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Mathematical modeling of drug release from swellable polymeric nanoparticles

Soha Azadi[1,2], Hajar Ashrafi[1,2], Amir Azadi[1,2*]

[1]Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
[2]Department of Pharmaceutics, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

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ABSTRACT

This study aims to provide a comparative mathematical analysis of drug release from swellable polymeric delivery systems to find a general model applicable to multi-mechanistic release. Drug release data from various swellable polymeric nanoparticles extracted from the literatures were applied to the eight conventional models. Coefficient of determination (R^2) and absolute percent error (E%) were calculated for each set as well as the overall error (OE), the number of error (NE) and the akaike information criterion (AIC) for all sets. The model has the highest R^2 and the number of the error, as well as both the lowest overall error (OE) and the akaike information criterion, was considered as the best one. Among the models Weibull (W) model produced R^2 and OE values of 0.93 and 8.79, respectively. Also, the AIC value and the number of errors less than 5% for the model was -34.93 and 46.15% of a total number of data sets respectively. Mathematical modeling of drug release from a carrier is often attempted to recognize the main determinants of the drug release rate from the carrier with the final goal of the identification of the ideal set of conditions leading to the desired release profile *in vivo*.

INTRODUCTION

In recent decades, increasing attention has been devoted to the nanotechnology role in various sciences including biomedical and pharmaceutical fields. Nanoparticles have emerged as promising carriers for the delivery of a wide range of therapeutic drugs. Currently many materials such as polymers, lipids, proteins, carbons, and inorganic metals are under investigation for drug delivery (Yoon *et al.*, 2013). To improve the delivery systems, several types of nanoparticulate systems including polymeric nanoparticles (Hamidi *et al.*, 2011; Azadi *et al.*, 2012; Hamidi *et al.*, 2012; Azadi *et al.*, 2015), polymeric micelles, solid nanoparticles, lipid-based nanoparticles, such as solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and lipid drug conjugate (LDC) (Ashrafi *et al.*, 2013), nanoliposomes (Azadi and Ashrafi, 2016), inorganic nanoparticles, dendrimers, magnetic nanoparticles, Ferrofluids, and quantum dots have been introduced and investigated previously (Hamidi *et al.*, 2008). Among the various types of nanocarriers, polymeric nanoparticles which are classified to swellable and non-swellable ones, have been considered as promising devices in controlled drug release systems. Thus swellable polymeric nanoparticles, are frequently used in such formulations to improve the therapeutic value of various drugs and bioactive molecules due to their interesting physiochemical properties containing improvement of bioavailability, specificity and prolongation of circulating time, as well as reduction of the drug side effects, and risks of toxicity (Kumari *et al.*, 2010). As a matter of fact "drug release" refers to a process in which a drug molecule migrates from an initial position in a polymeric system to release medium and after subjecting to pharmacokinetic procedures, eventually becoming available for its pharmacological action. Accordingly, the drug release from nanoparticles influences its pharmacological effects as a major determinant. Studies on drug release kinetics provide important information into realizing and optimizing of such formulations (Hamidi *et al.*, 2013). A mathematical modeling of drug release from a carrier is often attempted to recognize the release mechanisms considered as an

* *Corresponding Author*
Amir Azadi, Department of Pharmaceutics, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.
E-mail: aazadi @ sums.ac.ir

essential determinant for designing of controlled drug release systems. Additionally, kinetics with one or two parameters can represent several release data (Barzegar-Jalali *et al.*, 2008). Kinetic models are also capable of characterizing the *in vivo* release profile. Therefore, the use of *in vitro* drug release data to predict *in vivo* performance of drug substances can be considered as the rational development of controlled release formulations. This study aims to provide a comparative mathematical analysis of drug molecules release from swellable polymeric drug delivery systems to find a general model the most applicable to determine the *in vivo* profile.

MATERIALS AND METHODS

To study the release kinetics of various drug molecules from the swellable polymeric nanoparticles, such as chitosan, alginate, gelatin, hyaluronic acid and etc, the release data were extracted from the literatures and fitted to the following eight conventional equations:

Zero order equation:

$$F = k_o \cdot t$$

where F stands for the fraction of drug released up to time t and k_o is the zero-order release rate constant

First order equation

$$ln(1 - F) = -k_1 t$$

where k_1 stands for first-order release rate constant

Higuchi's equation

$$F = k_H \cdot t^{1/2}$$

where k_H represents the Higuchi release rate constant

Hixson–Crowell model

$$1 - (1 - F)^{1/3} = -k_{HC} \cdot t$$

where k_{HC} stands for Hixson–Crowell release rate constant

Square root of mass

$$1 - (1 - F)^{1/2} = K_{SR} \cdot t$$

where k_{SR} stands for the square root of mass model release rate constant

Three seconds root of mass:

$$-(1 - F)^{2/3} = K_{TSR} \cdot t$$

where k_{TSR} stands for Three seconds root of mass model release rate constant

Weibull equation

$$ln[-ln(1 - F)] = \beta \ ln \ td + \beta \ ln \ t$$

Where td stands for the lag time before the drug release takes place and β characterizes the shape of the release curve

Korsmeyer–Peppas model

$$\ln F = \ln k_{kp} + n \ln t$$

Where k_{KP} is a constant corresponding to the geometric and structural characteristics of the device and "n" is the release exponent which determined the mechanism of the drug release.

