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CHITOSAN-GOLD NANOPARTICLES AS DELIVERY SYSTEMS FOR CURCUMIN

K. Satish Kumar* D. Gnanaprakash, K. Mayilvaganan, C. Arunraj and S. Mohankumar

Department of Chemical Engineering, SSN college of Engineering, Kalavakkam – 603110, Tamil Nadu, India

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Correspondence to Author:

K. Satish Kumar

Associate Professor, Department of Chemical Engineering, SSN college of Engineering, Kalavakkam – 603110, Tamil Nadu, India

E-mail: sathishkumark@ssn.edu.in

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ABSTRACT

The present study deals with investigating the effect of chitosan nano particles as carriers for an anticancer drug curcumin. The chitosan-curcumin nanocapsules were prepared in the presence and absence of gold nanoparticles via solvent evaporation method. Scanning electron microscopy and transmission electron microscopy was done to characterize the drug entrapped nanocapsules. The average diameter of gold nanoparticles was found to be in the range of 18-20 nm and size of the nanocapsules was found to be in the range of 200-250 nm. Fourier transform-infrared analysis revealed no possible interactions among the constituents with the chitosan nanoparticles. The controlled drug release of anticancer drug entrapped nanocapsules was carried out in 0.1M HCl and 0.1M phosphate buffer (pH 7). Experimental studies revealed that curcumin encapsulated chitosan with gold nanoparticles was controlled and steady when compared with curcumin encapsulated chitosan nanoparticles. Application of in vitro drug release date to various kinetic equations indicated higuchi matrix model indicating uniform distribution of curcumin in the nanocapsules.

INTRODUCTION: The field of nanoscience has undergone enormous changes over the last two decades and the very potential development is nanomedicine. Nanomedicine is the latest advancement which the world has seen the nanoparticles being the prime part of therapeutic and diagnostic agents. The advancement of this proportion depends on the ability to produce nanoparticles in suitable size and shapes thus extending its domain to sensors, computing and other biomedical applications.

Dispersion of preformed polymers, polymerization of monomers, ionic gelation or coacervation of hydrophilic polymers laser ablation ,inert gas condensation, chemical reduction are the various methods of preparing nanoparticles, in which first three are widely followed [1, 2].

Biodegradable polymers find a pivotal part in today's advancement of drug delivery as they can be degraded to non-toxic monomers inside the body. The second most abundant natural biopolymer available on earth is chitin. Chitosan is a natural nontoxic polymer derived by the deacetylation of chitin. Chitosan ($C_6H_{11}NO_4$) a linear polysaccharide polymer and a water soluble polymer is one such polymer and therefore used in number of biomedical uses [3, 4]. Chitosan causes the fine sediment particles to bind together.

In order to minimize toxicity in drug delivery application a promising field has been wide opened by nanotechnology called targeted drug therapy which is hugely strengthened by gold nanoparticles as it is non-toxic to human cells and biocompatible [5, 6].

Dating to ancient days of Roman Empire where gold nanoparticles were used as aesthetic agent it has turned in to a very versatile one. The latest foray is in to cancer therapy where its property of non-toxicity towards human cells has made it possible.

Curcumin ($C_{21}H_{20}O_6$) is the principal curcuminoid of the popular Indian spice turmeric. Curcumin's antioxidant [7], anti-inflammatory [8-10], anticarcinogenic and antimicrobial [11, 12] properties, and on its use in cardiovascular disease has enabled it to be in the limelight as a promising therapeutic agent, and is currently in human clinical trials for a variety of conditions, including multiple myeloma, pancreatic cancer, colon cancer [13-15].

Hence, an attempt was made to synthesize curcumin encapsulated chitosan nanocapsules in the presence of gold nanoparticles for controlled and sustained drug release applications. From the *in-vitro* release data, their kinetic studies were also carried out for various models.

EXPERIMENTAL

Materials: Chitosan was purchased from Sigma Aldrich Ltd. Curcumin and other chemicals like $HAuCl_4$ (Chloroauric Acid), $Na_3C_6H_5O_7$ (Sodium citrate) and Sodium tripolyphosphate $Na_5P_3O_{10}$ (STPP) used in the studies were purchased from Himedia Laboratories and Fine Chemicals. All chemical reagents were prepared with double distilled water.

