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Kinetic Studies for the Release of Hydroxychloroquine Sulphate Drug (HCQ) *In-vitro* in Simulated Gastric and Intestinal Medium from Sodium Alginate and Lignosulphonic Acid Blends

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Abstract

Biodegradable polymeric blends are used to study the controlled release of Hydroxychloroquine sulphate (HCQ) as the model drug used extensively in COVID-19 treatments. HCQ drug is loaded in sodium alginate (NaAlg) and lignosulphonic acid (NaLS) blends as matrix are crosslinked using calcium chloride solution. Its release is evaluated in different pH mediums of simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The HCQ release data obtained during experimentation is used to study kinetics using different models to investigate polymeric relaxation's drug diffusion and mechanism in water-soluble HCQ drug. The drug release mechanism best fits the Higuchi model with Fickian diffusion as the primary polymeric relaxation mechanism.

Keywords: Sodium alginate, COVID 19, Lignosulphonic acid, HCQ, Control drug release, Drug kinetics, Biopolymer, Crosslinking

Introduction

Over the decades, various biodegradable polymeric materials have been used as drug carriers for drug release. Several synthetic and biodegradable polymers are used as drug carriers [1-4]. Over the past few years, biodegradable polymers, for example, polycaprolactone, polylactic acid, polyethylene glycol and chitosan, etc., are being used extensively in controlled drug delivery applications because of their release profiles for a wide range of drugs [5-8]. Sodium alginate is a seaweed product used as a drug carrier because of its biodegradability, biocompatibility, pH responsiveness, and nontoxicity [9]. In the COVID-19 pandemic, HCQ is prescribed as an antimalarial drug, especially in 2021 [10]. After a while, it was reported that HCQ administration caused some side effects in some heart patients [11]. As a result, HCQ administration has been banned prescribing for COVID. To overcome these side effects, a controlled release mechanism is adopted to study release profiles of HCQ [12-13]. An exhaustive literature survey reveals that not much work is reported on control release studies of HCQ drugs.

Sodium alginate is an extensively found application in drug delivery, gelling, food industry, scaffolds, wound healing, etc. [14,15]. Lignosulphonic acid is another biodegradable polymer obtained from plant by-products used in the cement industry as a water reducer [16,17]. Biodegradable polymeric blends made of sodium alginate and lignosulphonic acid were used to load HCQ drug and study its release mechanism in different pH conditions to mimic body fluid conditions present in the stomach and intestine. The experimental values obtained *in-vitro* for control release of HCQ drug [18,19] are used to discuss the type of diffusion, reaction order, polymeric relaxation process such as Fickian or non-Fickian mechanism, and drug release mechanism.

Materials and methods

Materials

Alginic acid of sodium salt (NaAlg), generally called sodium alginate, and sodium salt of lignosulphonic acid (NaLS) are purchased from Sigma Aldrich, Germany. The buffer solutions such as pH 1 (0.1 M HCl) and buffer tablets (pH 4, 7 and 9.2) are used as received from Nice chemicals. The release studies are carried out in simulated mediums such as simulated intestinal fluid (pH 7 and 9.2), and simulated gastric fluid (pH 1 (0.1 M HCl) and pH 4) are used. Hydroxychloroquine sulphate drug is received as a gift sample, and calcium chloride from Nice chemicals is used as a crosslinking agent.

Synthesis of drug loaded NaAlg/ NaLS (80:20) blends

The sodium alginate (4 %) is soaked overnight in double distilled water and mixed with the sodium salt of lignosulphonic acid taken in a 100 ml beaker in the ratio of (80:20). To this polymeric blend mixture, 2 % HCQ drug solution (2 mg/1 mL) is added. A magnetic stirrer is used for stirring continuously for 30 min.

Crosslinking of NaAlg /NaLS beads

The HCQ-loaded NaAlg/NaLS beads are formed by dropping the mixture from a 5 mL syringe in 25 mL of 2 % calcium chloride solution. The beads are allowed to crosslink at different time intervals (10, 20, and 30 min) in an aqueous medium. The crosslinked beads are dried for 1 day in a hot air oven at 60 °C.

