuri, Gangappa (2016) The synthesis of an AB-type block copolymer from L-Alanine (L-Ala) and polycaprolactone (PCL) has resulted in the development of novel, biocompatible polymeric nano size cuboid particles and spherical nanoporous capsules. Particle morphology of dispersed (L-Ala)-b-(PCL) is solvent-dependent. When dispersed in ethanol, block copolymer (BCP) produces spherical nanoporous capsules, whereas in water, it produces cuboid particles. To improve anticancer drug (Imatinib-ITM) loading and regulated and sustained release for therapeutics in cancer treatment, we have constructed nano (200 nm) size polymer (cubic and spherical shaped) capsules. Then, without the use of surfactants or precursors, BCP was synthesized. Self-assembly of (L-Ala)-b-(PCL) is linked to the creation of cubic and spherical polymeric capsules owing to the presence of active functional groups. Cancerous (K562-leukemia blood cancer) cells have been targeted with the use of spherical nanoporous capsules containing nanoformulations designed to eradicate them. After incubation for 24 hours in a CO2 incubator, these nanoformulations showed promise as a means of loading nanomedicine that might test for the inhibition and rupture of cancer cells.

Ramalho, Maria & Pereira, M. (2016) The purpose of this paper is to provide a laboratory exercise designed to teach advanced undergraduates to nanotechnology. Poly (lactic-co-glycolic acid) (PLGA) nanoparticles were synthesized by students using either a single emulsion-solvent evaporation technique or a double emulsion-solvent evaporation approach. In addition, the students conducted a physicochemical assessment of the NPs they had generated by measuring their hydrodynamic size and zeta potential using Dynamic and Electrophoretic Light Scattering, respectively. Twenty-four graduate students were able to complete the trials in two sessions of 180 minutes each.

METHODOLOGY

3.1 Synthesis and Development of the Drug Formulation

3.1.1 Materials

Acros Organics Belgium was contacted for the acquisition of N-isopropylacrylamide, which was then recrystallized from n-hexane and kept at 4 degrees Celsius until usage. Before beginning polymerization, we imported freshly distilled vinyl pyrrolidone (VP) from Lancaster, USA. Sigma Chemicals (St. Louis, MO, USA) supplied the N, N-methylenebisacrylamide, while SRL (Mumbai, India) supplied the ammonium persulphate. Water that has been distilled twice in the United States. SIGMA's 12kD MWCO dialysis membrane was purchased. We ordered some Bovine Serum Albumin from CDH (India).

3.1.2 Methods

A. Synthesis of NIPAM-VP Microgel Particles

Microgel particles (MG1) made of NIPAM-VP have been manufactured according to the method described and reported in this thesis. The reaction was conducted briefly at 70oC with a constant 9:1 ratio of NIPAM to VP monomers. The microgels have undergone rigorous dialysis to eliminate any remaining monomers or initiator. Finally, the lyophilized powder form of the microgel particles (MG1) needed for research has been achieved.

B. Formulation of Bovine Serum Albumin in NIPAM-VP microgel particles (MGI)

Microgel particles MG1 include bovine serum albumin. The model protein, BSA, was incubated with the microgel particles (MG1) for 4 days at 4oC to achieve the swelling equilibrium, and the resulting mixture was weighed and added to double-distilled water. After being loaded, microgel particles are dialyzed for two to three days to remove any residual free BSA in the dispersion or that has been adsorbed to the particles' surfaces. Figure 3.1 shows the lyophilized powder that was obtained after dialysis of the formulation.