Apparatus: Samples were characterized by UV-vis spectrophotometry (Perkin-Elmer Lambda 25).The path length was 1 cm and matched 1cm x 1cm cuvettes were used. HR-TEM was undertaken employing a JEOL instrument with an accelerating voltage of 120 KV. FTIR spectroscopy was performed using a PE IR SPECTRUM ASCII PEDS 1.60 spectrometer and samples were presented as KBr pellets. Spectra were acquired at room temperature at resolution of 4 cm^{-1}. A JEOL JSM-6360 field emission scanning electron microscope was used and the samples were prepared by coating gold on the surface of the sample for SEM measurements.

Preparation of Citrate -capped Gold Nanoparticles: 5.0X 10^{-6} mol of $HAuCl_4$ was taken, dissolved in 200 ml of distilled water. The faint yellowish solution was heated until boiling, while 1ml of 0.5% sodium citrate solution was added under vigorous stirring. It was stirred for the next 30 minutes. The color of the solution gradually changed from faint yellowish to wine red. Water was added to the solution to bring the volume back up to 200 ml. It gives a characteristic absorbance at 526 nm in the UV-Vis spectrum.

Preparation of CC Nanocapsules: 400 mg of chitosan was dissolved in 200 ml of acetic acid (Chitosan – Acetic acid ratio, 2:1). The above solution was neutralized with the 10 N NaOH to obtain the pH level of 6 for strong binding. 100 mg of sodium tripolyphosphate was dissolved in 100 ml of the acetic acid. Ratio for acetic acid and sodium tripolyphosphate is 1:1. 3 ml of the Chitosan – Acetic acid solution was added to the above Solution. 30 mg of Curcumin was added to the above solution and was kept in magnetic stirring for 5 hours and then centrifugation was done for 20 minutes in 9000 rpm. Then the product was dried in hot air oven and dried sample was stored in a vial.

Preparation of CCG Nanocapsules: 400 mg of chitosan was dissolved in 200 ml of acetic acid (Chitosan – Acetic acid ratio, 2:1). The above solution was neutralized with the 10 N NaOH to obtain the P^H level of 6 for strong binding. 100 mg of sodium tripolyphosphate was dissolved in 100 ml of the acetic acid. Ratio for acetic acid and sodium tripolyphosphate is 1:1. 3 ml of the Chitosan – Acetic acid solution was added to the above Solution. 30 mg of Curcumin and 5 ml of Gold nano solution was added to the above mixture and was kept in magnetic stirring for 5 hours and then centrifugation was done for 20 minutes in 9000 rpm. Then the product was dried in hot air oven and dried sample was stored in a vial.

RESULTS AND DISCUSSIONS

UV-Visible characterization: The UV visible spectrum of citrate stabilized gold nanoparticles. **Figure 1(a)** shows the peak at 526 nm which confirms the presence of gold nanoparticles. **Figure 1(b)** shows, maximum absorbance of pure drug curcumin at 454 nm and with the addition of curcumin to gold nanoparticles, both bands 454 and 526 nm pertaining to pure drug and gold nanoparticles decrease in intensity steadily with time. This was shown in the **Figure 1(c)**.

