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Kinetics and Mechanisms of Doxorubicin Release from hydroxyapatite-sodium alginate nanocomposite

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ABSTRACT

In-vitro kinetics and mechanistic study helps the formulation and research scientists to forecast possible rate and mechanism of *in-vivo* drug release. This study investigates the kinetics and mechanism of Doxorubicin (DOX) (an anticancer drug) release from hydroxyapatite-sodium alginate nanocomposites (HASA). *In-situ* preparation of hydroxyapatite (HA) in the presence of sodium alginate (SA) was done by wet chemical precipitation method. Drug loading was carried out at neutral pH, while *in vitro* drug release study was carried out in synthetic body fluid (SBF) at pH 7.4 and 37 ^{0}C. The release experimental data was fitted into model-dependent and model independent methods using DDSolver software, an excel add-in. The release half time (t_{50}) increased with increase in SA content. Except for HA and HASA-1%wt, the release of DOX from other formulations can best be explained by first order kinetics. The value of n exponent in Korsmeyer-Peppas model ranged from 0.220 to 0.497, which indicate that DOX release from all the formulations followed Fickian diffusion mechanism. The results of profile comparison indicate that the following release profiles are similar: HASA-5%wt and HASA-20%wt, HASA-20%wt and HASA-33%wt, HASA-33%wt and HASA-50%wt. Addition of SA to HA prolonged the release of DOX and also influenced the kinetics and the mechanism of DOX release from the nanocomposite.

Keywords: kinetics, mechanism, doxorubicin, sodium alginate, hydroxyapatite, drug release

INTRODUCTION

Release mechanisms refer to the ways through which drug molecules are transported or released from the carrier system to the surrounding medium. The knowledge of release mechanisms and the physicochemical processes that influence drug release is important for the development of effective controlled drug delivery systems. Based on release of active agents from delivery systems, mechanisms of controlled drug release can be classified as diffusion, erosion/degradation, and swelling and dissolution-controlled delivery systems. More than one mechanism is often involved at a given time or different mechanisms may dominate at different stages of the drug delivery process (Siegel and Rathbone, 2012). Karimi (2011) defined diffusion as the process by which penetrants are moved from one part of the system to another as a result of random molecular motion. Numerous models of diffusion in polymer-based systems are based on Fick's first law which governs steady state diffusion. The equation is stated as:

$$J = -D\frac{\partial c}{\partial x} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where J is the flux which gives the quantity of penetrant diffusing across unit area of medium per unit time, D is the diffusion coefficient, c the concentration, and x the distance, and $\frac{\partial c}{\partial x}$ is the gradient of the concentration along the axis (Comyn, 1985). Fickian diffusion release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. The filled polymers with nanoparticles have lower diffusion coefficient than unfilled ones. Geometrical dimension, size distribution and amount of fillers as well as its level of dispersion into polymer matrix are important factors controlling the rate of mass transfer through the filled polymer especially nanocomposites (Karimi, 2011). Hydrophilic matrix shows a typical time-dependent profile by which the dissolution medium penetrate into the dosage form and the polymeric material swells and drug molecules start to move out from the system through diffusion (Landgraf *et al*., 2005). The most widely used model to describe diffusion controlled drug release systems is the Higuchi models (Higuchi, 1961). Although drug release may follow mixed mechanisms, in diffusion-controlled mechanism, diffusion is the rate limiting step (Huang and Brazel, 2001).

