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Research article

A comparison of models for the analysis of the kinetics of drug release from PLGA-based nanoparticles

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ABSTRACT

Purpose: Poly (lactic-co-glycolic acid) has received much academic attention for developing nanotherapeutics and FDA has approved it for several applications. An important parameter that dictates the bioavailability and hence the biological effect of the drug is drug release from its delivering system. This study offers a comparative mathematical analysis of drug release from Poly (lactic-co-glycolic acid)–based nanoparticles to suggest a general model explaining multi-mechanistic release they provide.

Methods: Eight release models, zero order, first order, Higuchi, Hixson-Crowell, the square root of mass, the three-second root of mass, Weibull and Korsmeyer-Peppas, as well as the second degree polynomial equation were applied to 60 data sets. The models analysed regarding several types of errors, regression parameters and average Akaike information criterion.

Results and discussion: Most of the data sets present the highest R^2, the lowest overall error and AIC for the Weibull model. Weibull model with the mean AIC = -36.37 and mean OE = 7.24 and the highest NE less than 5, 10, 15 and 20 % in most of the cases best fits the release data from various PLGA-based drug delivery systems that are studied. Weibull model seems to show enough flexibility to describe various release patterns PLGA provides.

1. Introduction

In recent decades, emerging concepts like targeted drug delivery, intelligent drug delivery systems (DDS) and personalised medicine have led medical sciences to a significant paradigm shift. Technology –as always-have been in service of this particular scientific revolution and among the various technological advances of 20th century, nanotechnology has been one of the most promising ones, offering a great potential to produce the "ideal drug" that is safer, more biocompatible, more specifically targeted and pharmacokinetically controllable than current conventional therapeutics; although until the day, clinical application of nano-sized therapeutics have been limited due to lack of data on their physicochemical properties as well as their exclusive in vivo behaviours, making them less predictable when compared to contemporary DDSs [1, 2, 3].

A group of trending nano-sized DDSs are based on poly (lactic-co-glycolic acid) (PLGA), a synthetic block copolymer usually fabricated via random melt copolymerization of cyclic lactides and glycolides that are products of lactic acid and glycolic acid dehydration, in the presence of high vacuum, temperature between 160 and 190 °C and a proper catalyst. PLGA is commercially available in grades different in lactic acid-glycolic acid ratio, molecular weight, inherent viscosity and ester vs. acid end groups [4, 5, 6, 7, 8]. PLGA characteristics including stability, biocompatibility, biodegradability, non-immunogenic non-toxic degradation residues, controllable molecular weight, various surface modifications potential, compatibility with numerous drugs and besides well-adjusted manufacturing process, makes the polymer a favorable candidate for designing nano-sized targeted controlled release DDSs, medical and surgical devices and tissue-engineering requirements [4, 5, 7]. Considering such appealing characteristics, FDA and European Medicine Agency have approved PLGA for several applications [6, 7].

In order to bring advantages of nano-scale DDSs into the patients' bedsides, an important step is to characterise their complicated drug release phenomenon as it is far different from that of larger DDSs. It is mentioned in the literature that smaller particles may have a greater initial burst release due to their capacity of entrapment or surface absorption [9]. For a single drug in an equal release medium under the same condition, drug release phenomenon (in particular, mechanism and rate)

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could vary among different nano-sized systems due to their physico-chemical properties including shape and size of the nanoparticle, ability of water absorption (swelling) or extent and rate of degradation, chemical composition, molecular weight, solubility and crystallinity of the material that forms the nanoparticles and the same parameters for its possible degradation products; Even the drug-drug or drug-polymer interactions seem to have significant effects on drug release from such delivery systems [10].

Despite f the aforesaid advantageous characteristics of PLGA-based nano-scale DDSs, its drug release phenomenon seems to be a hindrance to its widespread clinical application, as parameters that determine extent and rate of the phenomenon change through the time and make it extremely convoluted [7, 11]. A biphasic behavior is usually apparent in drug release of small PLGA particles. A burst release is expected at the initial phase because of non-encapsulated drug molecules attached to the surface, following drug diffusion from water-filled pores and polymeric matrix as well as drug release attributed to degradation of the matrix. Degradation is rather slow when it starts and gradually decreases polymer molecular weight and thus its solubility changes environment pH by its acidic products and under such condition degradation becomes faster in an autocatalytic way [8, 10].

To offer a better understanding of release phenomenon from various conventional and unconventional DDSs, different models have been used. Models are mathematical interpretations of empirical phenomena and experimental findings [12]. In case of drug release, mathematical models are essential means of predicting release mechanisms, as well as over-time drug concentration in the body, which determines the biological efficacy of developed DDSs. In this regard, several models have been introduced, but none of them could act as a perfect universal model. Hence, it is crucial to choose the best model that explains the release behavior of every particular DDS most properly [12, 13]. This study aims to provide a comparative mathematical analysis of drug release from PLGA-based nano-scale DDSs to find a general model applicable to multi-mechanistic drug release behavior PLGA reveals.