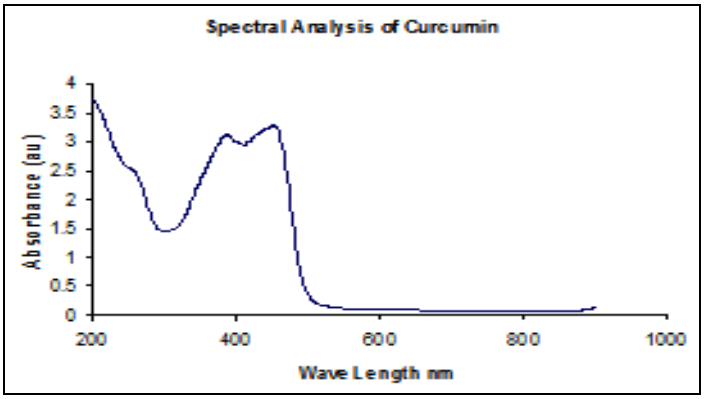


FIGURE 1(A) UV VISIBLE SPECTRUM OF GOLD NANOPARTICLES

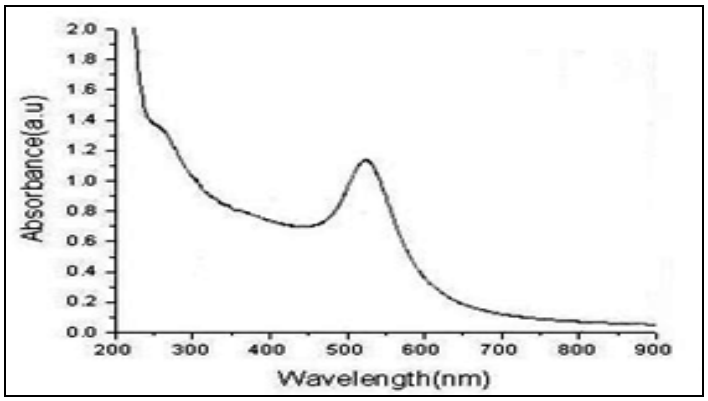


FIGURE 1(B) UV VISIBLE SPECTRUM OF CURCUMIN

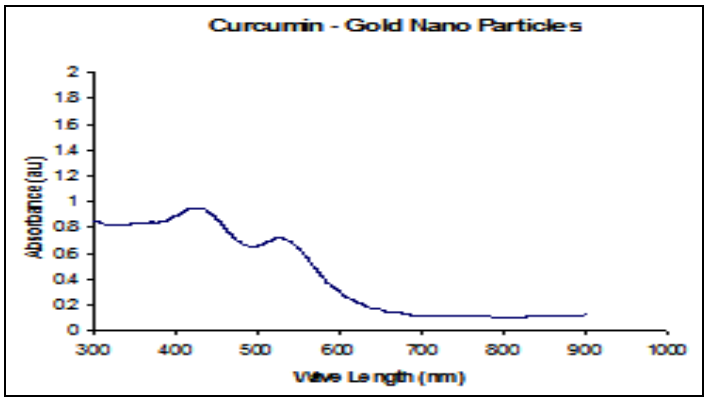


FIGURE 1 (C) UV VISIBLE SPECTRUM OF CURCUMIN – GOLD NANOPARTICLES

FT-IR Spectroscopy: Figure 2(a) represents, FT – IR spectrum of CC nanocapsules. Chitosan shows characteristic bands at 3415.03 cm^{-1} due to NH_2 and OH group stretching vibration and the band for the amide seen at 1610.59 cm^{-1}. **From Figure 3(a)** Curcumin shows OH stretching frequency between 3233.72 to 3415.03 cm^{-1} and C=C aromatic stretching frequency at 1419.63 cm^{-1}. Other significance bands 1610.59 cm^{-1} for C = O. and significance band was observed at 730 and 797 cm^{-1} for C = C – H aromatic stretching frequency.

The FT- IR spectra of CCG nanocapsules are shown in the **Figure 2(b)**. The spectra contains the peaks corresponding to stretching frequency of Chitosan along with the peaks corresponding to curcumin stretching frequencies, which confirms the presence of curcumin in CCG nanocapsules. The presence of gold is confirmed by the broadened peak at 3380 cm^{-1} due to the presence of NH_2.

Transmission Electron Microscopy (TEM): Figure 3(a) and (b) represents the TEM images of gold nanoparticles and Chitosan- Curcumin- Gold Nanocapsules. From the TEM measurements, the average diameters of the gold nanoparticles were found to be in the range of 18-20 nm. From the TEM pictures the aggregations of gold nanoparticles were observed which confirms the complex formation between curcumin and gold nanoparticles which confirms the presence of drugs in the nanocapsules. From **Figure 3(b),** it was concluded that the penetrations of drug-metal nanoparticles were observed during the process of encapsulation drugs, which confirms the presence of drugs in the nanocapsules.

