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Dual release kinetics of antimalarials from soy protein isolate-carbopol-polyacrylamide based hydrogels

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ABSTRACT: The currently used antimalarials suffer from drug resistance which is hampering the global management of malaria infection. To overcome drug resistance, they are administered as combination therapies which involve combination of two or more antimalarials. In this study, chloroquine diphosphate and curcumin were encapsulated onto prepared soy protein isolate-carbopol-polyacrylamide based hydrogels. The hydrogels were pH sensitive and exhibited enhanced swelling capability at pH 7.4. The hydrogels were biodegradable which was observed by their SEM images after drug release. The release mechanisms of both drugs were influenced by the degree of crosslinking of the soy protein isolate in the hydrogel network and the presence of the other drug in the network. The release mechanisms of both drugs from the hydrogel networks followed super case transport II. These results suggested that the hydrogels were potential dual drug delivery systems for antimalarials whereby both drugs could work over different period of time and hence, have the potential to overcome drug resistance that is common with the presently used antimalarials. © 2016 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 43918.

KEYWORDS: biodegradable; composites; drug delivery systems; gels

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INTRODUCTION

Malaria caused by *Plasmodium falciparum* is the cause of high mortality rates in the tropics. In 2013, 198 million cases of malaria infection were recorded worldwide with 584,000 deaths.[1] In the latest WHO report, there were 214 million new cases of malaria worldwide and 88% of the infection was reported in the African region, 10% in South-East Asia region, and 2% in Eastern Mediterranean region.[2] The disease is chronic and can result in severe complications such as respiratory distress, severe anemia, renal failure, severe headache, enlarged liver, hypoglycemia, spontaneous bleeding, stillbirths, low birth weight, etc.[3–5] The presently used antimalarials suffer from drug resistance which is hampering the global management of malaria. Chloroquine is used extensively in malaria endemic areas in Africa. However, chloroquine resistant to *P. falciparum* parasites has hindered its usage. Drug resistance of chloroquine is associated with increased efflux mechanism of chloroquine from the parasite resulting in reduced inhibition of heme polymerization.[6] The use of natural occurring bioactive agents have also been found to be effective for treatment of malaria.

Curcumin is a natural occurring bioactive agent with antimalarial activity. It acts as an adjunctive therapeutic in selected combination resulting in protection against parasite recrudescence and relapse: curcumin-artemisinin,[7] currcumin-arteether,[8] curcumin-artemether,[9] and curcumin-primaquine.[10] However, its poor bioavailability, chemical instability, poor absorption limits its therapeutic effectiveness.[11] To enhance its bioavailability, several drug delivery systems have been designed for targeted delivery and enhanced therapeutic effects. Some of the drug delivery systems are liposomes, micelles, dendrimers, polymer-drug conjugates, hydrogel, etc.

Hydrogels are three-dimensional polymeric network with porous structure that permits the loading and release of drugs. They can be prepared from variety of materials such as carbon based biomaterials, natural and synthetic polymers. There are few reports on the application of hydrogels for single and dual delivery of antimalarials. Munjero *et al.*, developed hydrogels for sustained delivery of chloroquine to the gastrointestinal tract. *In vivo* evaluation of the hydrogels on rats was found to result in significant plasma concentrations of chloroquine between 2 and 4 h after oral administration suggesting release in duodenum and ileum.[12] Aderibigbe *et al.*, developed soy protein based hydrogels for dual delivery of curcumin and N-(7-chloroquinolin-4-yl) propane-1,3-diamine.[13] Bajpai *et al.*, developed pH sensitive hydrogels for oral delivery of antimalarial drug. They exhibited non-Fickian release mechanism at pH 7.4 and a Fickian release profile at pH 1.2.[14] Chen *et al.*, developed thermosensitive carbopol hydrogels with good mechanical properties and release

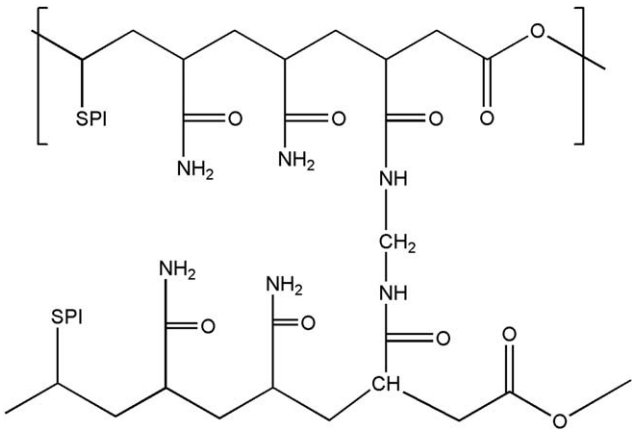

Figure 1. Soy protein-carbopol-polyacrylamide based hydrogels.

behaviour.[15] Varaprasad *et al.*, prepared carbopol based nanocomposite hydrogels with antimicrobial activity.[16]

In this work, soy protein isolate-carbopol-polyacrylamide based hydrogels were prepared and characterized by X-ray diffraction (XRD), Fourier transform infrared (FTIR), thermogravimetric (TGA), energy dispersive X-ray spectroscopy (EDX), and scanning electron microscopic (SEM) analysis. The pH sensitivity of the hydrogels was evaluated at pH 1.2 and 7.4 simulating gastric juice and blood environment, respectively. The drug release kinetics of the hydrogels was performed. To the best of our knowledge this is the first manuscript that reports the dual release mechanisms of antimalarials from carbopol-based hydrogels

EXPERIMENTAL

Materials

N,N,N′,N′-Tetramethylethylenediamine (TEMED) and potassium persulfate (KPS) were bought from Sigma Aldrich (South Africa). N,N′-methylenebisacrylamide (MBA) and acrylamide (AM) were obtained from Fluka (South Africa). Soy protein isolate powder was obtained from Honeyville Food Products, Salt Lake City, Utah, Carbopol^R 974 NF was obtained from Lubrizol, The United States, curcumin and chloroquine diphosphate salt were bought from Sigma Aldrich, South Africa. Distilled water was used for the preparation of the hydrogels.