Characterization

***In-vitro* HCQ drug release studies**

The kinetics of HCQ drug release from NaAlg /NaLS (80/20) beads is studied at different pH solutions of the physiological medium. Because the drug orally taken from the mouth passes through the stomach (SGF and its pH ranges between 1 and 4) and then passes through the intestine (SIF, whose pH ranges between 7 and 9.2). The drug-loaded NaAlg /NaLS beads are dropped in 25 mL buffer solutions at a physiological temperature of 37±1 °C. After every 1 h interval, the HCQ drug release was recorded at 342nm wavelength using UV-Visible Spectrophotometer (Shimadzu-2600). The HCQ drug release tests were performed in triplicate at different crosslinking beads in SGF and SIF.

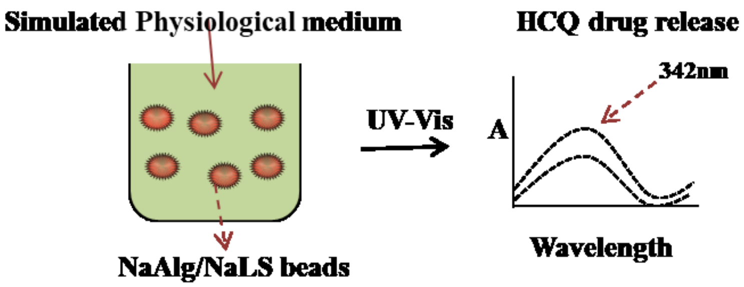

Figure 1 HCQ drug release from NaAlg/NaLS matrix *in-vitro* in SGF and SIF.

Study of kinetics using drug release data

Various models are reported to study the order of reaction and polymer reaction mechanism listed in **Table 1**. Efforts are made to emphasize kinetic models for calculating multiple parameters using Zero order, First order, and Higuchi model [20]. Also, drug release data are used to discuss the polymer relaxation process from the polymer matrix, which influences drug release. The diffusion models are used to fit the experimental data. Model 1 is based on the Korsmeyer-Peppas equation and describes the Fickian diffusion of a drug [21]. The drug transport mechanism was also discussed using the Peppas-Sahlin equation [13, 22] given in **Table 1**.

Table 1 List of kinetic models used to calculate various parameters to evaluate drug diffusion and polymer relaxation mechanism.

Model	Formula used		Parameters
Zero-order model	$M/M_\infty = k_0 t$	(1)	M/M_∞=is a fraction of the drug released,
First order model	$\text{Log}(M/M_\infty) = kt^n$	(2)	k_0, k_1, and k_2 are zero, first, and
Higuchi model	$M/M_\infty = k_2 t^{0.5}$	(3)	second-order constants of a reaction.
Krosmeyer-Peppas model	$M/M_\infty = kt^n$	(4)	n-diffusion exponent,
Peppas-Sahlin equation	$M/M_\infty = k_f t^m + k_r t^{2m}$	(5)	m = relaxation exponent
Ratio of the rate constant of Fickian to relaxation	$F/R = k_f/k_r \times 1/t^m$	(6)	k_f, and k_r are the Fickian and relaxation rate constant

Results and discussion

The drug release from the beads made of NaAlg/NaLS (80/20) HCQ compositions in different pH mediums of SGF and SIF are used to discuss the diffusion of drug and polymer relaxation in simulated mediums. The crosslinked HCQ drug-loaded NaAlg/NaLS beads are investigated for their drug release in SGF. The release behaviours of beads are observed in **Figure 2**. The drug release for 30 min crosslinked beads are more stable for water uptake for swelling, which influences drug release for a longer duration up to 7 h and beyond. It is observed that HCQ drug release is up to 40 - 70 % in pH 1 and 4 (assumed to be simulated gastric fluid). At the same time, the drug release is very high in pH7, releasing more than 80 ± 5 % HCQ drug in 7 h. But surprisingly, the results obtained are pretty contradictory in pH 9.2, and the release is minimal. The low release in pH 9.2 is due to the counter ions, i.e. Na^+, that shield the charge of the carboxylate anions and prevent efficient anion–anion repulsion. As a result, very low swelling of beads is observed, affecting the drug release behaviour of the NaAlg/NaLS matrix [23].