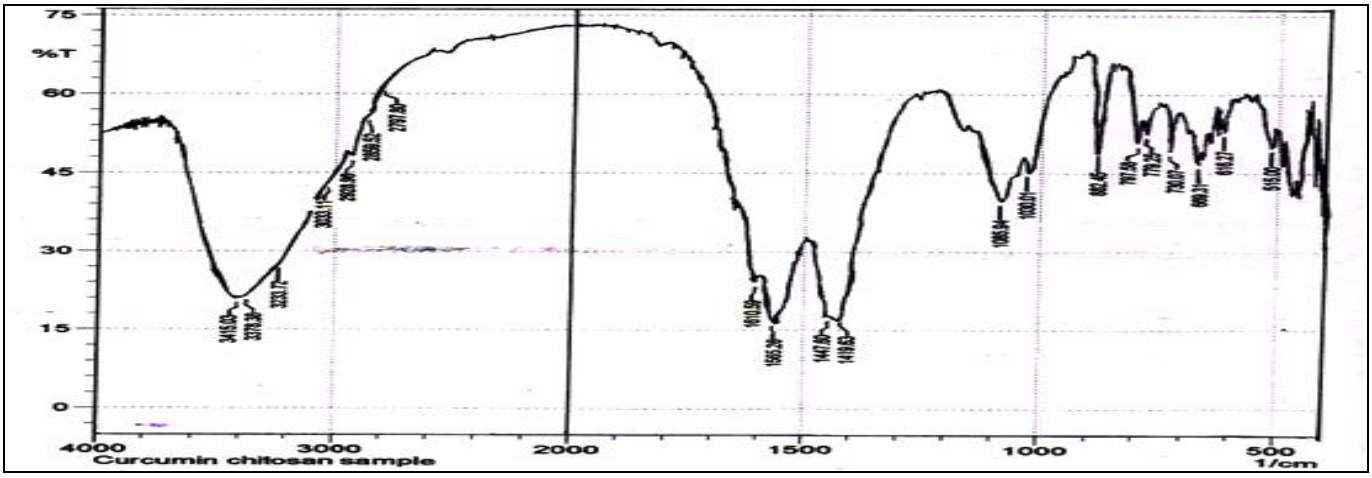


FIGURE 2(A): FT- IR SPECTROSCOPY OF CC NANOCAPSULES

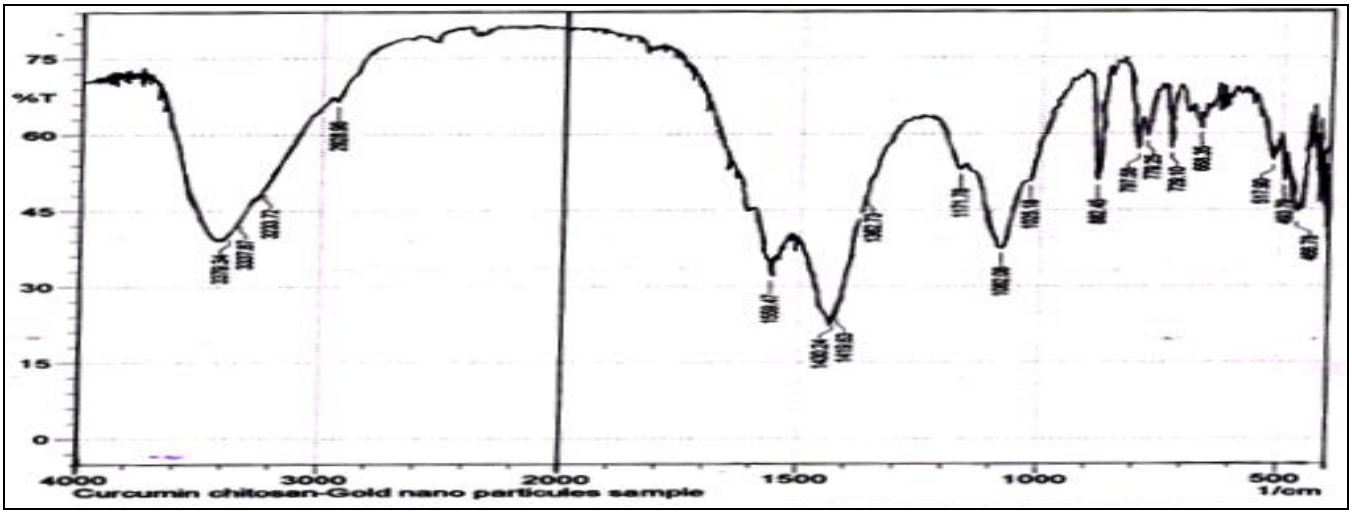


FIGURE 2(B): FT- IR SPECTROSCOPY OF CCG NANOCAPSULES

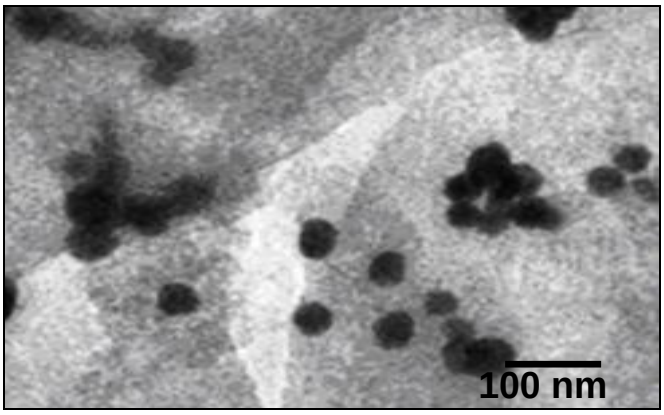


FIGURE 3(A): TEM IMAGE OF CURCUMIN-GOLD NANOPARTICLES

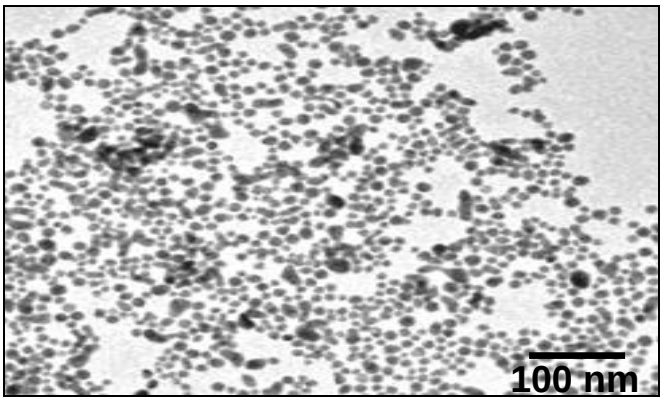
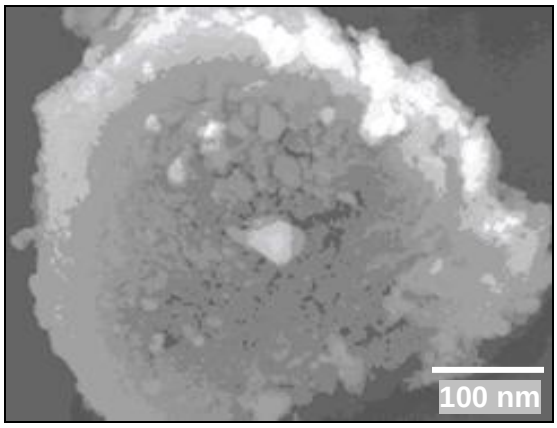


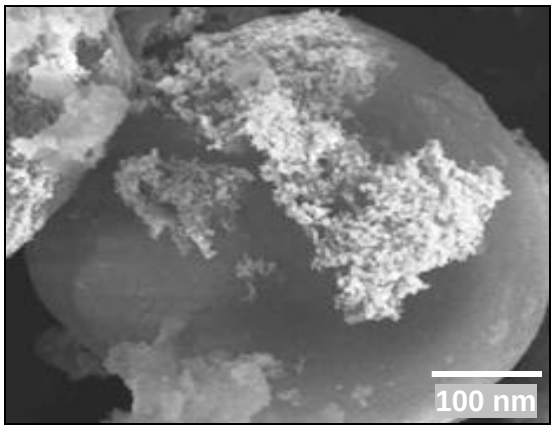
FIGURE 3(B): TEM IMAGE OF CCG NANOCAPSULES

Scanning Electron Microscopy (SEM): Morphology of all the nanocapsules Chitosan – Curcumin (CC) and Chitosan –Curcumin–Gold Nanoparticles (CCG) prepared were characterized by SEM analysis. CC nanocapsules were easily distinguished from CCG by its blue color. The colors of the CCG nanocapsules were blue because of the presence of gold nanoparticles. Surface morphology of CC and CCG nanocapsules was shown in the **Figure 4(a-b)**. It can be observed that the surface of CC nanocapsules is rough when compared to CCG nanocapsules. The SEM images manifested that CCG and CC nanocapsules were nearly oval in shape with an average size of 200-250 nm.

Figure 4(b) represents the SEM images of CCG nanocapsules with smooth surface and the shape of the nanocapsule was found to be spherical.