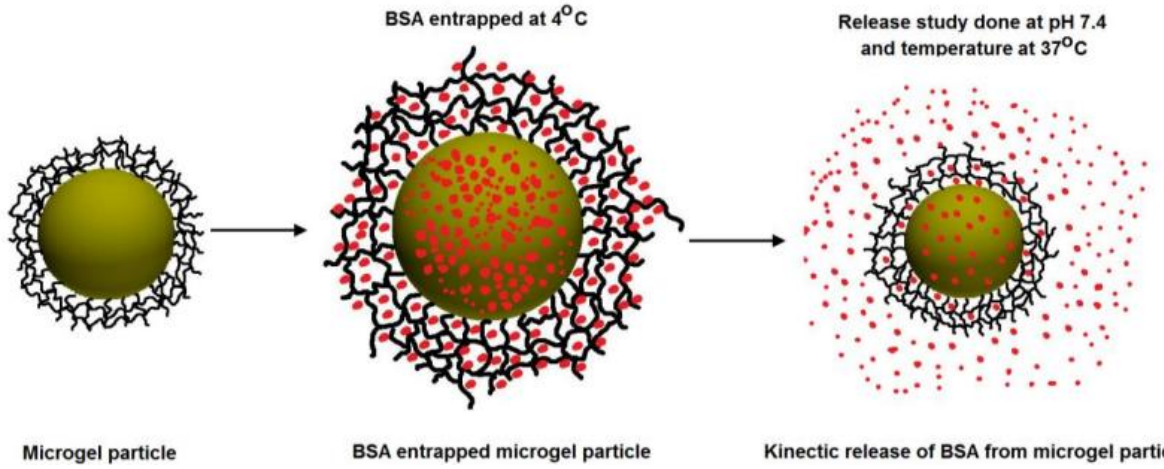


Figure 3.1 Microgel particle MG1 encapsulation of bovine serum albumin with respect to temperature

C. Procedure for entrapment efficiency

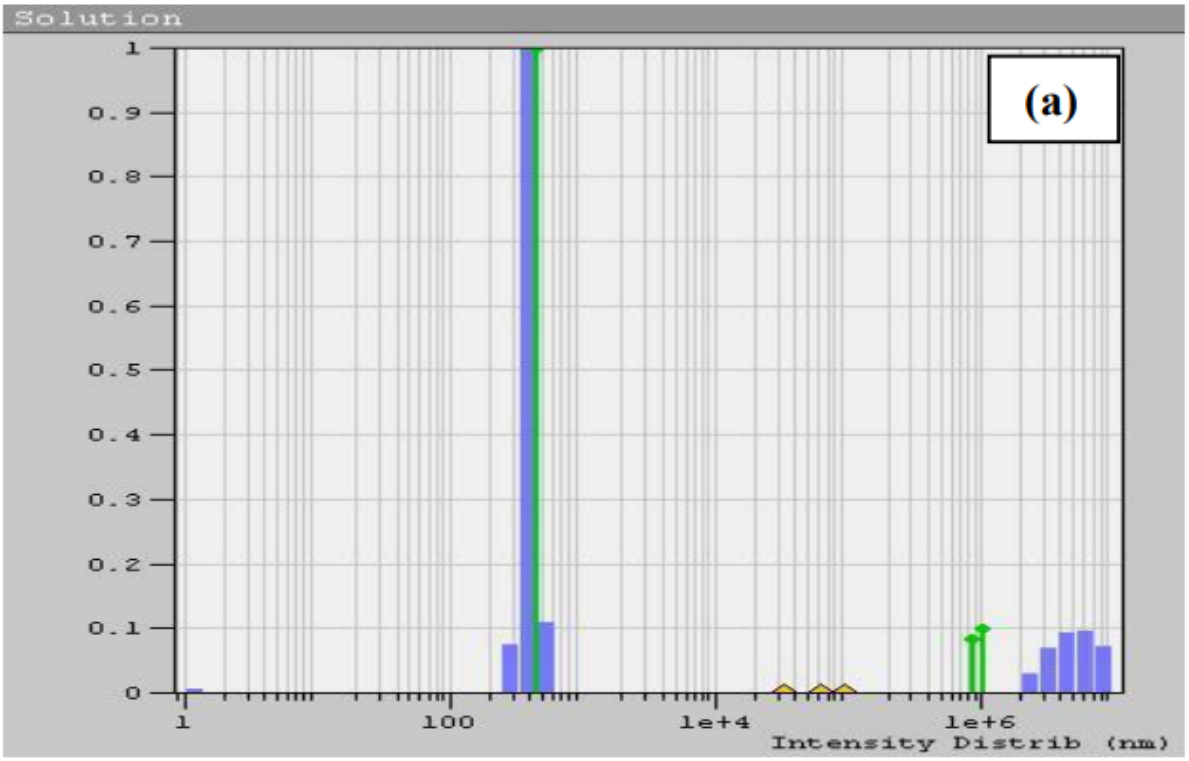
The lyophilized formulation containing BSA was diluted in 50 mL of methanol at a concentration of 10 mg, as determined by precise weighing. Sonicating the samples for 1 hour while intermittently shaking

them, then centrifuging at 10,000 rpm for 10 minutes has been used to remove the entrapped BSA in the lyophilized product. The methanol has been used to suitably dilute the supernatant. Using a UV-Vis spectrophotometer, we measured the absorbance of BSA at 278 nm and thereby determined the entrapment effectiveness.