Sum square of errors (SSE), sum square of regression (SSR) and sum square of total variation (SST) were calculated by further equations:

$$\mathrm{SSE} = \sum_{i=1}^{n} \mathrm{e}^2 = \sum_{i=1}^{n} (yi - yfi)^2$$

$$\mathrm{SST} = \sum_{i=1}^{n} (\mathrm{yi} - \mathrm{y})\text{^}2$$

$$SSR = SST - SSE$$

$$R^2 = 1 - \frac{SSE}{SST}$$

Where yi show the vector of dependent observed variables for an observation, yfi is a fitted variable value, y is the mean value of yi and e is the error vector.

Also, the accuracy and predictability of the models were distinguished by computing of absolute percent error (E%) for each set as well as number of error (NE) for all sets as given by Eqs.

$$\mathrm{E} = \frac{100}{N} \sum_{i=1}^{n} \frac{\mathrm{Fcal\ i} - \mathrm{F\ obs\ i}}{F\ obs\ i}$$

$$NE(i) = \frac{100 \times n(i)}{N}$$

F cal i and F obs i denote calculated fraction and an observed fraction of drug released at the *i*th sample, respectively. The value of N is the number of data in each set and n(i) represents the number of data points with the equal or lower "E" than "i" (Azadi *et al.*, 2013)

The Akaike Information Criterion (AIC) is also used to examine the applicability of the release models. The Akaike Information Criterion is a measure of goodness of fit based on maximum likelihood.

$$AIC = n \times ln\,(WSSR) + 2 \times p$$

Where n is the number of dissolution data points, p is the number of the parameters of the model, WSSR is the weighed sum of square of residues, calculated by this process:

$$\mathrm{WSSR} = \sum_{ki=1}^{n} [\mathrm{wi}(\mathrm{Fcal\ i} - \mathrm{Fobs\ i})\text{^}2]$$

Where w is an optional weighing factor and Fcal i and Fobs i denote calculated fraction and observed a fraction of drug released at the sample, respectively (Costa and Lobo, 2001).

RESULTS AND DISCUSSION

The release data of all formulations were fitted to 8 models mentioned above. The overall error, number of errors less than 5, 10, 15 and 20% and akaike information criterion for the models are shown in Table 1. R^2 is a statistical measure indicates how well data fit a statistical model. But in order to have more reliable results, absolute percent error (E) for each set and number of error (NE) for all sets were also calculated. These parameters represent the accuracy and predictability of models. The model had the highest R^2 and the number of the error, as well as the lowest overall error (OE), was considered as the best one. Also, the akaike information criterion was calculated to demonstrate the goodness of data fitting. The model associated with the smallest value of AIC is regarded as giving the best fit out of the models. Among the models, Weibull (W) model produced R^2 and OE values of 0.93 and 8.79, respectively. Also, the number of errors less than 5% was 46.15%of a total number of data set and akaike information criterion of this model is -34.93 (which is the smallest value of all). The values of E%, AIC, the coefficient of determination (R^2) and the regression parameters extracted from each data set was fitted to Weibull equation are given in Table 2.

Residual sum square (RSS), total sum square (TSS) and residual minus square (RMS) were calculated to evaluate the coefficient of determination (R^2) for each model and the accuracy of the best-fitted data by the suggested mathematical models. The values of them which extracted from Weibull equation are shown in Table 3. The relative sizes of the sums of squares terms demonstrate how "good" the regression is in terms of fitting the calibration data. If the regression is "perfect", R^2 will be 1. Weibull is an empirical model has been successfully used in analysis of both rapid and extended release data due to its versatility (Azadi *et al.*, 2013). This study provides valuable evidence for the practicable use of the Weibull model in drug release phenomena from swellable polymeric nanoparticles. Likely there are also several studies have experimentally investigated that, the release data from swellable polymeric nanoparticles fit best with the weibull model (Yang *et al*., 2000; Adibkia *et al*., 2007; Aksungur *et al*., 2011; Ji *et al*., 2011; Bei *et al*., 2012; Azadi *et al*., 2013; Sun *et al*., 2014; Liu *et al*., 2015; Ashrafi and Azadi, 2016; Jafari-Aghdam *et al*., 2016). Among the studied models, Weibull is regarded as a favorable model which includes parameters that are sensitive to ranges of release profile. This model offers a simple relation between the parameters and geometrical characteristic of system as well as Kosmidis *et al.* (2003) experimentally indicate the dependence of parameters on the specific surface. As previously mentioned, t_d in Weibull equation is a location parameter denotes the lag time before the onset of drug release procedure, while β, a shape parameter, characterizes the shape of the release curve (Azadi *et al.*, 2013) and it can be linked to physiological effect as it has been discussed in earlier study (vanBoekel, 2002). For more identification, when β=1, the shape of curve becomes an exponential profile. If β has a higher value than 1, the curve gets sigmoidal form and finally with the β lower than 1 the equation provides parabolic model (Kalam *et al.*, 2007). It is obvious that the external condition is capable to influence the release kinetic and be determined by the shape parameter as well (vanBoekel, 2002). Moreover, for better characterization of the drug release mechanisms, Korsmeyer–Peppas semi-empirical model was applied. In addition, Korsmeyer-Peppas model can correlate release data with release mechanisms which Weibull model cannot provide. At 1983, Korsmeyer *et al*. provided a relationship in drug release from a polymeric system. To discover the overall mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model (Dash *et al.*, 2010).