(a)



(b)

FIGURE 4(A): SEM IMAGES OF CC NANOCAPSULES; (B): CCG NANOCAPSULES DRUG RELEASE PROFILE

Drug Release Profile: The drug release profiles of Curcumin from CC and CCG nanocapsules in the hydrochloric acid (0.1 M) and the phosphate buffer saline (pH 7.0) were shown in the Figure 5 and 6 respectively. Desorption profiles were obtained as follows;

0.005 gram of drug encapsulated polymer nanoparticles were mixed with 10 ml of phosphate buffer solution and HCl solution. The absorbance of each solution was monitored in different time. One sample solution was used only once so that there was no change in the concentration of the solution. The intensity of absorption was plotted against time which gave the desorption profile of Curcumin.

From the **Figures 5 and 6**, it was observed that the drug release in CCG nanocapsules was slow and sustained compared to CC nanocapsules in both the dissolution media. This was in accord with the topographic results obtained from SEM analysis that the surface of CCG nanocapsules was smoother with smaller pores. It was observed that the drug release from CCG nanocapsules containing gold nanoparticles occurred in a controlled manner. The drug release from CCG nanocapsules was found to 55% in PBS medium and 46% in HCl medium for 120 hours whereas the drug release from CC nanocapsules was found to 92% in PBS medium and 65% in HCl medium.

Furthermore, the release rate of CCG and CC in basic medium is high compared to acidic medium because of solubility characteristics of dissolution medium.

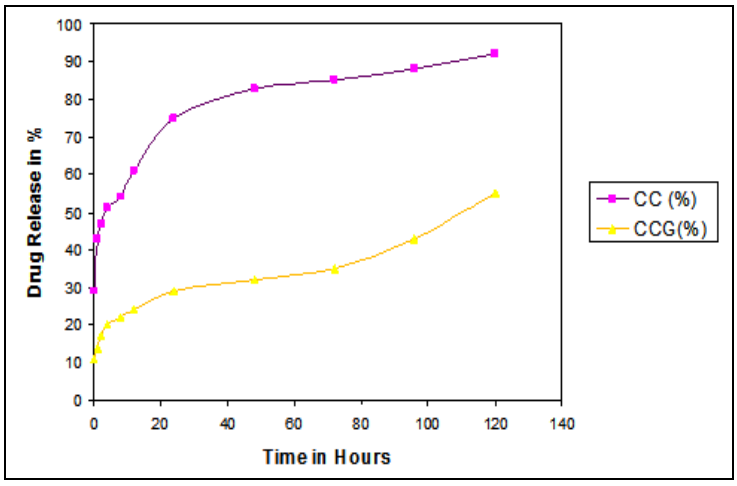


FIGURE 5: DRUG RELEASE PROFILE IN PBS MEDIUM

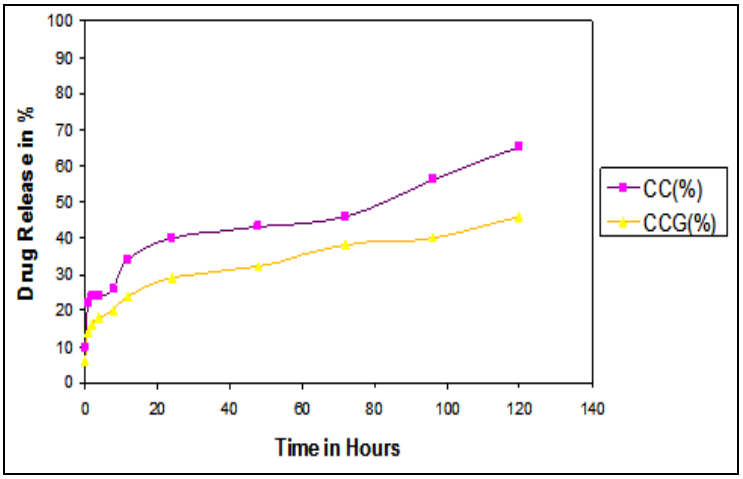


FIGURE 6: DRUG RELEASE PROFILE IN HCl MEDIUM

Kinetic Studies: Data of the Curcumin release from chitosan nanocapsules were analyzed to investigate the release kinetics. Drug release kinetics from nanocapsules was analyzed by using Zero – order kinetics, First order kinetics and Higuchi model.

1. **Zero Order Kinetics:** Zero order kinetics model follows the equation as $(Q / Q_0) = k_0 t$

Where k_0 = Zero order rate constant, $hour^{-1}$

Q = the amount of Curcumin released, mg

Q_0 = the amount of Curcumin initially, mg

Figures 7(a) and (b) shows the zero order kinetics in PBS and HCl medium. Due to the deviation of regression coefficient, these curves preclude the possibility of Zero order kinetics.