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Drug release mechanism can also be by polymer degradation or erosion. Degradation describes the polymer chain/bond cleavage reaction which is a chemical process, whereas erosion refers to loss of polymer material (chemical and physical processes) (Kanjickal and Lopina, 2004). Erosion can either be surface (heterogeneous) or bulk (homogeneous) erosion. Polymer systems with highly reactive functional groups undergo faster degradation than diffusion of water into it, leading to surface erosion (heterogeneous), while degradation of polymer with less reactive groups (e.g. poly (lacitide-co-glycolide) (PLGA)) is much slower than diffusion of water into it, leading to bulk or homogeneous erosion (Kanjickal and Lopina, 2004). Factors influencing the biodegradation kinetics of the selected polymers are the chemical structure, size, shape, chain defects, ion exchange, ionic strength, pH, morphology (amorphous, semi-crystalline, crystalline, microstructure and residual stress), mechanism of degradation (enzymatic, hydrolysis or microbial) molecular weight distribution, route of administration, and site of action (Badri *et al*., 2014). If degradation is relatively rapid, then the swelling state of the network may change during the release process, and a complex interplay between swelling and diffusion will determine the release kinetics (Siegel and Rathbone, 2012). Drug release mechanism for biodegradable material (e.g. SA, polylactic acid (PLA) and PLGA) are mainly through bulk erosion (Biondi *et al*., 2008). However, it has been shown that the release rates from such materials are not simply driven by degradation in earlier stage, the concentration gradient and shape of the device seem to have more profound impact on the release rate, while in the later stage, degradation becomes the dominant driving force (Biondi *et al*., 2008). Furthermore, polysaccharides also undergo dissolution in aqueous medium as result of solvent penetration effect, polymer swelling and polymer chain disentanglement and relaxation. For this reason, release mechanism for polysaccharide-based materials could be driven by diffusion and/or erosion (Bonacucina *et al*., 2009). In general, water soluble drugs are mainly released by diffusion, while self-erosion is the principal release mechanism for low water soluble drugs (Singhvi and Singh, 2011). Swelling-controlled systems consist of water soluble drugs dispersed in glassy polymer matrix. During swelling, there is uptake of water by a polymer system which leads to increase in volume and formation of gel layer in which the dissolved drug can be transported due to increased mobility of the polymeric chain. The drug release kinetics for this system can be modified by the gel layer thickness and the rate at which it is formed (Kanjickal and Lopina, 2004). As the proportion of the polymer increases, the gel formed reduces diffusion of the drug and delays erosion of the matrix (Ford *et al.*, 1985). Swelling dynamics are often complex and a variety of temporal release patterns are observed under swelling controlled system (Siegel and Rathbone, 2012). In dissolution-controlled mechanism, the drug is embedded in slow dissolving or erodible matrix or by coating with slow dissolving substance. In 1897, Noyes and Whitney developed an equation which formed the fundamental evaluation of the kinetics of drug release. This equation is known as Noyes-Whitney's Rule, and is stated as (Noyes and Whitney, 1987):

$$\frac{dM}{dt} = KS\,(C_s - C_t) \quad \text{………………………… (2)}$$

Where M is the mass transferred with respect to time, t, by dissolution from the solid particles of instantaneous surface, S, under the effect of prevailing concentration driven force (C_s- C_t), where C_t is the concentration at time t, and C_s is the equilibrium solubility of the solvent at the expected temperature. The rate of dissolution $\frac{dM}{dt}$ is the amount dissolved per unit area per unit time. The following models are commonly used to evaluate drug release data: zero order model, first order model, Higuchi model, Korsmeyer-Peppas model (power law), and Hixson – Crowell's model. Other mathematical models used in drug release study include, Weibul model, Gompertz model, Ritger-Peppas model, Baker Landsdale model. The efficacy and toxicity of drug delivery system depends upon drug release kinetics (Raval et al., 2010). The aim of this study is to evaluate the kinetics and mechanism of Doxorubicin release from hydroxyapatite-sodium alginate nanocomposites.

MATERIALS AND METHODS

Materials

Distilled water was used for the preparation of all the solutions used in this work. Sodium alginate (SA) was obtained from Fisher Scientific Company, USA, while DOX HCl was from Zuvius Lifescience Ltd. All other reagents were of analytical grade and were used without further purification.

Preparation of hydroxyapatite-sodium alginate nanocomposites.

Hydroxyapatite-sodium alginate nanocomposite was prepared as previously reported (Onoyima et al., 2017). Previously prepared phosphate solution (200 cm^3 of 0.06M) was added in drop-wise manner to a 100 cm^3 separately prepared SA solution (1%wt) while stirring vigorously. The mixture was added drop by drop to 200 cm^3 aqueous solution of calcium nitrate tetrahydrate ($Ca(NO_3)_2.4H_2O$) (0.1M) prepared earlier with continuous stirring for 24 h. The pH was maintained at approximately 10.5 throughout the experiment using 1M sodium hydroxide solution.

The suspension was then stored for 24h at room temperature for aging, after which the precipitate was separated by centrifugation, and subsequently washed with distilled water thrice. The resulting gel-like paste was dried at 60^{o}C for 24 h and then ground using agate mortar to obtain fine powders. The procedure was repeated using varying quantities of SA (5% wt, 20% wt, 33% wt, and 50% wt).