Preparation of the Soy Protein-Carbopol-Polyacrylamide Based Hydrogel

Soy protein-carbopol-polyacrylamide based hydrogels (Figure 1) were prepared by copolymerization of acrylamide, MBA, soy protein isolate and acrylic acid using KPS as initiator. The hydrogels were prepared by dissolving known quantity of soy protein isolate powder in 1 mL of 0.05*M* solution of sodium hydroxide solution followed by addition of acrylamide, MBA solution, carbopol and acrylic acid, respectively. The mixture was stirred at room temperature until a homogenous mixture was obtained before the addition of KPS. The hydrogels were formed at 40–60 °C and then soaked in large volume of distilled water overnight in order to get rid of unreacted amine. The hydrogels were dried at ambient temperature for 5 days and glassy to rubbery hydrogels were isolated. The formulations for the soy protein-carbopol-polyacrylamide based hydrogels and their abbreviations are summarized in Table I.

Water Uptake Mechanism

The water uptake capacity of the prepared hydrogels with varied amount of soy protein isolate and acrylic acid were evaluated at room temperature over a period of 72 h at pH 1.2 (simulating gastric pH) and for 24 h at pH 7.4 (simulating intestinal pH). The water uptake capacity of the hydrogels was used to evaluate the pH sensitivity of the hydrogels. Hydrogels of known weights were placed in empty teabags and immersed in buffer solutions. They were allowed to swell until the equilibrium swelling was reached. The immersion time and drying of the hydrogels were repeated until the weight of the swollen hydrogels was constant. The teabags containing the hydrogels were removed from the buffer solutions and blotted gently with blotting paper to remove the overloaded water on the surface and weighed. The swelling ratio at equilibrium (ESR) was calculated from eq. (1):

$$\mathrm{ESR} = \frac{M_y - M_x}{M_x} \quad (1)$$

where M_y and M_x represent the weights of the hydrogels at equilibrium and before swelling, respectively.

FTIR. FTIR analysis was performed in the range of 500–4000 cm^{-1}. The FTIR spectroscopy was performed on (Perkin Elmer Spectrum 100 FTIR spectrometer), The United States.

XRD. XRD was performed using (PANalyticalX'Pert PRO), Netherlands. It was performed at (Cu K_α radiation, $\lambda = 0.1546$ nm) running at 45 kV and 40 mA. This analysis was performed so as to evaluate the state of the hydrogels (amorphous or crystalline) and to investigate the effect of the encapsulation on the crystallinity of the drugs.

SEM/EDX. The hydrogels were sputtered with gold nanoparticle before SEM analysis using JEOL-JSM 7500F SEM. SEM was used to evaluate the surface morphology of the drugs and

Table I. Formulation for the Soy Protein-Carbopol-Polyacrylamide Hydrogels

Hydrogel	MBA 65 m*M*	Acrylic acid	SPI (g)	Carbopol (g)	KPS 37 m*M*	% loading of curcumin	% loading of chloroquine
Blank	1 mL	0.5 mL	—	0.05	1 mL	—	19.10
CA 1	1 mL	0.5 mL	0.05	0.05	1 mL	—	—
CA 2	1 mL	0.5 mL	0.10	0.05	1 mL	15.45	17.30
CA 3	1 mL	—	—	0.05	1 mL	—	—
CA 4	1 mL	—	0.05	0.05	1 mL	16.00	16.40