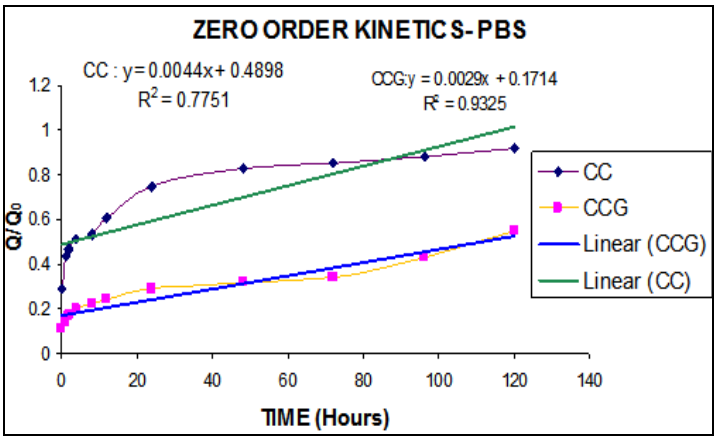


FIGURE 7(A): ZERO ORDER KINETICS – PBS MEDIUM

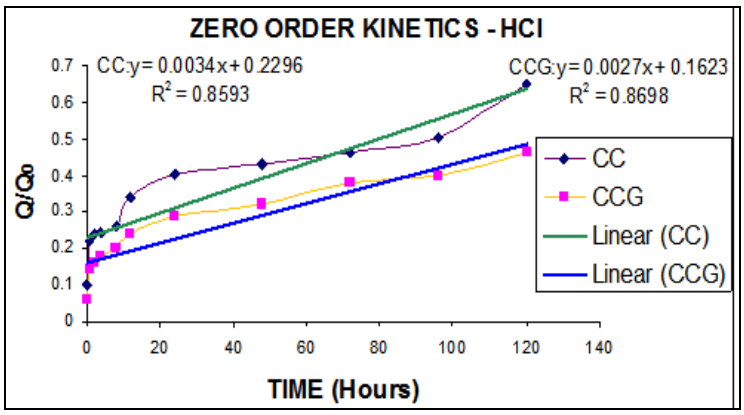


FIGURE 7(B): ZERO ORDER KINETICS – HCL MEDIUM

First order kinetics

First order kinetics model follows the equation as;

$$\log (Q / Q_0) = -k_1 t / 2.303$$

Where k_1 = first order rate constant, hour^{-1}, Q = the amount of Curcumin released, mg; Q_0 = the amount of Curcumin initially, mg

Due to the lack of linearity of these curves from the **Figure 8(a) and (b)** it precluded the possibility of first order kinetics.