Preparation of drug-loaded nanocomposites

Drug loading was done according to the method by Raj *et al.,* (2013). In order to load the drugs on HASA particles, 100 mg of the HASA was added to 10 cm^3 of the drug solution (2 mg/ml) and stirred using magnetic stirrer for 40 min. Then the solution was left undisturbed overnight. The suspension was then centrifuged (2000 rpm, 5 min) and the supernatant and precipitate were separated. The amount of drug loaded was determined by finding the difference in the concentrations in the aqueous solution before and after loading.

In-vitro drug release study

The *in vitro* drug release study was carried out following a method reported by Sivakumar and Rao, (2002). In order to determine the drug release profile, 100 mg each of the drug loaded nanocomposite was introduced into a screw capped glass bottle containing 50 cm^3 of synthetic body fluid (SBF) medium at 37^{o}C and pH 7.4 under sterile conditions. Aliquots of 5 cm^3 samples were withdrawn by a pipette at regular intervals and replaced immediately with 5 cm^3 of fresh SBF medium (this was accounted for when calculating the amount released). Drug concentrations in the collected samples were measured using UV-VIS Spectrophotometer.

Drug release kinetics and mechanistic study

In order to elucidate the release kinetics and the mechanism of drug release, model-dependent approach was followed, and the release experimental data was fitted into the following:

Zero order model (Dash *et al*., 2010)

$$Q_t = Q_0 + K_0 t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Where Q_t is the quantity released at time t, Q_0 is the initial quantity of drug and K_0 is the zero order release constant.

First order model (Gibaldi and Feldman (1967) as reported by Chime *et al*., (2013)

$$\text{Log } C = \text{Log}C_0 - \frac{Kt}{2.303} \quad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

where C is the concentration at time t, and C_0 is the initial concentration, and K is the first order constant.

Higuchi model (Higuchi, 1961)

$$Q = A\sqrt{D(2C - C_s)C_s}t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Where Q is the amount of drug released in time t, A is the area of the matrix, D is the diffusivity of the drug (diffusion coefficient), C_s is the drug solubility in the matrix media.

Korsmeyer-Peppas model (Peppas and Korsmeyer, 1986)

$$\frac{M_t}{M_\infty} = Kt^n \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (6)$$

where M_t is the amount of drug released at time t, and M_∞ is the amount of drug loaded. The value of the exponent n is used to indicate the type of release mechanism, where K is a constant which depends on diffusion coefficient and thickness of the film.

Table 1: Exponent n of the Korsmeyer-Peppas law and drug release mechanisms from delivery systems of different geometry

Exponent (n)			Drug release mechanism
Thin film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
0.5<n<1.0	0.45<n<0.89	0.43<n<0.85	Anomalous transport
1	0.89	0.85	Case 11 transport

In order to find out mechanism of drug release from polymeric system, 60% of drug release data is fitted into Korsmeyer-Peppas model (Dash *et al*., 2010).

Hixson-Crowell model (Dash *et al*., 2010)

$$W_t^{\frac{1}{3}} = W_0^{\frac{1}{3}} - Kt \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (7)$$

Where W_t is the weight (mg) of the drug released at time t, W_0 is the initial amount (mg) in the release material, and K is a constant.

Hopfenberg model (Shaikh *et al*., 2015)

$$\frac{M_t}{M_\infty} = 1 - [1 - \frac{K_0 t}{C_0 a_0}]^n \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (8)$$

Where M_t is the amount of drug released at time t, M_∞ is the amount of drug loaded, K_0 is the erosion rate constant, C_0 is the initial concentration of the drug in the matrix, a_0 is the initial radius of the particle and n denotes the geometry. These were done using a combination of DDSolver software and excel sheet.

Comparison of drug release profiles

A release profile is a measure of *in vitro* drug release from a preparation in receptacle media over a period of time. *In-vitro* release study for HA and

the nanocomposites was conducted for 57 hours. Profile comparison of the different formulations was carried out using DDSolver, an excel add-In. Pair-wise model independent procedure was followed and similarity factor (F_2) and the difference factor (f_1) were chosen for comparison (Zhang *et al.*, 2010)

$$f_1 = \{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=i}^{n} R_t}\} \times 100 \quad \text{.....(8)}$$

$$f_2 = 50 \times \log\{[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\} \quad \text{..... (9)}$$

Where n is the number of time points and R_t and T_t are the average percentage of drugs released in reference and test products respectively at time t. Two profiles are considered to be similar when f_2 ranges between 50 and 100 (Zuo *et al.*, 2014). f_1 is zero when the test and reference profiles are identical and increases proportionally with the dissimilarity between the two profiles. f_1 values above 15 are considered dissimilar (Moore and Flanner, 1996). In order to reduce calculation time and eliminate calculation errors, DDSolver program (excel plug-in program) was used for the calculations.