$$\ln F = \ln k_{kp} + n \ln t$$

Where F stands for the fraction of drug released up to time t, k_{KP} is a Korsmeyer-Peppas release rate constant and "n" is the release exponent. The n value is used to characterize different release mechanisms as given further.

According to the Korsmeyer- Peppas equation (Dash *et al*., 2010), $0.45 \leq n$ are described with a Fickian diffusion mechanism, $0.45 < n < 0.89$ with non-Fickian transport, $n = 0.89$ with Case II transport, and $n > 0.89$ with super case II transport.

The release exponent of Korsmeyer-Peppas equation for all data sets are shown in Table 4. The data produced the $n<0.45$, $0.45<n<0.89$ and $0.98<n$ percent of 61.5%, 33.9% and 4.6%, respectively. Based on results Weibull model seems to be more applicable for identification of drug release from swellable polymeric nanoparticles leading to the desired release profile *in vivo*.

Table 1: The overall error, number of errors less than 5, 10, 15 and 20% and akaike information criterion for the models.

Model	OE	NE<5 (%)	NE<10 (%)	NE<15 (%)	NE<20 (%)	AIC
Zero order	27.25	6.15	13.85	41.54	60	-13.46
First order	25.35	10.77	43.08	61.54	66.15	-19.01
Higuchi	19.46	12.31	33.85	56.92	63.08	-23.57
Hixson- Crowell	23.58	9.23	35.38	58.46	66.15	-19.55
Square rout of mass	24.94	12.31	33.85	56.92	63.08	-17.03
Three second rout of mass	25.88	12.31	30.77	53.85	61.54	-16.91
Weibull	8.79	46.15	73.85	83.08	93.85	-34.93
Korsmeyer- Peppas	11.89	32.31	56.92	64.62	75.38	-26.87

Table 2: The values of E%, AIC, coefficient of determination (R^2) and the regression parameters extracted from each data set was fitted in Weibull equation.