In these experiments, the pH responsiveness of alginate gels shows a more significant role in drug release from the matrix due to the swelling of beads in a medium of SGF and SIF. The swelling of beads is very high in an aqueous medium of pH 7 because the guluronic acid present in NaAlg undergoes hydrolysis and exchange of Ca^{2+} ions present in crosslinked beads with Na^+ ions present in pH 7 (sodium phosphate buffer solution). Swelling of beads ultimately causes enhancing the porosity and absorbing water, which dissolves the HCQ drug embedded/trapped in the alginate gel and gets released in an aqueous solution through diffusion. In SGF (pH 1 and 4), the HCQ drug release is minimal since the guluronic acid in sodium alginate gel is stabilized by intermolecular hydrogen bonding, which leads to shrinkage in the alginate structure [24], which results in very low swelling of NaAlg/NaLS beads. The shrinkage is attributed to the Fickian diffusion of drug molecules from beads.

In-vitro HCQ drug release kinetics in 4 different pH mediums are discussed by plotting cumulative drug release (CDR) versus time (Zero order, First order and Higuchi equation). The correlation coefficient values obtained by the best fitting method are furnished in **Table 2**.

Table 2 shows the HCQ drug release data values obtained by best fit method attributes for Zero-order and Higuchi model for 30 min crosslinked beads in all pH media. The release in the Zero-order rate constant and Higuchi model are 2 - 5 %/h range, and the correlation coefficient is 0.8 - 0.99 %. The self-assembled alginate matrix, associated with diffusion and swelling, erosion-based drug release characteristics results in the approximately Zero-order and Higuchi model release features in SGF and SIF.

In general, the experimental data is used to estimate n and k values for the drug release in all pH mediums, and these values are furnished in **Table 2**. If n = 0.45, the drug diffuses and releases from the polymer matrix, which is said to be Fickian diffusion, whereas n < 0.45 is Fickian or quasi-Fickian [21]. The n' values between 0.45 and 1 are said to be anomalous. The n and k values were observed based on experimental data, and the best fit method showed dependence on the extent of crosslinking as well as on the pH of the medium. The n' values fall in the range of 0.139 to 0.378 (**Table 2**), showing Fickian or quasi-Fickian transport. These results indicate that HCQ drug releases from SA/LS (80/20) beads are swelling dependant, which is attributed to 'swelling dependant Fickian transport'.

The Sahlin-Peppas model is used to evaluate the drug release mechanism, and plots are shown in **Figure 3**. It was observed that polymer relaxation had played a vast role in drug release characteristics because the value R/F < 1 is found to be the best fit model for the Higuchi method as shown in **Figure 2**. The relaxation exponent 'm' values obtained are in the range of 0.1 - 0.2, which indicates the dominant drug transport mechanism appeared to be Fickian diffusion (n < 0.45).

Not much HCQ drug release was observed in pH9.2 (SIF) because of its alkalinity causing de-swelling, which affects the drug release, which is supported by shallow values of 'n' and 'k', which fits the Higuchi model, i.e., furnished in **Table 2**.

It was reported that the values M/M∞ ≤ 0.6 are to be considered for best fit, whereas in the case of the values obtained for 10 and 20 min crosslinked NaAlg/NaLS (80/20) beads are M/M∞ ≥ 0.6, hence n and k values obtained are ignored are highlighted in dark in **Table 2**.