RESULTS AND DISCUSSION

DOX release mechanisms and kinetics

DOX release profiles (Figure 1) show that formulations containing highest relative amount of HA displayed fast and higher release rate than those formulations containing relatively lower amount of HA. After 33 hours, the percent cumulative release for these formulations – HASA-5%wt, HASA-20%wt, HASA-33%wt and HASA-50%wt are 95.15%, 88.70%, 85.82%, and 78.72% respectively. The decreasing percent cumulative release is an indication of increase in more sustained release and decreasing burst release effect. That is to say that increase in the relative amount of SA increased the sustained release of DOX. As has been earlier reported, increase in the relative amount of SA increased the sustained release of DOX (Onoyima *et al.*, 2017). Higher polymer concentration in a nanocomposite material gives rise to more effective diffusion barrier leading to decrease in release rate (Liew *et al.*, 2006). Also the release half time t_{50} (time required for releasing 50% wt of the loaded drug) increased with increase in SA content, which indicates that a sustained release can be obtained by incorporating SA into HA. In order to understand the underlying kinetics and mechanism of DOX release from the different formulations, the release profiles were fitted to different kinetic and mechanistic models such as zero order model, first order model, Korsmeyer-Peppas model, Higuchi model, Hixon-Crowel model, and Hopfenberg model (Table 2).

A number of statistical criteria exist for selection of a suitable model for fitting dissolution data. The most popular ones in the field of dissolution model identification are the adjusted coefficient of

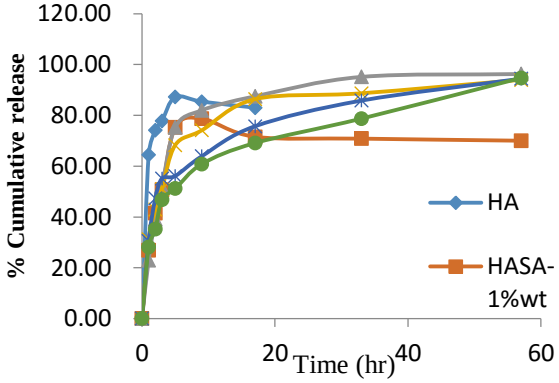

Figure 1: Drug release profiles of DOX from HA and HASA of different formulations

determination (R^2_{adj}), the Akaike Information Criteria (AIC), and the Model Selection Criteria (MSC) (Adams *et al.*, 2001). MSC was selected for evaluation of the goodness of fit in this study because of its simplicity and ease of interpretation. An MSC value of more than two indicates a good fit (Zhang *et al.*, 2010). It was observed that none of the formulations followed zero order kinetics. The ideal release profile for most drugs is the one that follows zero order kinetics, which means that the release rate is constant independent of the concentration in the release material (Cojocariu *et al.*, 2012). Except for HA and HASA-1%wt, the release of DOX from other formulations can best be explained by first order kinetics. This means that the release rate is directly proportional to the concentrations of the drug in the nanocomposites. The observation here indicates that DOX release kinetics is governed by the amount of SA. This is in line with the report by Jesus *et al.*, (2016) that two main factors that influence drug release kinetics are material pore size and functional groups present in both the material and the drug. The purpose of fitting into Korsmeyer-Peppas model is to elucidate the potential transport mechanism. Release mechanisms refer to the ways through which drug molecules are transported or released from the carrier system to the surrounding medium. The value of the exponent n is used to indicate the type of release mechanism, where K is a constant which depends on diffusion coefficient and thickness of the film (Siepmann and Peppas, 2001). When mechanistic models are evaluated, model selection is based on the mechanistic plausibility of the model in addition to its goodness of fit (Zhang *et al.*, 2010). The value of n in Table 2 ranged from 0.220 to 0.497. These values indicate that DOX release from all the formulations followed Fickian diffusion mechanism. Drug

release from systems with n < 0.45 is due to diffusion through matrix and water filled pores (Shende and Marathe, 2015). These values are similar to observation by Cojocariu *et al*., (2012) where n = 0.39, 0.46, and 0.44 for Chitosan-Dellite, Chitosan and Chitosan-Dellite 2 release respectively; and report by Shende and Marathe, (2015) where n ranged from 0.221 to 0.345. These were explained to be due to Fickian diffusion mechanism, where molecular diffusion of the drug due to chemical potential gradient is the rate limiting step.