RESULTS

4.1 QELS Analysis of the Microgel Particles

The size of the microgel particles (MG1) generated from NIPAM-VP co-polymer has been analyzed using a Quasi Elastic Light Scattering device. Quantitative energy-loss spectroscopy information for microgel MG1 was collected in double-distilled water at a concentration of 10 mg microgel particles per 10 mL of water. After gentle sonication, the microgel samples have been incubated for 24 hours at the specified temperatures. Analysis of the QELS data showed that the NIPAM-VP co-polymer MG1 exhibited temperature-dependent behavior. Important to this study, the size analysis was performed at 25 degrees Celsius, 35 degrees Celsius, and 37 degrees Celsius. Particles of MG1 are typically 400 nm in diameter at 25°C (Figure 4.1a), 339 nm at 35°C (Figure 4.1b), and 38 nm at 37°C (Figure 4.1c). Particle size study revealed that at temperatures between 25 and 37 degrees Celsius, the MG1 microgel particles gradually became more monodisperse. From 25 to 35 degrees Celsius, a gradual shrinkage in microgel particle size was observed; however, this trend reversed sharply at 37 degrees Celsius, when microgel particles shrank to a size of 38 nm, definitively identifying this temperature as the Least Critical Solution Temperature of the microgel particles (MG1). As the temperature rose, the particles shrank and the polydispersity fell.