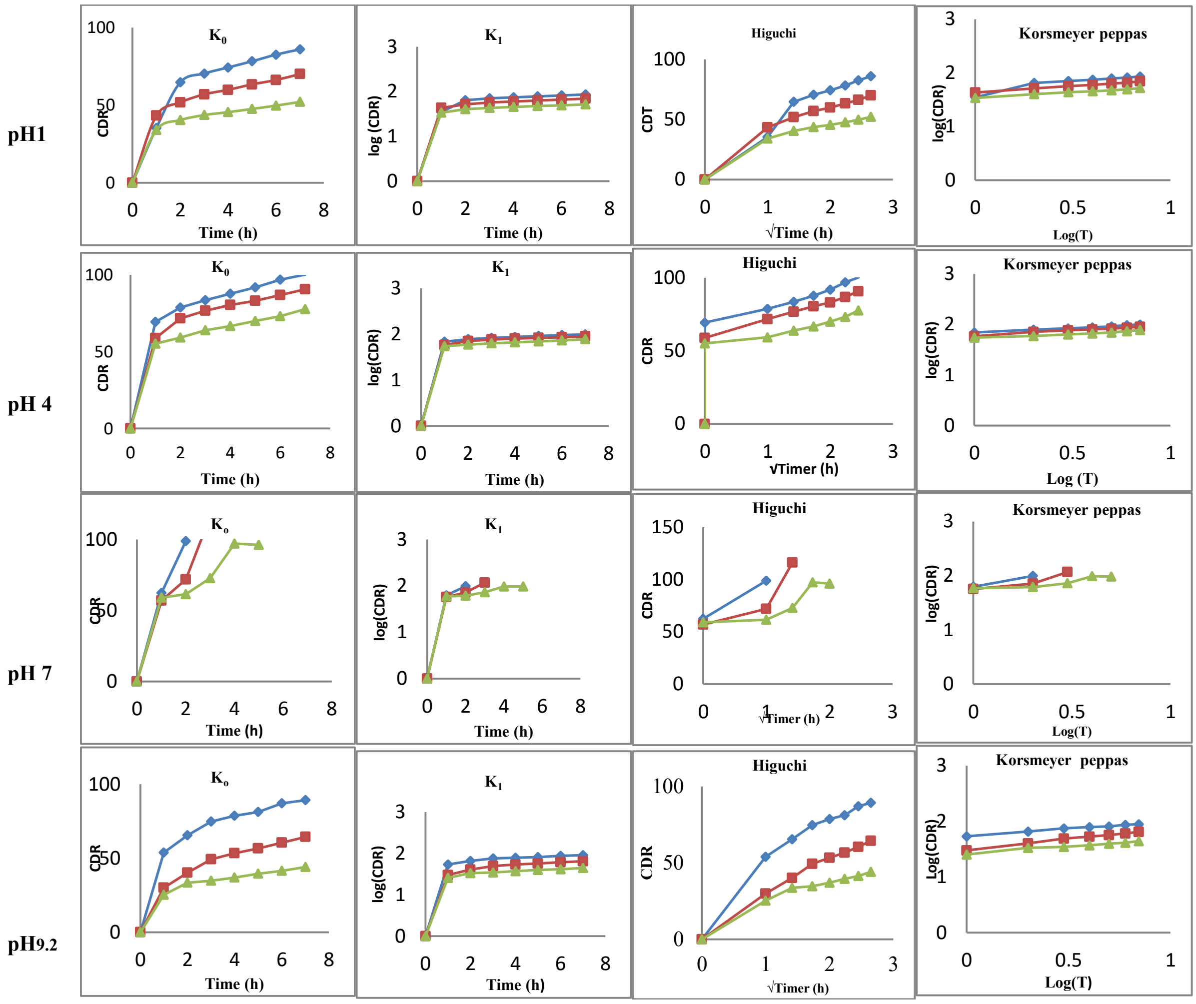

Figure 2 Plots of kinetics of HCQ drug release using different models (Zero order, First order, Higuchi and Korsmeyer-Peppas model in different pH (1, 4, 7, and 9.2).