Table 2: Kinetic and mechanistic models of DOX release from HA and HASA

MODELS	Parameters	HA	HASA-1%wt	HASA-5%wt	HASA-20%wt	HASA-33%wt	HASA-50%wt
Zero Order	R^2	0.5711	0.4346	0.5201	0.7884	0.7830	0.8360
	R^2-adj	0.4281	0.3403	0.4402	0.6216	0.7468	0.8087
	MSC	0.0464	0.0702	0.2343	0.4718	1.0278	1.3078
	K_0(mol.L^{-1}s^{-1})	2.791	0.726	1.024	0.928	0.967	1.055
First Order	R^2	0.6379	0.5555	0.9720	0.9555	0.9334	0.9454
	R^2-adj	0.6379	0.5555	0.9720	0.9481	0.9223	0.9363
	MSC	0.6159	0.5608	3.3258	2.6161	2.2094	2.4084
	K1 (s^{-1})	1.000	0.2350	0.2640	0.138	0.0700	0.0540
Korsmeyer-Peppas	R^2	0.9760	0.9089	0.9185	0.9590	0.8175	0.9599
	R^2-adj	0.9639	0.8785	0.8913	0.9453	0.7566	0.9465
	MSC	2.728	1.595	1.707	2.384	0.9008	2.416
	N	0.220	0.4580	0.4970	0.3740	0.2500	0.3350
Higuchi	R^2	0.6067	0.6005	0.6004	0.6955	0.8410	0.8955
	R^2-adj	0.4755	0.5340	0.5338	0.6448	0.8145	0.8781
	MSC	0.1331	0.4176	0.4173	0.6892	1.3388	1.7584
	K_H	23.03	7.313	13.92	12.82	12.68	12.68
Hixon-Crowel	R^2	0.9007	0.5635	0.8203	0.8931	0.9177	0.9248
	R^2-adj	0.8677	0.4908	0.7904	0.8752	0.9040	0.9122
	MSC	1.510	0.3291	1.216	1.735	1.997	2.087
	KHC	0.092	0.0160	0.0220	0.0200	0.0150	0.012
Hopfenberg	R^2	0.9263	0.6304	0.9720	0.9555	0.9332	0.9454
	R^2-adj	0.8525	0.4825	0.9673	0.9377	0.9064	0.9235
	MSC	1.407	0.2453	3.075	2.362	1.955	2.157
N		1.160	179.2	2816	1573	146.6	932.4

Comparison of drug release profiles

The results of profile comparison (Table 3) indicate that the following release profiles are similar: HASA-5%wt and HASA-20%wt, HASA-20%wt and HASA-33%wt, HASA-33%wt and HASA-50%wt. The similarity factors (f2) for the similar profiles (indicated in bold in Table 3) are above 50. (Note: two release profiles are similar if $50 \leq F_2 \leq 100$ (Zuo *et al*., 2014)). The results show that release profiles which have close composition of alginate are similar. This means that the similarity of different profiles depends on the closeness of their SA compositions.

Table 3: Comparison of DOX release profiles from nanocomposites of different formulations using similarity factor (f2)

	HA	HASA -1%wt	HASA-5%wt	HASA-20%wt	HASA-33%wt	HASA-50%wt
HA	100					
HASA-1%wt	32.39	100				
HASA-5%wt	31.59	43.92	100			
HASA-20%wt	33.13	46.75	63.89	100		
HASA-33%wt	31.42	44.46	48.15	58.26	100	
HASA-50%wt	26.84	43.45	43.01	49.26	59.96	100

CONCLUSION

The study indicates that a sustained release can be obtained by incorporating SA into HA. DOX release kinetics followed first order release and is governed by the amount of SA. The ideal release kinetics is zero order. DOX release from all the formulations followed Fickian diffusion mechanism. It was also observed that release profiles which have close composition of alginate are similar. This means that the similarity of different profiles depends on the closeness of their SA compositions.

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