No	Name of bioactive molecule	Nanoparticle type	E%[a] of weibull eq.	AIC[b] of weibull eq.	$(R^2)^c$ of weibull eq.	M[d] of weibull eq.	B[e] of weibull eq.	Ref[f].
1	5- fluorouracil	Chitosan	1.02	-75.63	0.998	0.31	-0.44	(Li *et al*., 2011)
2	5-Fluorouracil	Chitosan coated sodium alginate–chitosan	2.12	-54.66	0.996	0.67	-1.11	(Nagarwal *et al*., 2012)
3	All-trans retinoic acid (ATRA)	carboxymethylated (CM)-curdlan with a sulfonylurea (SU)	5.55	-59.31	0.982	0.59	-2.86	(Na *et al.*, 2000)
4	Amphotericin B	Gelatin	3.75	-43.75	0.891	0.39	-1.3	(Nahar *et al.*, 2008)
5	Artificial tear fluid	Chitosan–sodium alginate	9.8	-25.36	0.956	0.72	-0.92	(Motwani *et al.*, 2008)
6	Aspirin	Chitosan	1.96	-31.81	0.953	0.22	-0.52	(Shi *et al*., 2014)
7	BMP-7/TGF-b2	Alginate	3.38	-26.29	0.986	0.55	-1.34	(Patel and Nesamony, 2014)
8	Brimonidine Tartrate	Eudragit	11.2	-36.25	0.935	0.66	-1.89	(Bhagav *et al*., 2011)
9	Broadleaf holly leaf	Chitosan	6.75	-23.97	0.938	0.54	-0.71	(Zhang *et al.*, 2015)
10	BSA as a model protein drug	Chitosan	7.86	-14.39	0.836	0.34	-0.48	(Gan and Wang, 2007)
11	BSA as a model protein drug	Poly(vinyl alcohol)	2.71	-53.49	0.997	0.77	-1.42	(Li *et al*., 1998)
12	BSA as a model protein drug	Chitosan/alginate	16.42	-14.49	0.844	0.61	-1.91	(Li *et al*., 2007)
13	BSA as a model protein drug	Chitosan (L-aspartic acid)–polyethylene glycol	2.28	-47.07	0.96	0.3	-1.3	(Shu *et al.*, 2009)
14	Chloroquine phosphate	Gelatin	6.62	-13.11	0.952	0.47	-1.35	(Bajpai and Choubey, 2006)
15	Cisplatin	Hyaluronic Acid	18.96	-23.62	0.924	0.93	-2.85	(Jeong *et al*., 2008)
16	Curcumin	Alginate-Chitosan-Pluronic	17.4	-21.68	0.954	0.98	-3.79	(Das *et al*., 2010)
17	Curcumin	Galactosylated chitosan–polycaprolactone	2.2	-52.1	0.994	0.54	-2.01	(Zhou *et al.*, 2013)
18	Curcumin	Chitosan-g-poly (N-isopropylacrylamide)	19.89	-16.85	0.965	1.19	-3	(Rejinold *et al.*, 2011)
19	Cyclosporin A	Chitosan	1.67	-33.03	0.7	0.04	0.05	(De Campos *et al.*, 2001)
20	Diclofenac sodium	Eudragit® RS100	6.1	-42.37	0.936	0.52	0.26	(Barzegar-Jalali *et al*., 2012)
21	Docetaxel	Chitosan	3.67	-49.35	0.989	0.53	-3.23	(Jain *et al*., 2014)
22	Doxorubicine	Acetylated hyaluronic acid(low molecular weight)	3.35	-53.11	0.985	0.46	-1.48	(Park *et al*., 2010)
23	Doxycycline	Chitosan–gelatin	2.55	-28.22	0.983	0.67	-1.26	(Tormos *et al*., 2015)
24	Essential oil	Alginate/cashew gum	2.15	-56.34	0.993	0.3	-0.9	(de Oliveira *et al*., 2014)
25	FITC-BSA	Chondroitin sulfate–chitosan	13.84	-12.83	0.884	0.39	-2.01	(Yeh *et al*., 2011)
26	FITC-BSA	Recombinant human gelatin	9.15	-60.51	0.969	1.02	-3.15	(Won and Kim, 2008)
27	FITC-Dextran	Gelatin	1.65	-49.19	0.997	0.97	-1.3	(Gupta *et al*., 2004)
28	FITC–dextran	Polyvinylpyrrolidone	5.82	-60.1	0.985	0.87	-1.89	(Bharali *et al*., 2003)
29	Gentamicin	Chitosan	8.31	-31.66	0.93	0.52	-1.03	(Ji *et al.*, 2011)
30	Heparin	Chitosan–hyaluronic acid	6.52	-8.09	0.989	1.12	-2.19	(Oyarzun-Ampuero *et al.*, 2009)
31	Insulin	Hyaluronic Acid	47.89	-9.34	0.861	1.63	-8.56	(Han *et al*., 2012)
32	Insulin	Chitosan and Arabic gum	8.75	-29.66	0.975	0.64	-3.36	(Avadi *et al*., 2010)
33	Insulin	Gelatin	1.58	-34.51	0.958	0.5	-1.96	(Goswami *et al*., 2009)
34	Insulin	Alginate/Chitosan	3.2	-35.92	0.87	0.43	-2.31	(Sarmento *et al*., 2007)
35	Insulin	Calcium Alginate	3.36	-24.35	0.949	0.2	-0.27	(Lim *et al*., 2010)
36	Insulin	Chitosan	0.93	-32.13	0.976	0.21	-0.85	(Hecq *et al.*, 2015)
37	Insulin	Alginate/Trimethyl Chitosan nanoparticle Containing Cationic β-Cyclodextrin Polymers	51.1	-14.85	0.866	1.67	-8.89	(Mansourpour *et al*., 2015)
38	Insulin	Chitosan/alginate	18.55	-18.86	0.708	0.71	-1.7	(Mukhopadhyay *et al.*, 2015)
39	Ketoconazole	Chitosan	4.67	-48.48	0.994	1.04	-5.43	(Modi *et al.*, 2013)
40	Measles antigen	low molecularweight chitosan	3.37	-27.26	0.988	0.43	-2.11	(Biswas *et al.*, 2015)
41	Methotrexate	Gelatin	4.45	-56	0.994	0.93	-2.83	(Cascone *et al.*, 2002)
42	Methotrexate	Gelatin	10.21	-39.68	0.972	0.84	-2.79	(Cascone *et al.*, 2002)
43	Methotrexate	Gelatin	13.76	-34.98	0.958	0.79	-2.89	(Cascone *et al.*, 2002)
44	Methotrexate	chitosan	17.97	-30.98	0.937	0.81	-2.61	(Azadi *et al*., 2013)
45	Methylene blue as a drug model	k-Carrageenan	13.8	-31.96	0.807	0.88	-3.36	(Daniel-da-Silva *et al.*, 2011)
46	Naproxen	Eudragit® RS100	29	-22.61	0.822	0.7	-1.31	(Adibkia *et al.*, 2011)
47	Nile red (NR)	Eudragit	0.56	-19.52	0.75	0.26	1.41	(Yoo *et al.*, 2011)
48	Nimodipine	Hyaluronan–methylcellulose	5.51	-18.4	0.889	0.4	-0.69	(Wang *et al*., 2009)
49	Ovalbumin	Alginate coated chitosan	17.3	-18.55	0.821	0.44	-2.56	(Borges *et al.*, 2006)
50	Ovalbumin as model protein	Chitosan/Carrageenan	26.7	-22.71	0.834	1.21	-3.14	(Grenha *et al.*, 2010)