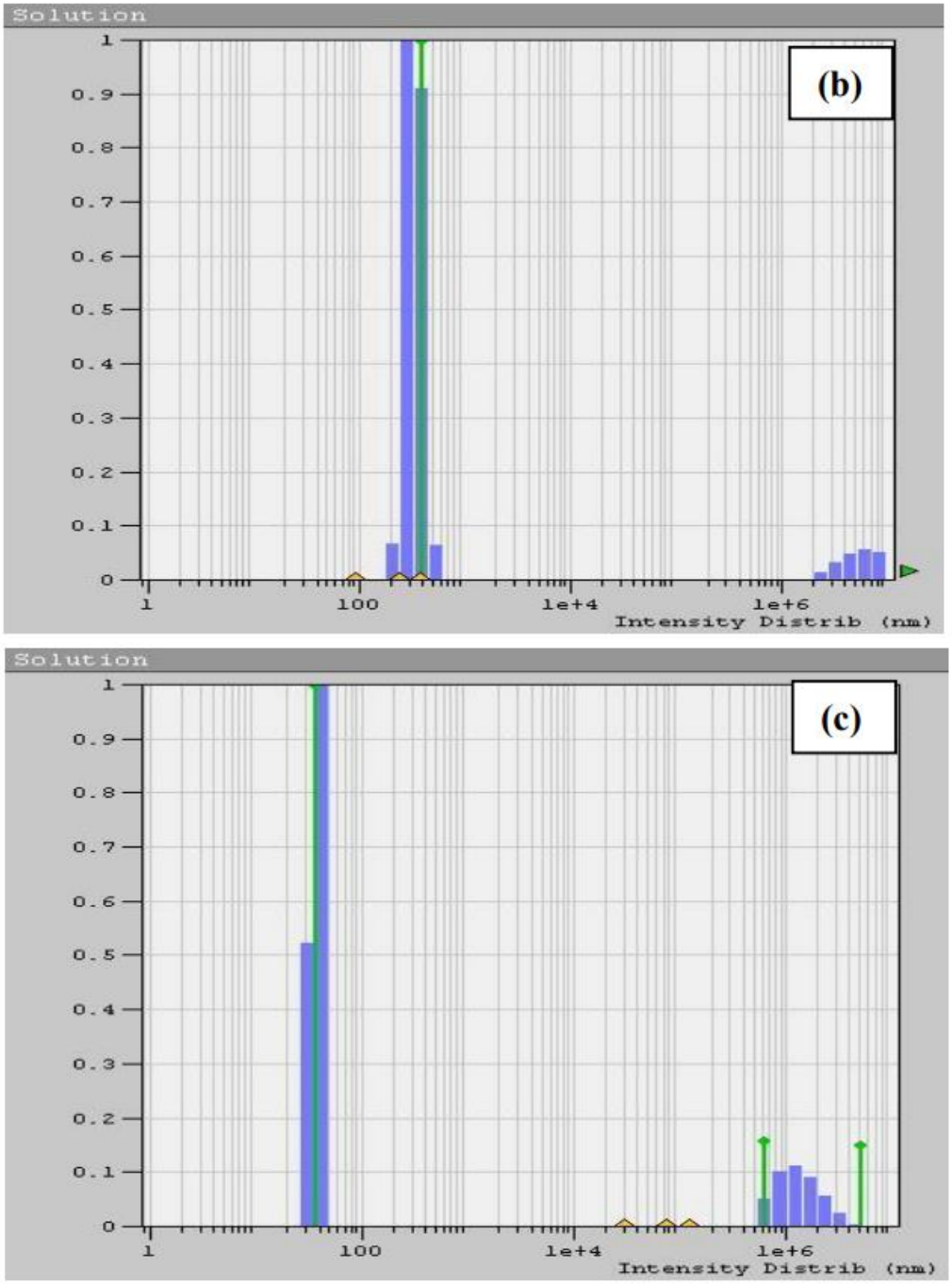


Figure 4.1 QELS Data for Microgel Particles MGI at different temperatures (a) Particle size at 25°C (400 nm) (b) Particle size at 35°C (339 nm) (c) Particle size at 37°C (39 nm).

4.2 Entrapment efficiency

The BSA in the formulation has an 84% weight-based entrapment efficiency.

4.3 Study of the Release Kinetics of Model Protein BSA

4.3.1 Calibration Curve of BSA

A calibration curve for the model drug must be established before the release data can be analyzed. The UV range of 400 nm - 200 nm has been documented using a calibration curve for the model protein BSA at various concentrations, including 250 ppm, 500 ppm, 1000 ppm, and 1500 ppm. Absorption maxima

for BSA may be seen in the calibration curve at at 276nm (Figure 4.2). Regression analysis has been used to further process the instrument's data. Beer-Lambert law is supported by the fact that the slope of the regression line, r2, is close to 1 (Figure 4.3).