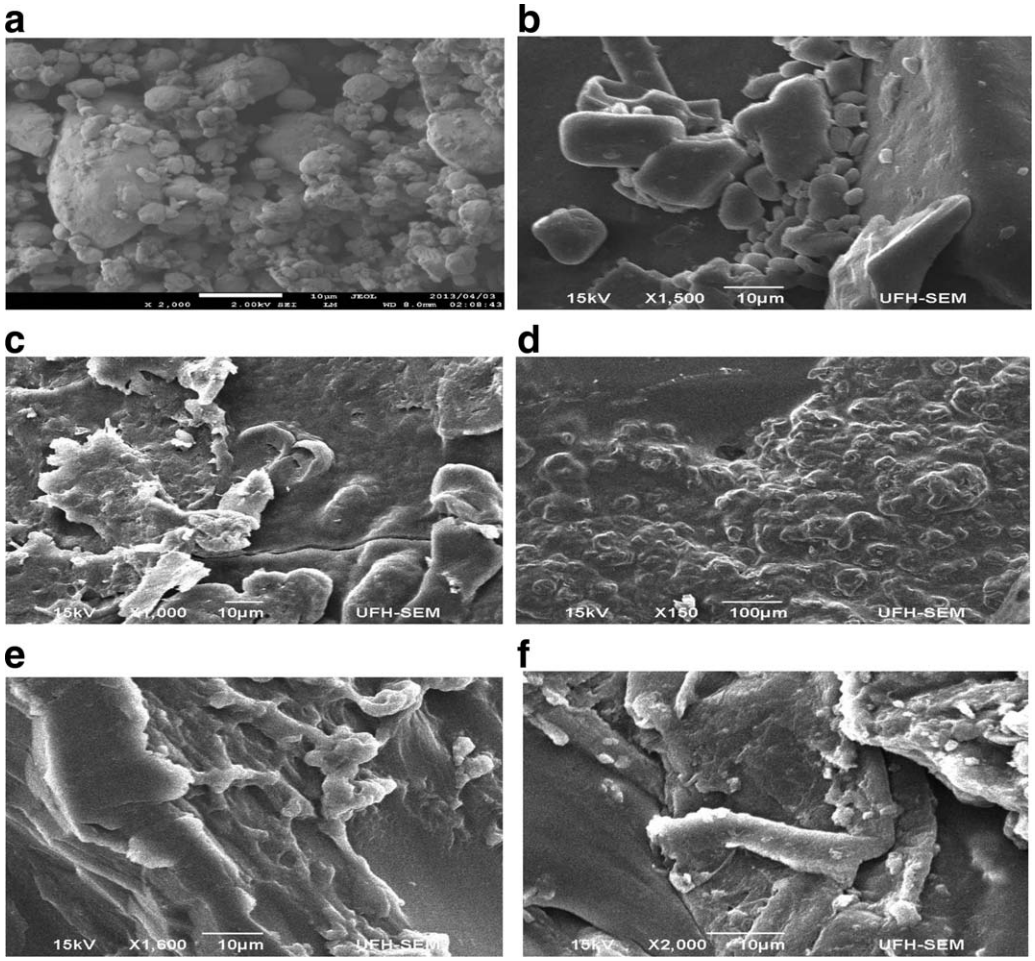

Figure 2. (a) SEM image of curcumin. (b) SEM image of chloroquine diphosphate. (c) SEM image of blank. (d) SEM image of CA1. (e) SEM image of CA2. (f) SEM image of CA4.

hydrogels before and after drug release process. EDX was used to determine the chemical composition of the hydrogels.

Drug Loading

Dual drug loading process was performed by preparing a solution of 2 mg of curcumin dissolved in 1:1 (20 mL water:ethanol). The aforementioned solution was mixed with a solution of 5 mg of chloroquine diphosphate dissolved in 20 mL of distilled water. About 50 mg of CA2 and CA4 were soaked separately in 20 mL of the drug solution for 2 days. The hydrogels were removed from the drug solution, rinsed with water so as to get rid of excess of curcumin and chloroquine at the surface of the hydrogels and were allowed to dry at room temperature for 5 days.

Hydrogels loaded with chloroquine were prepared by dissolving 50 mg of chloroquine diphosphate in 100 mL of distilled water. About 50 mg of the hydrogels (blank, CA2, and CA4 hydrogels) were soaked separately in 30 mL of chloroquine diphosphate solution. The hydrogels were left in the drug solution overnight at room temperature. The hydrogels were then removed from drug solution, rinsed with water so as to get rid of excess chloroquine at the surface of the hydrogels and were allowed to dry for 5 days at room temperature.

In Vitro Release Kinetics

In vitro release studies were performed by placing chloroquine and curcumin loaded hydrogel in 50 mL of selected buffer solution (1.2 and 7.4) at 37 °C in a shaker. The release study was performed over a period of 24 h at pH 7.4 and for 72 h at pH of 1.2 by collecting 4 mL of the sample solution and replacing it with equivalent amount of buffer solution. The drug release profiles were obtained using UV–Visible spectroscopy at wavelengths of 427 and 335 nm for curcumin and chloroquine diphosphate, respectively. For the calibration graph, five standard solutions for chloroquine and curcumin were used in ranges of $9.93 \times 10^{-11}-3.88 \times 10^{-5} M$ and $1.09 \times 10^{-7}-0.001\,M$, respectively.

RESULTS AND DISCUSSION

SEM Analysis

SEM analysis was performed so as to evaluate the surface morphologies of hydrogels without the drugs, after drug loading and drug release process. The SEM images of curcumin were spherically shaped [Figure 2(a)].[13] Chloroquine diphosphate exhibited blocked shaped morphology with smooth surface [Figure 2(b)]. Blank hydrogels surface morphology was coarse, irregular with swollen topologies [Figure 2(c)]. CA1 displayed a