51	Paclitaxel	Gelatin	1.38	-39.02	0.979	0.37	0.42	(Lu *et al.*, 2004)
52	Paclitaxel	Chitosan	2.42	-51.81	0.995	0.7	-2.99	(Majedi *et al.*, 2014)
53	Piroxicam	EudragitwRS100	3.6	-50.62	0.992	0.59	-0.55	(Adibkia *et al.*, 2007)
54	Prednisone acetate	Poly-r,â-[N-(2-hydroxyethyl)-L-aspartamide]-g-poly(E-caprolactone)	6.51	-47.76	0.954	0.4	-1.5	(Miao *et al.*, 2006)
55	Propofol	Alginate	4.09	-72.58	0.979	0.39	-1.39	(Najafabadi *et al.*, 2015)
56	Rivastigmine	Chitosan	6.16	-33.23	0.989	0.57	-3.27	(Fazil *et al.*, 2012)
57	Silk peptide	Chitosan–poly(acrylic acid)	8.16	-43.71	0.894	0.68	-2.73	(Hu *et al.*, 2002)
58	Sulphamethoxazole	Gelatin	2.12	-25.04	0.991	0.73	-2.84	(Bajpai and Choubey, 2005)
59	Tetramethylrhodamine-labeled dextran	Gelatin	4.68	-45.48	0.994	1.15	-1.98	(Kaul and Amiji, 2002)
60	Tetramethylrhodamine-labeled dextran	Gelatin	5.6	-32.94	0.977	1.25	-1.61	(Kaul and Amiji, 2002)
61	Timolol Maleate	Chitosan	4.82	-25.44	0.918	0.33	-0.44	(Agnihotri and Aminabhavi, 2007)
62	Timolol maléate	Hyaluronic acid modified chitosan	8.72	-32.44	0.954	0.82	-0.61	(Wadhwa *et al.*, 2010)
63	Timolol maléate	Chitosan	9.06	-33.4	0.97	0.73	-0.7	(Wadhwa *et al.*, 2010)
64	Tizanidine hydrochloride	Gelatin	13.91	-33.09	0.893	0.77	-1.75	(Lee *et al.*, 2012)
65	Vascular endothelial growth factor (VEGF)	Hyaluronic acid/Chitosan	2.84	-14.72	0.78	0.26	0.53	(Parajó *et al.*, 2010)

[a] absolute percent error. [b] akaike information criterion. [c] Coefficient of determination. [d] slope of Weibull equation. [e] intercept of weibull equation. [f] references.

Table 3: Residual sum square (RSS), total sum square (TSS) and residual minuse square (RMS) for each data sets.