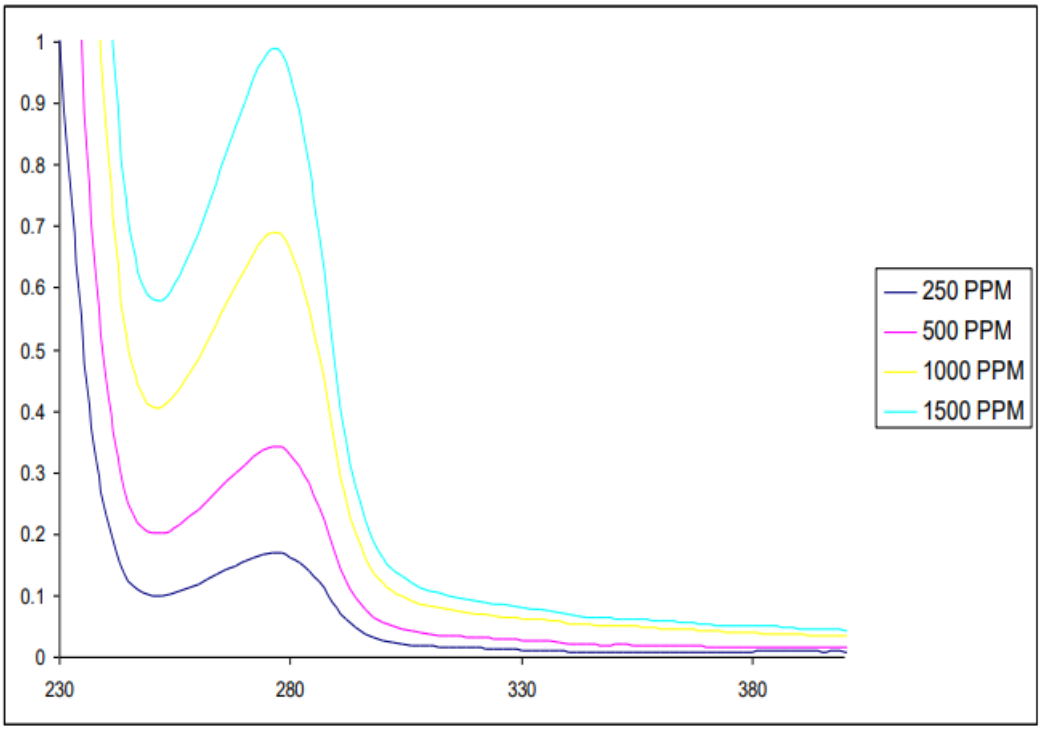


Figure 4.2 Phosphate BSA in a pH 7.4 buffer, as measured by an overlaid UV spectrum

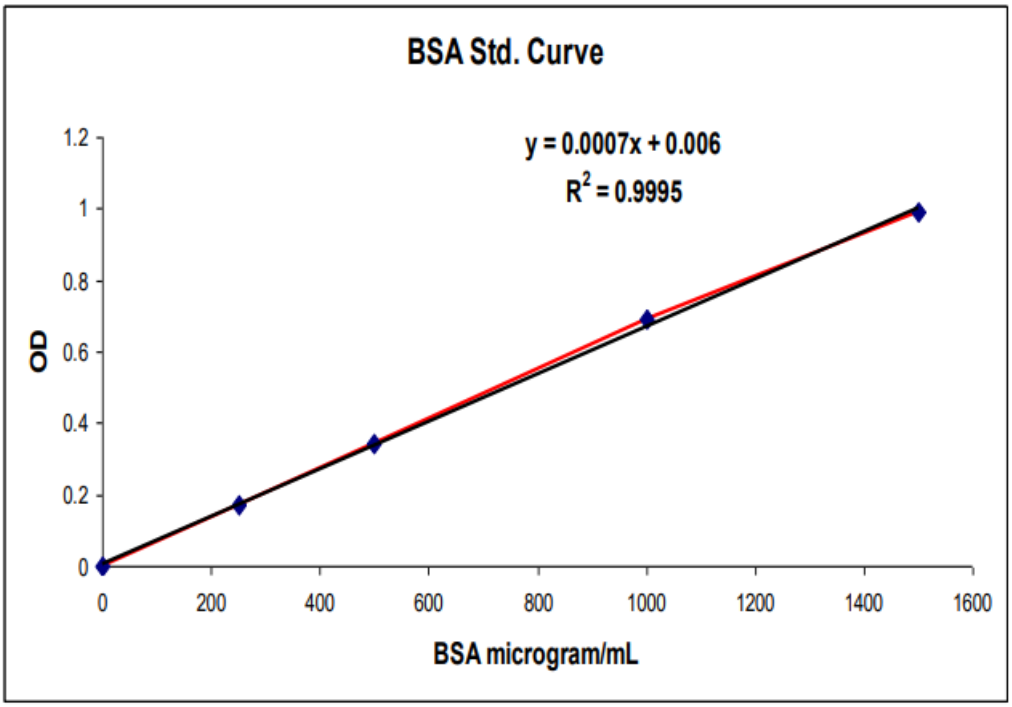


Figure 4.3 Calibration curve for BSA in buffer pH 7.4

4.3.2 Drug Release Kinetics

Figure 4.4 displays the dissolution data for BSA drug release as a concentration (mg) vs. time (h) plot, which may be used to anticipate when the drug will be completely released. In order to get a straight

line in accordance with the goodness of fit parameter of different release models, the provided data has been further evaluated by regression analysis. Table 4.1 below summarizes all the graphed data.