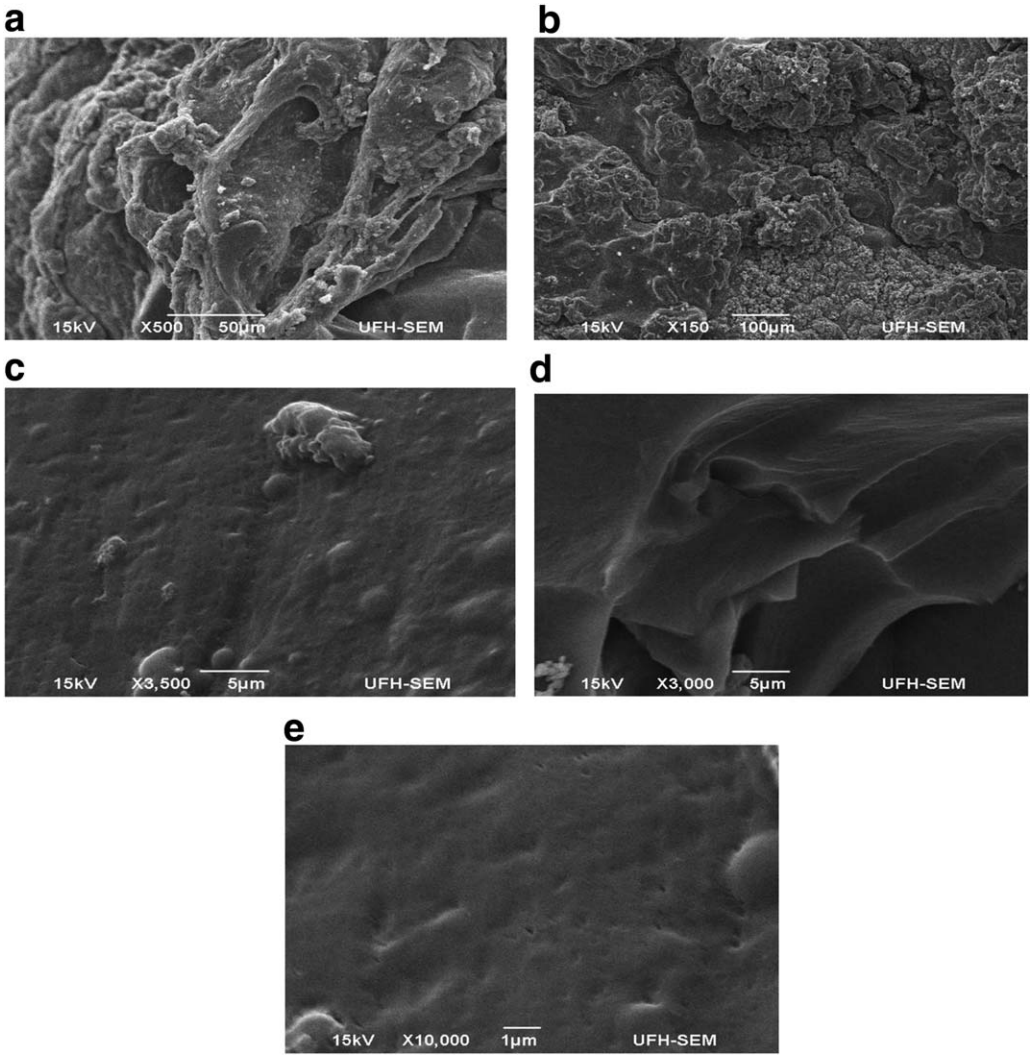

Figure 3. (a) SEM image of blank hydrogel loaded with chloroquine diphosphate. (b) SEM image of CA2 loaded with chloroquine diphosphate and curcumin. (c) SEM image of CA2 after drug release at pH 1.2. (d) SEM image of CA2 after drug release at pH 7.4. (e) SEM image of CA2 after drug release at pH 1.2 (higher magnification).

combination of swollen and folded topologies which is attributed to the presence of soy protein isolate [Figure 2(d)].[13] CA2 and CA4 both exhibited coarse and swollen topologies and these features were very outstanding in CA4 [Figure 2(e,f)]. Blank hydrogel loaded with chloroquine diphosphate exhibited irregular morphology [Figure 3(a)]. CA2 loaded with chloroquine and curcumin still maintained the swollen, spherical, and folded morphologies that was found to be predominant in CA2 [Figure 3(b)]. CA2 hydrogel did not retain its characteristic morphologies (i.e., swollen and spherical) after drug release at pH 1.2 and 7.4 suggesting degradation of the hydrogel [Figure 3(c,d)]. At a higher magnification, small porous holes were visible on CA2 hydrogel after drug release at pH 1.2. This finding further suggested that these hydrogels are biodegradable and the rate of biodegradability is influenced by the pH [Figure 3(e)]. EDX result portrayed the elemental composition of the hydrogels (Table II).

Table II. Elemental Composition of the Hydrogels

Hydrogel	C (%)	N (%)	O (%)
Blank	14.28	1.66	22.22
CA 1	14.21	2.85	14.09
CA 2	20.59	7.48	27.90
CA 3	17.01	7.10	18.02
CA 4	10.57	1.97	24.90

FTIR Analysis. The hydrogels displayed absorption peaks for NH stretch between 3550 and 3250 cm^{-1}. The intensity of the peak was low in CA3 and CA4 suggesting that the peak signify polymerization of acrylic acid which was very pronounced in blank, CA1, and CA2. C—O amide stretch was visible at 1626 cm^{-1} [Figure 4(a)]. The hydrogels loaded with chloroquine and curcumin exhibited absorption peaks at 3422 cm^{-1} for NH stretch, 1635 cm^{-1} for C=O stretch, 1535 cm^{-1} for C=C aromatic stretch, 1384 cm^{-1} for C—N aromatic stretch and 1123 cm^{-1} for C—O stretch [Figure 4(b)]. These peaks confirmed the successful loading of the drugs to the hydrogels.