No	Name of bioactive molecule	Nanoparticle type	RSS of weibull eq.	TSS of weibull eq.	RMS of weibull eq.	Ref.
1	5- fluorouracil	Chitosan	0.004	2.01	0.0005	(Li *et al*., 2011)
2	5-Fluorouracil	Chitosan coated sodium alginate–chitosan	0.01	3.22	0.002	(Nagarwal *et al*., 2012)
3	All-trans retinoic acid (ATRA)	carboxymethylated (CM)-curdlan with a sulfonylurea (SU)	0.12	6.42	0.01	(Na *et al.*, 2000)
4	Amphotericin B	Gelatin	0.06	3.37	0.01	(Nahar *et al.*, 2008)
5	Artificial tear fluid	Chitosan–sodium alginate	0.49	11.25	0.06	(Motwani *et al.*, 2008)
6	Aspirin	Chitosan	0.01	0.21	0.002	(Shi *et al*., 2014)
7	BMP-7/TGF-b2	Alginate	0.03	1.95	0.01	(Patel and Nesamony, 2014)
8	Brimonidine Tartrate	Eudragit	0.48	7.33	0.04	(Bhagav *et al*., 2011)
9	Broadleaf holly leaf	Chitosan	0.24	3.86	0.034	(Zhang *et al.*, 2015)
10	BSA as a model protein drug	Chitosan	0.23	1.4	0.06	(Gan and Wang, 2007)
11	BSA as a model protein drug	Poly(vinyl alcohol)	0.03	8.81	0.003	(Li *et al*., 1998)
12	BSA as a model protein drug	Chitosan/alginate	0.99	6.4	0.14	(Li *et al*., 2007)
13	BSA as a model protein drug	Chitosan (L-aspartic acid)–polyethylene glycol	0.04	1.16	0.005	(Shu *et al.*, 2009)
14	Chloroquine phosphate	Gelatin	0.03	0.67	0.01	(Bajpai and Choubey, 2006)
15	Cisplatin	Hyaluronic Acid	1.19	15.68	0.13	(Jeong *et al*., 2008)
16	Curcumin	Alginate-Chitosan-Pluronic	0.7	15.24	0.09	(Das *et al*., 2010)
17	Curcumin	Galactosylated chitosan–polycaprolactone	0.03	4.51	0.003	(Zhou *et al.*, 2013)
18	Curcumin	Chitosan-g-poly (N-isopropylacrylamide)	0.46	13.08	0.11	(Rejinold *et al.*, 2011)
19	Cyclosporin A	Chitosan	0.01	0.03	0.002	(De Campos *et al*., 2001)
20	Diclofenac sodium	Eudragit® RS100	0.76	11.82	0.07	(Barzegar-Jalali *et al*., 2012)
21	Docetaxel	Chitosan	0.06	5.06	0.006	(Jain *et al*., 2014)
22	Doxorubicine	Acetylated hyaluronic acid(low molecular weight)	0.07	4.67	0.01	(Park *et al.*, 2010)
23	Doxycycline	Chitosan–gelatin	0.1	5.81	0.02	(Tormos *et al*., 2015)
24	Essential oil	Alginate/cashew gum	0.02	2.34	0.002	(de Oliveira *et al*., 2014)
25	FITC-BSA	Chondroitin sulfate–chitosan	0.32	2.78	0.08	(Yeh *et al*., 2011)
26	FITC-BSA	Recombinant human gelatin	0.67	21.53	0.03	(Won and Kim, 2008)
27	FITC-Dextran	Gelatin	0.01	3.26	0.002	(Gupta *et al*., 2004)
28	FITC–dextran	Polyvinylpyrrolidone	0.17	11.38	0.01	(Bharali *et al*., 2003)
29	Gentamicin	Chitosan	0.62	8.72	0.05	(Ji *et al.*, 2011)
30	Heparin	Chitosan–hyaluronic acid	0.04	4.01	0.04	(Oyarzun-Ampuero *et al.*, 2009)
31	Insulin	Hyaluronic Acid	3.45	24.81	0.43	(Han *et al*., 2012)
32	Insulin	Chitosan and Arabic gum	0.19	7.81	0.03	(Avadi *et al*., 2010)
33	Insulin	Gelatin	0.03	0.73	0.01	(Goswami *et al*., 2009)
34	Insulin	Alginate/Chitosan	0.03	0.26	0.01	(Sarmento *et al*., 2007)
35	Insulin	Calcium Alginate	0.09	1.79	0.02	(Lim *et al*., 2010)
36	Insulin	Chitosan	0.002	0.1	0.001	(Hecq *et al.*, 2015)
37	Insulin	Alginate/Trimethyl Chitosan nanoparticle Containing Cationic β-Cyclodextrin Polymers	7.34	54.72	0.46	(Mansourpour *et al*., 2015)
38	Insulin	Chitosan/alginate	4.35	14.92	0.2	(Mukhopadhyay *et al.*, 2015)
39	Ketoconazole	Chitosan	0.06	8.63	0.01	(Modi *et al.*, 2013)