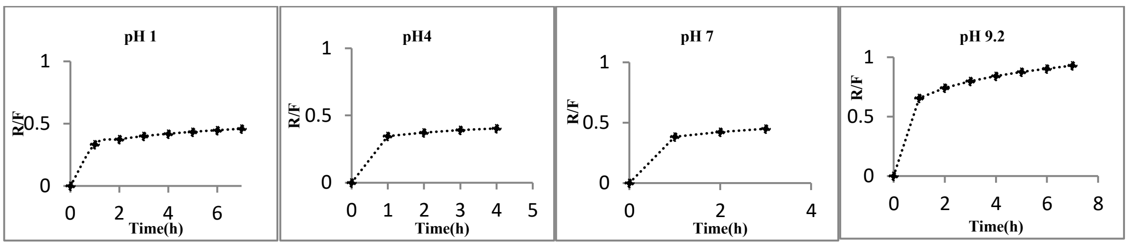

Figure 3 Plots of kinetics of HCQ drug using Sahlin-Peppas model for drug transport mechanism from Relaxation mechanim to Fickian transport (R/F) vs time.

Table 2 Kinetic parameters obtained from Zero-order, First-order, Higuchi, Ritger-Peppas and Sahlin-Peppas models.

	Cross-linking time	Zero order		First order		Higuchi model		Korsmeyer -Peppas			Sahlin-Peppas			
		K_0	R^2	K_1	R^2	K_2	R^2	K	n	R^2	K_f	K_r	m	R^2
pH 1	**10 min**	0.154	0.766	0.38	0.48	0.36	0.95	-	-	-	-	-		-
	20 min	0.125	0.69	0.24	0.43	0.24	0.92	0.44	0.23	0.69	-	-		-
	30 min	0.095	0.658	0.15	0.43	0.22	0.90	0.34	0.21	0.65	0.25	0.09	0.16	0.7
pH 4	**10 min**	0.183	0.635	0.86	0.40	0.43	0.99	-	-	-	-	-		-
	20 min	0.166	0.650	0.32	0.42	0.39	0.67	-	-	-	-	-		-
	30 min	0.140	0.628	0.55	0.4	0.33	0.62	0.55	0.14	0.63	0.41	0.14	0.11	0.7
pH 7	**10 min**	0.520	0.97	-	0.80	0.67	0.99	-	-	-	-	-		-
	20 min	0.401	0.95	0.73	0.70	0.52	0.8	-	-	-	-	-		-
	30 min	0.230	0.83	0.59	0.52	0.45	0.8	0.57	0.18	0.83	0.41	0.16	0.14	0.8
pH 9.2	**10 min**	0.163	0.71	0.48	0.43	0.38	0.93	-	-	-	-	-	-	
	20 min	0.112	0.82	0.19	0.49	0.25	0.98	0.31	0.38	0.72	0.06	0.25		0.8
	30 min	0.078	0.72	0.11	0.45	0.18	0.93	0.26	0.26	0.72	0.16	0.11	0.17	0.7

Conclusions

Biodegradable beads of NaAlg and NaLS are used for HCQ drugs to demonstrate and evaluate drug release kinetics in SGF and SIF. Different kinetic models are addressed to study drug transportation and drug-polymer mechanism. Experimental values show that the surrounding pH medium influences HCQ drug release. It is observed that HCQ drug releases for a longer duration in pH1 and 9.2. Meanwhile, the release is moderate in pH 4 and high in pH 7. It is confirmed that release data agree with Zero-order and Higuchi models. Thorough evaluations are made to understand the drug transport mechanism, and it is confirmed that the NaAlg/NaLS (80/20) matrix follows a Fickian diffusion transport mechanism which plays a vast role in drug diffusion. The HCQ drug, once a life-saving drug during the COVID-19 pandemic, is ignored because of its side effects. At the same time, this control release evaluation of HCQ drug using NaAlg/NaLS matrix could provide some results which can overcome side effects.

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