Table 4.1 Microgel particle formulation controlled by BSA release parameters

Zero Order		First order		Higuchi		Hixson-Crowell	
$_r2$	k_o (h^{-1})	$_r2$	k_1(h^{-1})	$_r2$	k_H ($h^{-1/2}$)	$_r2$	kHC ($h^{-1/3}$)
0.9909	0.5249	0.8355	-0.013	0.9875	7.0091	0.9716	-18.579

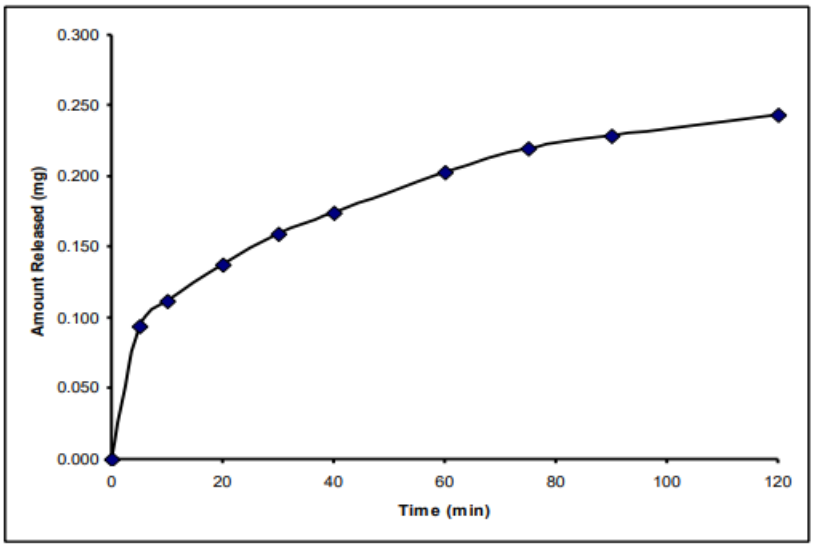


Figure 4.4 Concentration dependent release profile of BSA.