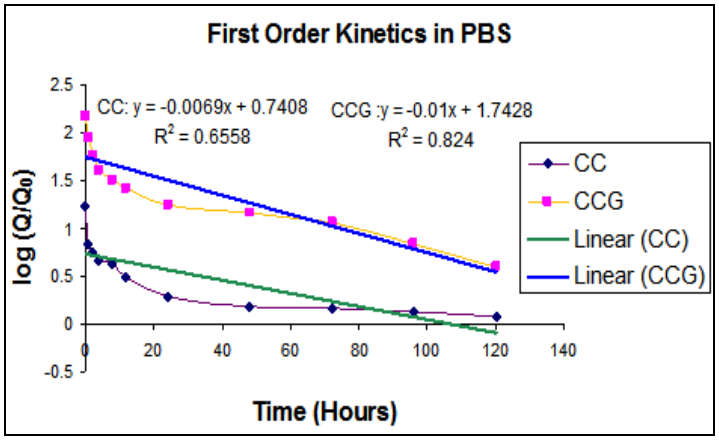


FIGURE 8(A): FIRST ORDER KINETICS IN PBS MEDIUM

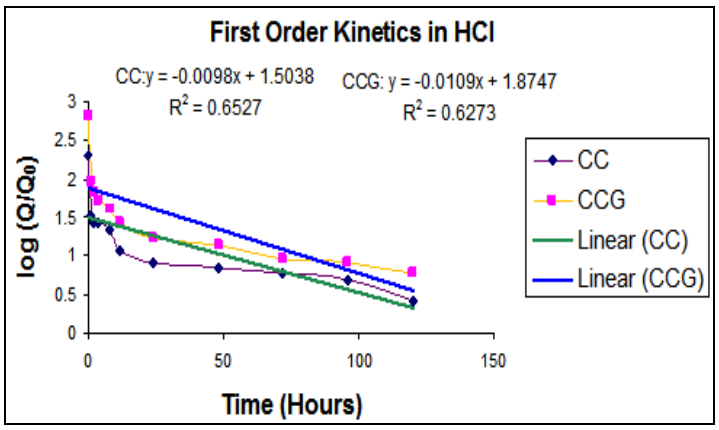


FIGURE 8(B): FIRST ORDER KINETICS IN HCL MEDIUM

Higuchi Model: Figure 9(a) and (b) shows the profile of half order kinetics in PBS and HCl medium. Values of R^2 indicated that the Higuchi model was best fitted with the release kinetic data of Curcumin for both HCl and PBS medium

$$\text{Higuchi equation: } Q / Q_0 = k_h t^{1/2}$$

Where, Q = the amount of Curcumin released, mg; Q_0 = the amount of Curcumin initially, mg; k_h = Higuchi matrix release kinetics, hour$^{-1/2}$

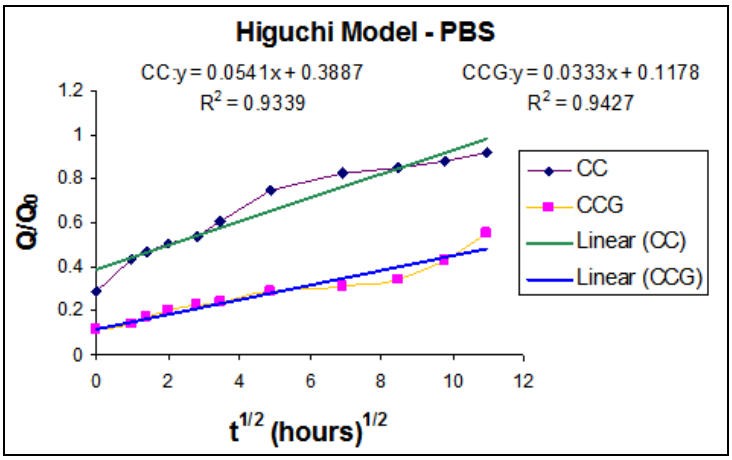


FIGURE 9(A): HIGUCHI MODEL – PBS MEDIUM

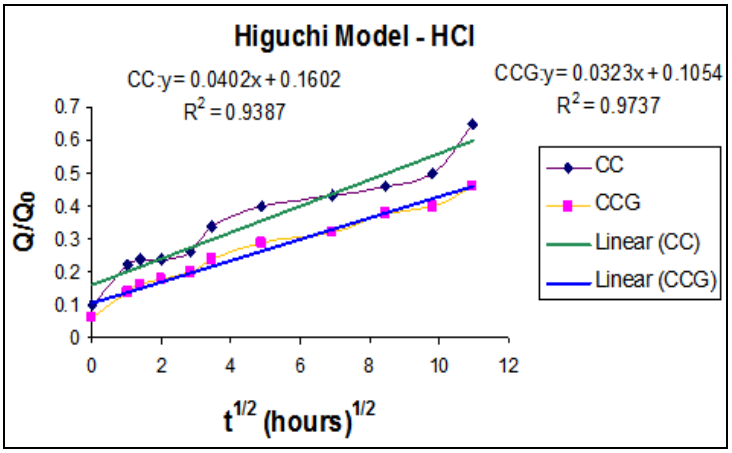


FIGURE 9(B): HIGUCHI MODEL – HCL MEDIUM

CONCLUSION: Curcumin encapsulated in polymer nanocapsules with Chitosan and Gold nanoparticles were synthesized by solvent evaporation method. The synthesized nanocapsules were analyzed by UV spectroscopy, FT – IR spectroscopy, Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM). From the TEM measurements, the average diameters of the gold nanoparticles were found to be in the range of 18-20 nm.

Drug delivery studies were conducted and their release profiles in 0.1 M HCl and PBS (pH 7.0) media showed that both CC and CCG nanocapsules released curcumin in a slow and sustained manner. Furthermore the percentage of drug release was found to be slow in 0.1 M HCl solution for both CC and CCG nanocapsules. The rate constant and regression coefficient calculated from various kinetic models inferred that the Higuchi model was best fitted for the drug release of the nanocapsules.

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