40	Measles antigen	low molecularweight chitosan	0.02	1.81	0.01	(Biswas *et al.*, 2015)
41	Methotrexate	Gelatin	0.14	22.37	0.014	(Cascone *et al.*, 2002)
42	Methotrexate	Gelatin	0.74	25.77	0.07	(Cascone *et al.*, 2002)
43	Methotrexate	Gelatin	0.58	13.98	0.06	(Cascone *et al.*, 2002)
44	Methotrexate	chitosan	0.88	14.04	0.09	(Azadi *et al.*, 2013)
45	Methylene blue as drug model	k-Carrageenan	1.36	4.81	0.1	(Daniel-da-Silva *et al.*, 2011)
46	Naproxen	Eudragit® RS100	2.66	14.89	0.22	(Adibkia *et al.*, 2011)
47	Nile red (NR)	Eudragit	0.02	0.09	0.02	(Yoo *et al.*, 2011)
48	Nimodipine	Hyaluronan–methylcellulose	0.21	1.87	0.05	(Wang *et al.*, 2009)
49	Ovalbumin	Alginate coated chitosan	0.56	3.11	0.09	(Borges *et al.*, 2006)
50	Ovalbumin as model protein	Chitosan/Carrageenan	2.61	15.71	0.29	(Grenha *et al.*, 2010)
51	Paclitaxel	Gelatin	0.02	1.06	0.004	(Lu *et al.*, 2004)
52	Paclitaxel	Chitosan	0.04	8.75	0.005	(Majedi *et al.*, 2014)
53	Piroxicam	EudragitwRS100	0.03	3.91	0.004	(Adibkia *et al.*, 2007)
54	Prednisone acetate	Poly-r,â-[N-(2-hydroxyethyl)-L-aspartamide]-g-poly(E-caprolactone)	0.3	6.51	0.02	(Miao *et al.*, 2006)
55	Propofol	Alginate	0.13	6.23	0.007	(Najafabadi *et al.*, 2015)
56	Rivastigmine	Chitosan	0.13	11.53	0.02	(Fazil *et al.*, 2012)
57	Silk peptide	Chitosan–poly(acrylic acid)	0.9	8.45	0.05	(Hu *et al.*, 2002)
58	Sulphamethoxazole	Gelatin	0.01	1.55	0.004	(Bajpai and Choubey, 2005)
59	Tetramethylrhodamine-labeled dextran	Gelatin	0.06	10.03	0.01	(Kaul and Amiji, 2002)
60	Tetramethylrhodamine-labeled dextran	Gelatin	0.27	11.95	0.03	(Kaul and Amiji, 2002)
61	Timolol Maleate	Chitosan	0.07	0.86	0.01	(Agnihotri and Aminabhavi, 2007)
62	Timolol maléate	Hyaluronic acid modified chitosan	0.05	14.19	0.08	(Wadhwa *et al.*, 2010)
63	Timolol maléate	Chitosan	0.33	11.04	0.04	(Wadhwa *et al.*, 2010)
64	Tizanidine hydrochloride	Gelatin	1.04	9.66	0.07	(Lee *et al.*, 2012)
65	Vascular endothelial growth factor (VEGF)	Hyaluronic acid/Chitosan	0.1	0.46	0.05	(Parajó *et al.*, 2010)

Table 4: The release exponent of Korsmeyer- Peppas equation for all data sets.

No	Name of bioactive molecule	Nanoparticle type	N of Korsmeyer Peppas equation	Ref.
1	5- fluorouracil	Chitosan	0.19	(Li *et al.*, 2011)
2	5-Fluorouracil	Chitosan coated sodium alginate–chitosan	0.5	(Nagarwal *et al.*, 2012)
3	All-trans retinoic acid (ATRA)	carboxymethylated (CM)-curdlan with a sulfonylurea (SU)	0.46	(Na *et al.*, 2000)
4	Amphotericin B	Gelatin	0.24	(Nahar *et al.*, 2008)
5	Artificial tear fluid	Chitosan–sodium alginate	0.47	(Motwani *et al.*, 2008)
6	Aspirin	Chitosan	0.14	(Shi *et al.*, 2014)
7	BMP-7/TGF-b2	Alginate	0.39	(Patel and Nesamony, 2014)
8	Brimonidine Tartrate	Eudragit	0.44	(Bhagav *et al.*, 2011)
9	Broadleaf holly leaf	Chitosan	0.32	(Zhang *et al.*, 2015)
10	BSA as a model protein drug	Chitosan	0.19	(Gan and Wang, 2007)
11	BSA as a model protein drug	Poly(vinyl alcohol)	0.48	(Li *et al.*, 1998)
12	BSA as a model protein drug	Chitosan/alginate	0.38	(Li *et al.*, 2007)
13	BSA as a model protein drug	Chitosan (L-aspartic acid)–polyethylene glycol	0.14	(Shu *et al.*, 2009)
14	Chloroquine phosphate	Gelatin	0.19	(Bajpai and Choubey, 2006)
15	Cisplatin	Hyaluronic Acid	0.62	(Jeong *et al.*, 2008)
16	Curcumin	Alginate-Chitosan-Pluronic	0.81	(Das *et al.*, 2010)
17	Curcumin	Galactosylated chitosan–polycaprolactone	0.36	(Zhou *et al.*, 2013)
18	Curcumin	Chitosan-g-poly (N-isopropylacrylamide)	0.82	(Rejinold *et al.*, 2011)
19	Cyclosporin A	Chitosan	0.02	(De Campos *et al.*, 2001)
20	Diclofenac sodium	Eudragit® RS100	0.25	(Barzegar-Jalali *et al.*, 2012)
21	Docetaxel	Chitosan	0.38	(Jain *et al.*, 2014)
22	Doxorubicine	Acetylated hyaluronic acid(low molecular weight)	0.28	(Park *et al.*, 2010)
23	Doxycycline	Chitosan–gelatin	0.36	(Tormos *et al.*, 2015)
24	Essential oil	Alginate/cashew gum	0.2	(de Oliveira *et al.*, 2014)
25	FITC-BSA	Chondroitin sulfate–chitosan	0.31	(Yeh *et al.*, 2011)
26	FITC-BSA	Recombinant human gelatin	0.79	(Won and Kim, 2008)
27	FITC-Dextran	Gelatin	0.61	(Gupta *et al.*, 2004)
28	FITC–dextran	Polyvinylpyrrolidone	0.67	(Bharali *et al.*, 2003)
29	Gentamicin	Chitosan	0.32	(Ji *et al.*, 2011)
30	Heparin	Chitosan–hyaluronic acid	0.86	(Oyarzun-Ampuero *et al.*, 2009)
31	Insulin	Hyaluronic Acid	1.35	(Han *et al.*, 2012)
32	Insulin	Chitosan and Arabic gum	0.48	(Avadi *et al.*, 2010)
33	Insulin	Gelatin	0.24	(Goswami *et al.*, 2009)
34	Insulin	Alginate/Chitosan	0.26	(Sarmento *et al.*, 2007)
35	Insulin	Calcium Alginate	0.2	(Lim *et al.*, 2010)