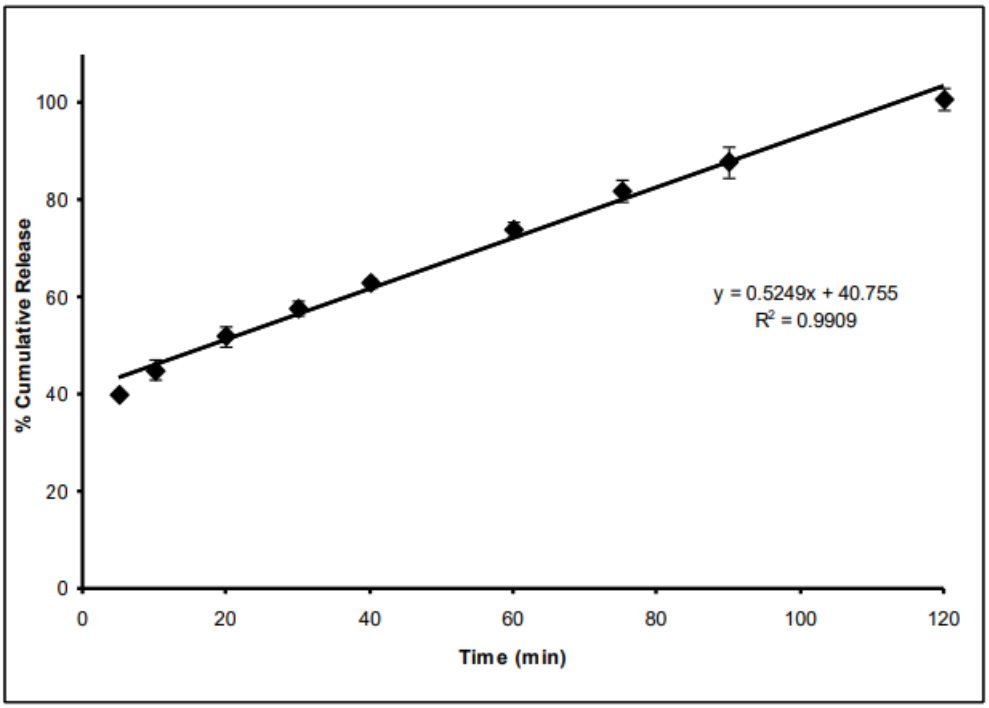


Figure 4.5 Zero-order release profile of BSA

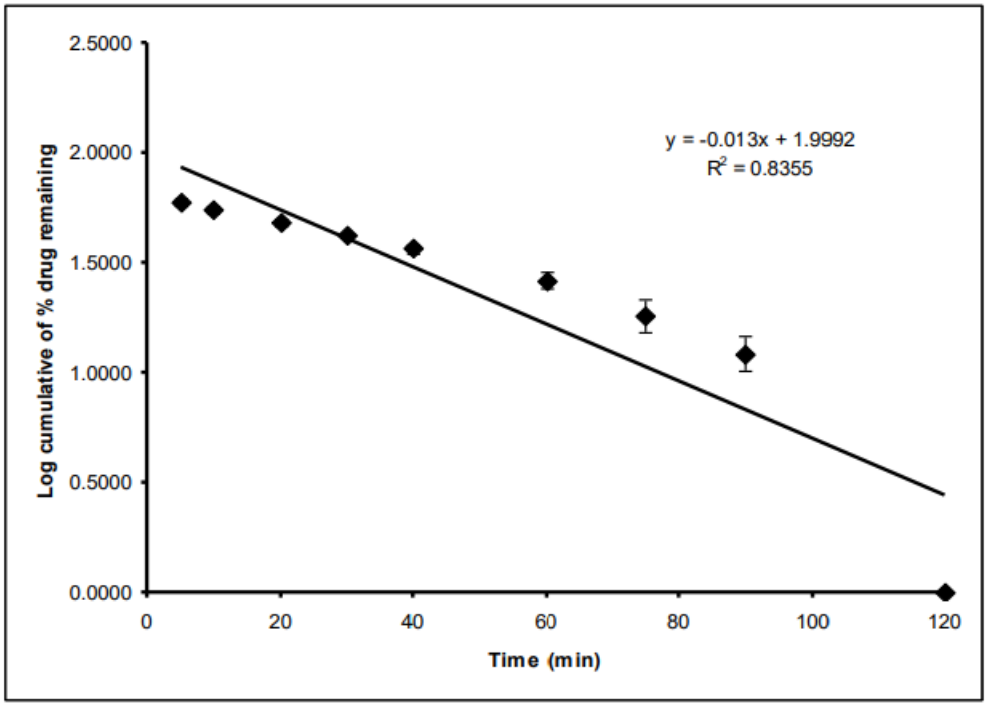


Figure 4.6 First-order release profile of BSA.