2. Materials and method

Sixty data sets describing the over-time drug release of sixty distinct PLGA-based nanoformulation were extracted from forty-seven articles, several introducing more than one nanoformulation. The articles were selected by investigating a combination of the terms "polylactic-co-glycolic acid, PLGA, nanoparticle, nanomedicine, drug delivery, kinetics of release and cumulative release" as keywords in Google Scholar, PubMed and Scopus. It was considered that the release experiments had been done in the physiologic pH (7.4) and temperature (37 °C) (except 46th data set, where pH = 5 was mentioned for release test and 54th data where pH is not mentioned but could be inferred about seven as the medium is distilled water). Table 1 reveals the name of the drug, polymeric carrier and its characteristics, surface modification and nanoparticles' shape and size related to each analysed dataset.

Eight conventional release models including zero order, first order, Higuchi, Hixson-Crowell, square root of mass, three-second root of mass, Weibull and Korsmeyer-Peppas, as well as the second degree polynomial model were fitted to each of 60 data sets and analysis of regression was performed in each case. The linear regression indices including slope, intercept, regression coefficient, mean of square (MS) residual, sum square of residuals (SSR) and sum square of total variation (SST) were calculated using Microsoft Excel 2011, for all datasets as well as percent of error (equation1). Table 2 shows the results in brief.

Overall error (equation 2) and numbers of error bellow 5, 10, 15 and 20 percent (equation 3) for each model also stipulated in Table 3 as well as the name of the models and their equations. Akaike information criterion (AIC) that is a measure of fitting excellence was also calculated (equation4) for each data set, and their average was reported for each model. In Eqs. (1), (2), (3), and (4), f_{cal} and f_{obs} stand for the model parameter that is obtained from the regression equation and the cumulative release curve of each article. N is the number of measuring points and p is the number of model's parameters.

$$E = (100/N)\sum_{i=1}^{N}(f_{cal}i - f_{obs}i)\Big/ f_{obs}i \quad (1)$$

$$OE = \sum_{i=1}^{N} E_i \Big/ N \quad (2)$$

$$NE_i = (100 \times n_i)/N \quad (3)$$

$$AIC = N \times \left[\sum_{i=1}^{N}(f_{cal}i - f_{obs}i)^2\right] + 2 \times p \quad (4)$$

3. Results and discussion

More than 93 percent of referred journals are indexed at ISI, and it can be inferred that 100 percent of datasets are extracted from authentic sources. Table 1 gives a clear image of investigated nanoparticles contents including drug, polymer and surface modifications and also nanoparticles characteristics including shape and size. Lactide/glycolide ratio in PLGA is 50:50 in more than 83% of data sets and in almost all of the cases, lactide is a mixture of L and D stereoisomers. Many articles did not mention PLGA molecular weight or only provided inherent viscosity of the polymer, but Table 1 reveals that more than 50 percent of all the data sets are associated with PLGA with a molecular weight less than 40 kDa. Variety of drugs, nanoparticles spherical shapes and their size that is between 100 and 200 nm in most cases are also noticeable in further interpretations.

Considering the fact that release phenomenon takes place in the context of time and release medium, these two factors are demonstrated in Table 2. In article selection, it was tried to choose those similar in release medium conditions (composition, pH and temperature) that affect drug release, although the time for release tests ranged from a few minutes to 30 days; hence those studied during a short time may depict only a snapshot of a dynamic reality.

Also, Tables 2 and 3 summarise the results from fitting the models on 60 data. To support the data in Tables 2 and 3, and illustrate the overall superiority of the Weibull model in the 60 data sets we studied, the percent of data sets that present higher R^2, lower OE, and lower AIC for the Weibull model are brought in Table 4. Obviously, the Weibull model, an empirical model describing both immediate and delayed releases from various DDSs, with lowest AIC and mean OE as well as highest NE 5, 10, 15 and 20% in the most cases best portrays drug release behavior of PLGA-based nanoparticles. AIC that is now a standard measure of conformity of model and data based on the maximum probability shows the best fit model when comparing a group of models and the model with the lowest AIC would be the best-fitted one [61]. Nevertheless, minor deviations that are observable in the Table 4 imply that the Weibull model might not always be the perfect drug release model and all of the parameters that affect the release phenomenon must be figured out and be controlled.