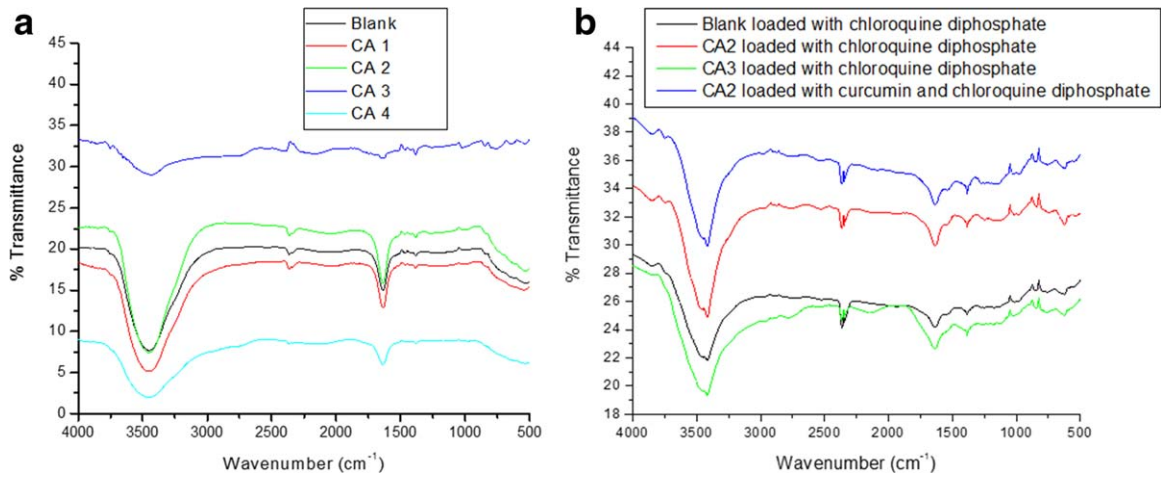

Figure 4. (a) FTIR spectra of soy protein-carbopol-polyacrylamide hydrogels. (b) FTIR spectra of soy protein-carbopol-polyacrylamide hydrogels loaded with drugs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Swelling Analysis. The swelling capacity of the hydrogels was investigated at pH 1.2 and 7.4. The degree of swelling of the hydrogel network is an important factor that can be used to control the rate of release of drug from the network because it correlate with the rate of diffusion of drug in and out of the hydrogel matrix.[17] At pH 1.2, the degree of swelling of the hydrogels was minimal and as a result, the hydrogels were allowed to swell over a period of 72 h. The low swelling abilities of the hydrogels at acidic pH could be attributed to the degree of crosslinking. The highest cross-linked hydrogel CA2 exhibited a low degree of swelling when compared with CA1 with 0.05 g of SPI. This finding further confirmed the role of natural polymers in hydrogel networks on the swelling ability of the hydrogels. The minimal swelling capacity of the hydrogels is due to the protonation of the carboxylic groups. At pH 7.4, the hydrogels displayed an enhanced swelling capacity which was dependent on the degree of crosslinking and the presence of natural polymer, SPI. CA1 and CA2 hydrogels exhibited the highest degree of swelling (Figure 5). The carboxylate groups were ionized resulting in electrostatic repulsion between the carboxylate groups and an enhanced swelling capacity. CA3 and CA4 hydrogels that did not contain acrylic acid exhibited the least swelling ratio at pH 7.4 suggesting that acrylic acid enhanced the degree of swelling the hydrogel matrices.

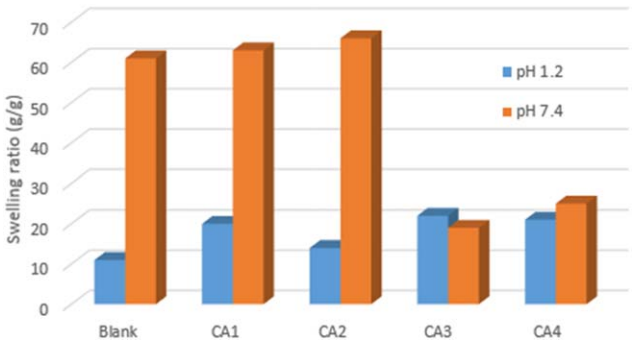

Figure 5. A graph of the swelling ability of the hydrogels. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

XRD Analysis. XRD was used to evaluate the diffraction pattern of the hydrogel networks before and after encapsulation with antimalarials. It was also used to evaluate if there is an interaction of the drugs with the hydrogel networks. The diffraction pattern for the hydrogels was broad due to their amorphous nature. Their characteristic peaks were found at $2\theta = 25$, 39.24, 61.59, and 81.88 [Figure 6(a)]. Chloroquine diphosphate due to its crystalline nature displayed characteristic sharp peaks at $2\theta = 19.11$, 22.43, 28.70, 31.99, and 36.02. These peaks were absent in the thermograms of hydrogels loaded with chloroquine diphosphate [Figure 6(b)]. The characteristic peaks for curcumin were also absent in the thermograms of hydrogels loaded with curcumin. These observations suggest that curcumin and chloroquine diphosphate were molecularly dispersed in the hydrogel networks. The thermographs also showed reduced crystallinity of drugs due to the aforementioned reason.