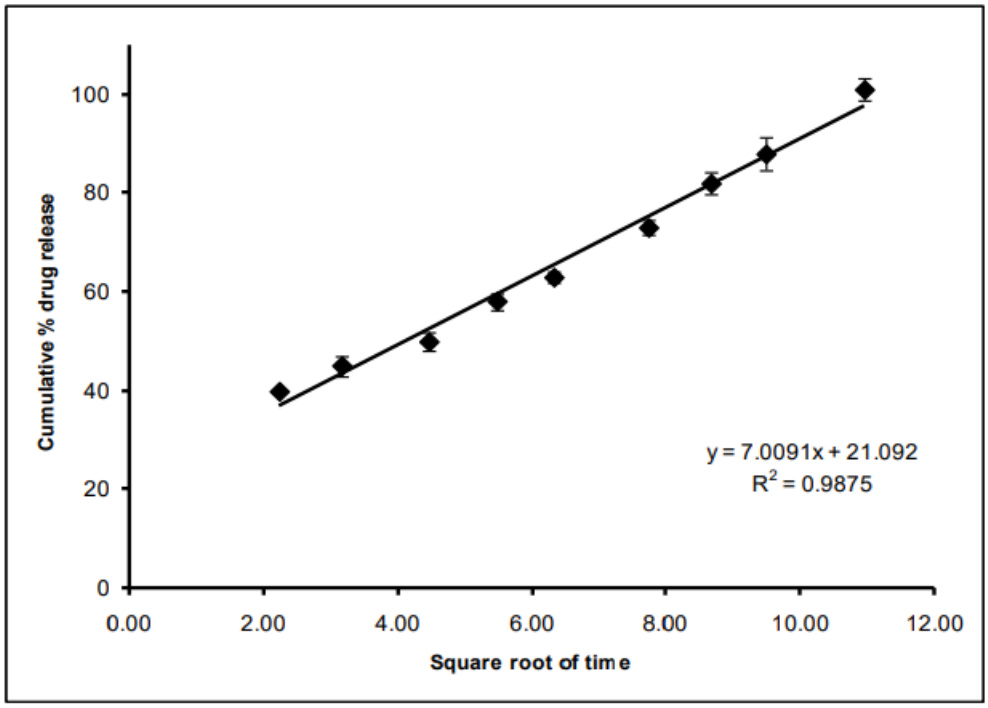


Figure 4.7 Higuchi release model of BSA

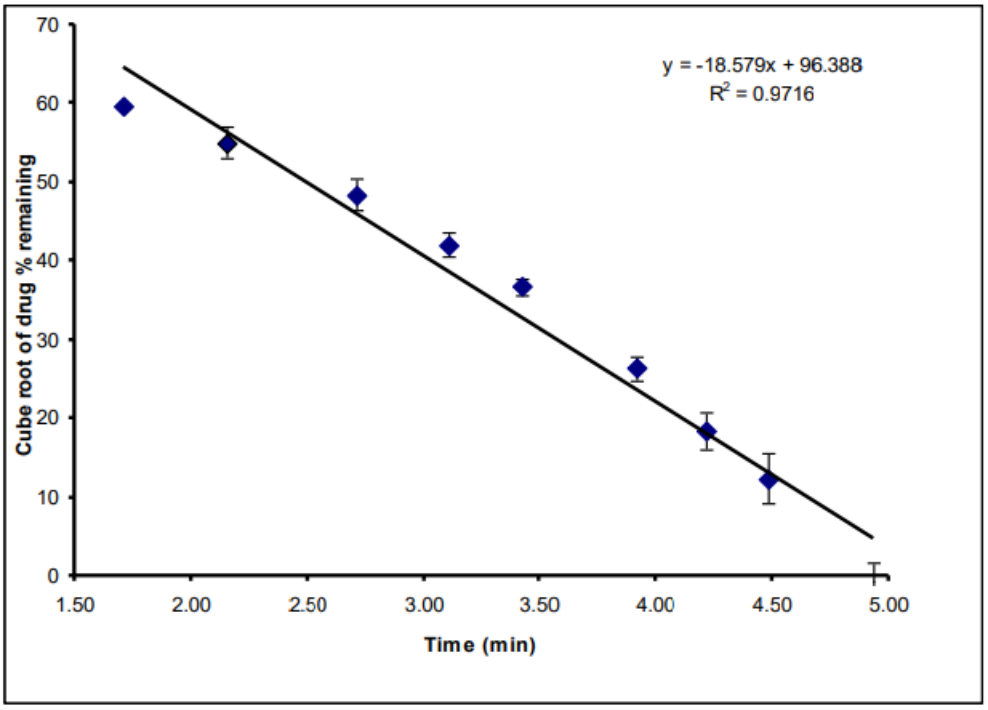


Figure 4.8 Hixson-Crowell release model of BSA

Zero order plot (Figure 4.5) showed a r2 value of 0.9909, first order plot (Figure 4.6) showed a r2 value of 0.8355, the Higuchi model (Figure 4.7) showed a r2 value of 0.9875, and the Hixson-Crowell model (Figure 4.8) showed a r2 value of 0.9716, all describing the drug release rate relationship with concentration the of drug. The highest degree of linearity (0.9909) was obtained in the plot of the zero order equation. This demonstrates that the formulation's drug release was not concentration- but time-dependent. This also suggests that the rate of administration has been stable throughout time and is not reliant on the residual drug concentration in the dose form.

CONCLUSION

For the purpose of transporting proteins, NIPAM-VP microgel nanoparticles were produced and purified. The protein medicine BSA used as a model. Different theoretical release models were used to explain the findings of an analysis of the drug's release kinetics as a function of concentration and time. As expected, the model protein drug's release rate was shown to rely on time rather than concentration. The controlled release formulation claim was validated by the formulation's adherence to ZeroOrder kinetics.

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