36	Insulin	Chitosan	0.12	(Hecq *et al.*, 2015)
37	Insulin	Alginate/Trimethyl Chitosan nanoparticle Containing Cationic β-Cyclodextrin Polymers	1.22	(Mansourpour *et al*., 2015)
38	Insulin	Chitosan/alginate	0.48	(Mukhopadhyay *et al.*, 2015)
39	Ketoconazole	Chitosan	0.81	(Modi *et al.*, 2013)
40	Measles antigen	low molecularweight chitosan	0.33	(Biswas *et al.*, 2015)
41	Methotrexate	Gelatin	0.62	(Cascone *et al.*, 2002)
42	Methotrexate	Gelatin	0.62	(Cascone *et al.*, 2002)
43	Methotrexate	Gelatin	0.59	(Cascone *et al.*, 2002)
44	Methotrexate	chitosan	0.68	(Azadi *et al*., 2013)
45	Methylene blue as drug model	k-Carrageenan	0.5	(Daniel-da-Silva *et al.*, 2011)
46	Naproxen	Eudragit® RS100	0.47	(Adibkia *et al.*, 2011)
47	Nile red (NR)	Eudragit	0.02	(Yoo *et al.*, 2011)
48	Nimodipine	Hyaluronan–methylcellulose	0.16	(Wang *et al*., 2009)
49	Ovalbumin	Alginate coated chitosan	0.34	(Borges *et al.*, 2006)
50	Ovalbumin as model protein	Chitosan/Carrageenan	0.87	(Grenha *et al.*, 2010)
51	Paclitaxel	Gelatin	0.15	(Lu *et al*., 2004)
52	Paclitaxel	Chitosan	0.44	(Majedi *et al.*, 2014)
53	Piroxicam	EudragitwRS100	0.43	(Adibkia *et al.*, 2007)
54	Prednisone acetate	Poly-r,â-[N-(2-hydroxyethyl)-L-aspartamide]-g-poly(E-caprolactone)	0.25	(Miao *et al.*, 2006)
55	Propofol	Alginate	0.26	(Najafabadi *et al.*, 2015)
56	Rivastigmine	Chitosan	0.87	(Fazil *et al.*, 2012)
57	Silk peptide	Chitosan–poly(acrylic acid)	0.3	(Hu *et al.*, 2002)
58	Sulphamethoxazole	Gelatin	0.43	(Bajpai and Choubey, 2005)
59	Tetramethylrhodamine-labeled dextran	Gelatin	0.92	(Kaul and Amiji, 2002)
60	Tetramethylrhodamine-labeled dextran	Gelatin	0.85	(Kaul and Amiji, 2002)
61	Timolol Maleate	Chitosan	0.19	(Agnihotri and Aminabhavi, 2007)
62	Timolol maléate	Hyaluronic acid modified chitosan	0.44	(Wadhwa *et al*., 2010)
63	Timolol maléate	Chitosan	0.43	(Wadhwa *et al*., 2010)
64	Tizanidine hydrochloride	Gelatin	0.55	(Lee *et al.*, 2012)
65	Vascular endothelial growth factor (VEGF)	Hyaluronic acid/Chitosan	0.05	(Parajó *et al.*, 2010)

CONCLUSIONS

Since drug release kinetics provide important information into realizing and optimizing nanoparticle drug delivery systems, there are different methods for the determination of release kinetics from such formulations(Hamidi *et al.*, 2013). In this study we try to provide a comparative mathematical analysis of drug release from swellable polymeric delivery systems to find a general model applicable to multi mechanistic release. Drug release data from various swellable polymeric nanoparticles extracted from literatures were applied to the eight conventional models. Based on results, Weibull model seems to describe the release process with the major applicability. These viewpoints endorse that Weibull model seems to be flexible enough to describe the effect of system properties on release process and be more applicable for identification of drug release from swellable polymeric nanoparticles leading to the desired release profile in vivo.

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