Single Drug *In Vitro* Release Kinetics. The single release of chloroquine diphosphate from the soy protein isolate-carbopol-acrylamide based hydrogels was studied. Chloroquine diphosphate salt is water soluble (50 mg/mL). The release of chloroquine diphosphate from the hydrogels was dependent on the pH of the buffer solutions used, the degree of cross-linking of the hydrogel network and also on the high solubility of the salt in water. At pH 1.2, the release of chloroquine diphosphate from the hydrogels over a period of 24 h was 22.68, 36.4 and 45%, respectively, for blank, CA2, and CA4, respectively [Figure 7(a)]. After 3 days the % released was 24.97, 40 and 50% for blank, CA2 and CA4, respectively [Figure 7(b)]. The rate of release of encapsulated drug was slow at acidic pH and this is attributed to the pH sensitivity of the hydrogels. The degree of crosslinking and presence of natural polymer in the hydrogel network also influenced the rate of release of at pH 1.2. At pH 7.4, the release of chloroquine diphosphate over a period of 24 h was 57.58, 88.32, and 91.49% for CA4, blank, and CA2, respectively. The quick release of the drug from the hydrogel networks at pH 7.4 is attributed to the enhanced swelling ability

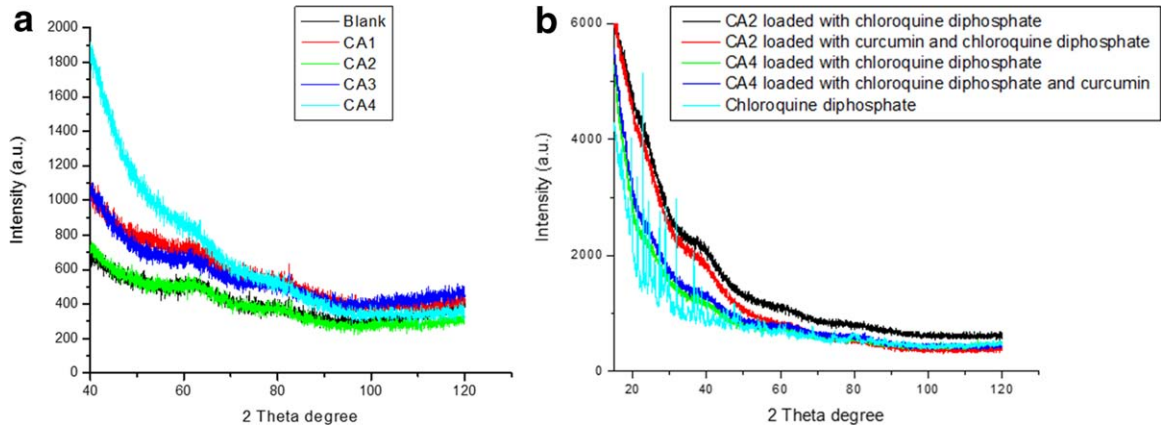

Figure 6. (a) The thermograms of the soy protein-carbopol-polyacrylamide hydrogels. (b) The thermograms of the soy protein-carbopol-polyacrylamide hydrogels loaded with chloroquine diphosphate and curcumin. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of the hydrogels resulting from ionization of the carboxylate groups. The aforementioned factor also results in enhanced diffusion of the drug from the hydrogel networks.[18] The slow release of the drug at acidic pH suggests that the hydrogels are potential delivery devices for sustained release mechanism to the gastrointestinal region. There are similar findings reported by other researchers.[19,20] The release kinetic of chloroquine diphosphate from the hydrogels was studied using Peppas eqs. (2) and (3) at a temperature of 37 °C and at pH of 1.2 and 7.4.

$$\frac{M_t}{M_\infty} = Kt^n \tag{2}$$

$$\log \frac{M_t}{M_\infty} = n \log t + \log K \tag{3}$$

where n is the diffusion or release exponent, K is the kinetic constant, M_t is the amount of drug released at time t and M_∞ is the total amount of drug loaded onto the hydrogels. A graph of $\log(M_t/M_\infty)$ against log t of the obtained data was drawn according to eqs. (2) and (3). Diffusion exponent, n was estimated from the linear regression of the graph. According to Peppas equation, $n = 0.5$ indicates Fickian diffusion, $0.5 < n < 1$ indicates anomalous or non-Fickian diffusion which refers to a combination of diffusion and erosion controlled rate release. $n = 1$ and above indicates case 2 relaxation[21] or super case transport-2. The n values for chloroquine diphosphate was found to be 1.08, 1.15, 1.25 for blank, CA2, and CA4, respectively at pH 1.2 and 1.06, 1.25, 1.25 for CA4, CA2, and blank at pH 7.4, respectively. The n values suggested super case transport-2 (Table III). The coefficient of determination R^2 was between 0.9996 and 0.9998 indicating good linearity.

***In Vitro* Dual Drug Release Kinetics.** Curcumin and chloroquine diphosphate were both loaded onto the hydrogels. Chloroquine diphosphate is very soluble in water whereas curcumin is poorly soluble in water (<0.1 mg/mL). The single loaded hydrogels released drugs faster than the hydrogels loaded with two drugs. Hydrogels CA2 and CA4 were selected for dual drug delivery studies so as to study the effects of natural polymers, SPI and acrylic acid in the network on the release profile of water soluble and water insoluble drug. At pH 1.2, 33 and 37% of chloroquine diphosphate was released from CA2 and CA4, respectively, over a period of 3 days [Figure 7(a)]. At pH 7.4, 77 and 58% of chloroquine diphosphate was released from CA2 and CA4, respectively, over a period of 24 h [Figure 7(b)]. The rate of release of curcumin from the hydrogels at pH 1.2 was 31 and 34% from CA2 and CA4, respectively, over a period of 3 days [Figure 7(c)]. 50 and 81% of curcumin was released at pH 7.4 from CA2 and CA4, respectively, over a period of 24 h [Figure 7(d)]. In the presence of both drugs, the rate of release of curcumin was higher at pH of 7.4 than chloroquine diphosphate. Factors that influenced the rate of release of drugs from the hydrogel networks are degree of cross-linking, water solubility of the drug and the pH of buffer solution used. A graph of $\log(M_t/M_\infty)$ against log$t$ was drawn for the data according to eqs. (2) and (3). Diffusion exponent, n was estimated from the linear regression of the graph. For CA2 and CA4 loaded with curcumin and chloroquine diphosphate, the n values for chloroquine diphosphate were 1.47 and 1.82, respectively, at pH 1.2. The n values were 1.06 for chloroquine diphosphate from CA2 and CA4 at pH 7.4. The diffusion exponent, n for curcumin at pH 1.2 were 1.03 and 1.04 for CA2 and CA4, respectively. At pH 7.4, n values were 1.05 and 1.04 for curcumin for CA2 and CA4, respectively (Table IV). The coefficient of determination R^2 were in a range of 0.9990–0.9999 indicating good linearity. The n values suggested super case transport 2. The different release mechanisms for the drug when alone and in combination suggest that chloroquine diphosphate and curcumin were influenced by the presence of each other in the hydrogel networks. Similar findings were reported by Castro *et al.*, in the dual release studies of aminophylline and triamterene from hydrogel composites whereby the release of both drugs from the composites were influenced by the presence of the other drug in the composites.[22] The release behavior of both drugs from the hydrogels suggest that these hydrogels are potential dual drug delivery systems for antimalarials.

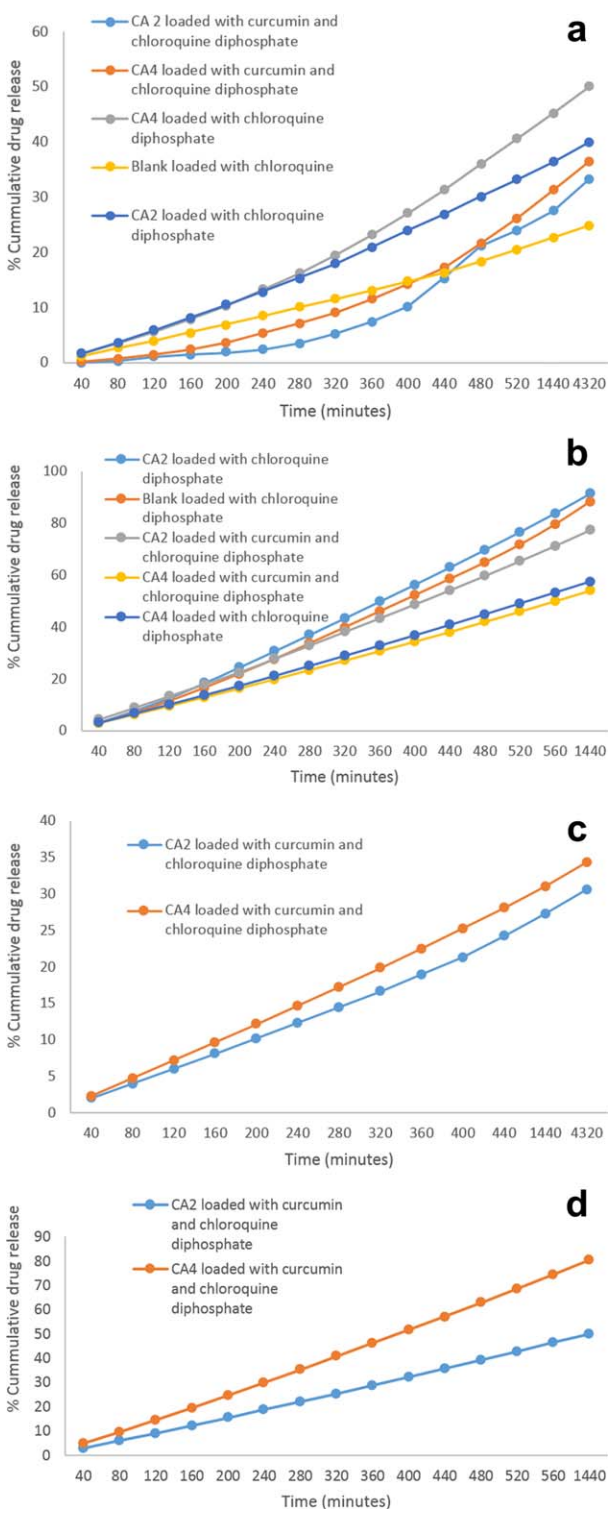

Figure 7. (a) The release profile of chloroquine diphosphate from blank, CA2, and CA4 at pH 1.2. (b) The release profile of chloroquine diphosphate from blank, CA2, and CA4 at pH 7.4. (c) The release profile of curcumin from CA2 and CA4 at pH 1.2. (d) The release profile of curcumin from CA2 and CA4 at pH 7.4. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table III. Kinetic Release Data for Chloroquine Diphosphate from the Hydrogels

Hydrogels	pH	*n*	*K*	R^2
Blank	1.2	1.08	1.64	0.9998
CA2	1.2	1.15	1.63	0.9996
CA4	1.2	1.25	1.84	0.9957
CA4 loaded with curcumin and chloroquine diphosphate	1.2	1.82	3.57	0.9975
CA2 loaded with curcumin and chloroquine diphosphate	1.2	1.47	4.74	0.9810
Blank	7.4	1.25	3.53	0.9999
CA2	7.4	1.25	3.43	0.9998
CA4	7.4	1.06	2.76	0.9999
CA4 loaded with curcumin and chloroquine diphosphate	7.4	1.06	2.83	0.9990
CA2 loaded with curcumin and chloroquine diphosphate	7.4	1.06	2.49	0.9996

Table IV. Kinetic Data for Dual Release of Chloroquine Phosphate and Curcumin

Hydrogel	pH	Chloroquine diphosphate			Curcumin		
		n	*K*	R^2	*n*	*K*	R^2
CA2	1.2	1.47	4.74	0.9810	1.03	3.13	0.9995
CA4	1.2	1.82	3.57	0.9975	1.04	3.00	0.9999
CA2	7.4	1.06	2.49	0.9996	1.05	2.81	0.9999
CA4	7.4	1.06	2.83	0.9990	1.03	2.27	0.9998

CONCLUSIONS

Soy protein isolate-carbopol-polyacrylamide based hydrogels were prepared by crosslinking soy protein isolate and acrylic acid in different ratios with acrylamide. The hydrogels swelling capacity was dependent on the pH of buffer solution used and the degree of crosslinking. The highest cross-linked hydrogel CA2, exhibited minimal swelling ability whereas CA1 with 0.05 g of SPI displayed a higher swelling ability. This findings further confirmed that the role of natural polymers in swelling ability of hydrogels. The single release profile of the chloroquine diphosphate at pH 7.4 was quick over a period of 24 h. The dual release of both drugs from the hydrogels was influenced by the other drug in the hydrogel. This further suggests that these hydrogels are potential dual drug delivery systems whereby both drugs can work over different period of time to overcome drug resistance that is common with antimalarials.

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REFERENCES

1. Fact Sheet. World Malaria Report **2015**: http://www.who.int/malaria/media/world_malaria_report_2014/en/. Accessed 14th December 2015.
2. Fact Sheet. World Malaria Report **2015**: http://www.who.int/malaria/media/world-malaria-report-2015/en/9TH. Accessed 14th December 2015.
3. Bartoloni, A.; Zammarchi, L. *Mediterr. J. Hematol. Infect. Dis* **2012**, *4*, e2012026.
4. Taylor, W. R.; Hanson, J.; Turner, G. D.; White, N. J.; Dondorp, A. M. *Chest* **2012**, *142*, 492.
5. Rijken, M. J.; McGready, R.; Boel, M. E.; Poespoprodjo, R.; Singh, N.; Syafruddin, D.; Rogerson, S.; Nosten, F. *Lancet Infect. Dis.* **2012**, *12*, 75.
6. Ward, S. A.; Bray, P. G.; Ritchie, G. Y. Chloroquine Transport in the Malarial Parasite *Plasmodium falciparum*. In Drug Transport in Antimicrobial and Anticancer Chemotherapy; Georgopapadakou, N. H., Ed.; Dekker: New York, **1995**; p 353.
7. Padmanaban, G.; Nagaraj, V. A.; Rangarajan, P. N. *Curr. Sci.* **2012**, *102*, 704.
8. Memvanga, P. B.; Coco, R.; Préat, V. *J. Control. Release* **2013**, *172*, 904.
9. Laware, R. B.; Kuchekar, B. S. *Int. J. Pharm. Pharm. Sci.* **2015**, *7*, 41.
10. Aditya, N. P.; Patankar, S.; Madhusudhan, B. *Pharmacology* **2009**, *3*, 49.
11. Anand, P.; Kunnumakkara, A. B.; Newman, R. A.; Aggarwal, B. B. *Mol. Pharm.* **2007**, *4*, 807.
12. Munjeri, O.; Hodza, P.; Osim, E. E.; Musabayane, C. T. *J. Pharm. Sci.* **1998**, *87*, 905.
13. Aderibigbe, B.; Sadiku, E.; Jayaramudu, J.; Ray, S. S. *J. Appl. Polym. Sci.* **2015**, *132*, DOI: 10.1002/app.41613.
14. Bajpai, S. K.; Saggu, S. P. S. *Des. Monom. Polym.* **2007**, *10*, 543.
15. Chen, J.; Zhou, R.; Li, L.; Li, B.; Zhang, X.; Su, J. *Molecules* **2013**, *18*, 12415.
16. Varaprasad, K.; Reddy, G. S. M.; Jayaramudu, J.; Sadiku, R.; Ramam, K.; Ray, S. S. *Biomater. Sci.* **2014**, *2*, 257.
17. Peppas, N. A.; Bures, P.; Leobandung, W.; Ichikawa, H. *Eur. J. Pharm. Biopharm.* **2000**, *50*, 27.
18. Omidian, H.; Park, K. *J. Drug Deliv. Sci. Technol.* **2008**, *18*, 83.
19. Saparia, B.; Solanki, A.; Murthy, R. S. R. *Indian J. Exp. Biol.* **2001**, *39*, 902.
20. Sahu, S. K.; Ram, A. *Curr. Drug Deliv.* **2013**, *10*, 601.
21. Ritger, P. L.; Peppas, N. A. *J. Control. Release* **1987**, *5*, 23.
22. Castro, E.; Mosquera, V.; Katime, I. *Nanomater. Nanotechnol.* **2012**, *2*, 1.