4. Discussion

Eight drug release models as well as the second degree polynomial model were compared in this study to find out whether a nearly universal model for describing drug release from PLGA-based nanoparticles, regardless of their physicochemical properties like the polymer components ratio, the polymer's molecular weight, and the nanoparticles size, is achievable or not. The zero order model describes drug release from a system that liberate its content with a constant rate regardless of its concentration and the release is only a function of time. The first order model refers to a system, whom its drug release rate is only a function of

Table 1. Drug, polymer and nanoparticle characteristics.

NO. of data set	Drug	Polymer	Lactide stereo-isomeric form	(Lactide: Glycolide ratio)/[PLGA: second polymer ratio]	PLGA MW or inherent viscosity	Surface modification	NP shape	NP size (nm) [analytical method]	Reference
1	Camptothecin	PLGA	NM*	(50:50)	0.59 dL/g	-**	sphere	119 ± 37 [SEM] 206 ± 32 [DLS]	[14]
2	Doxycycline	PLGA-PCL	D, L	(50:50)/[80:20]	0.55–0.75 dL/g ~50 kDa	-	sphere	230-360 [DLS]	[15]
3	Insulin	PLGA (ISTPPLG4)	NM	(78:22)	15.4 kDa	PEG2000	sphere	180 ± 20 [EM]***	[16]
4	Insulin	PLGA (ISTPPLG6)	NM	(68:32)	11 kDa	PEG2000	sphere	120 ± 20 [EM]	[16]
5	Lansoprazole	PLGA	NM	(50:50)	28 kDa	-	sphere	219.2 ± 2.9 [DLS]	[17]
6	Loperamide	PLGA	D, L	(50:50)	24–38 kDa	-	Sphere	318 ± 26 [DLS]	[18]
7	Loperamide	PLGA	D, L	(50:50)	24–38 kDa	octa-arginine	Sphere	328 ± 3.0 [DLS]	[18]
8	Tacrolimus	PLGA	NM	(50:50)	50–75 kDa	-	Sphere	218 ± 51 [DLS]	[19]
9	Tacrolimus	PLGA	NM	(50:50)	50–75 kDa	PEG	Sphere	220 ± 33 [DLS]	[19]
10	Nitric oxide	PLGA-PEI	D,L	(50:50)	71 kDa	-	Sphere	162 ± 19 [SEM] 179 ± 25 [qNano]	[20]
11	Rhein	PLGA	NM	(50:50)	15 kDa	-	Sphere	80-210 [DLS]	[21]
12	VEGF	PLGA	NM	(50:50)	7–17 kDa	-	NM	203 ± 9 [DLS]	[22]
13	Calcitriol	PLGA	D,L	(50:50)	24–38 kDa	-	Sphere	186 ± 3 [DLS]	[23]
14	Cerebrolysin	PLGA	D, L	(50:50)	0.38 dl/g	-	Sphere to collapsed reservoir systems	200 [DLS]	[24]
15	Carboplatin (alone)	$PLGA_{17K}$-PEG_{3K}	D, L	NM	17 kDa	-	NM	116.3 ± 3.5 [DLS]	[25]
16	Carboplatin (co-encapsulated with Paclitaxel)	PLGA-PEG	D, L	NM	17 kDa	-	NM	125.1 ± 3.9 [DLS]	[25]
17	Paclitaxel (alone)	PLGA-PEG	D, L	NM	17 kDa	-	NM	88.2 ± 2.7 [DLS]	[25]
18	Paclitaxel (co-encapsulated with Carboplatin)	PLGA-PEG	D, L	NM	17 kDa	-	NM	125.1 ± 3.9 [DLS]	[25]
19	18-β-glycyrrhetinic acid	PLGA	D, L	(50:50)	48 kDa	-	Sphere	184 ± 25 [DLS]	[26]
20	Etoposide (co-encapsulated with Paclitaxel)	PLGA	NM	(50:50)	15 kDa	PEG	Sphere	70 ± 4.5 [TEM] 100 ± 3.68 [DLS]	[27]
21	Dopamine	PLGA	D, L	(50:50)	30–60 kDa	-	Sphere	119.7 ± 2.69 [DLS]	[28]
22	Cyclosporine A	PLGA	NM	(50:50)	NM	PEG- liver targeting peptide	NM	229 [DLS]	[29]
23	Dnase I	PLGA	NM	NM	58.8 kDa	-	sphere	257 ± 2.83 [DLS]	[30]
24	Flutamide	PLGA	D, L	NM	NM	methoxy polyethene glycol 5000	non-spherical	133.46 ± 0.87 [DLS]	[31]
25	Clozapine (co-encapsulated with Risperidone)	PLGA (LMW)	D, L	(50:50)	20 kDa 0.2 dl/g	-	sphere	248.48 ± 11.71, 261.45 ± 12.86, 331.27 ± 19.31 [DLS]	[32]
26	Risperidone (co-encapsulated with Clozapine)	PLGA (LMW)	D, L	(50:50)	20 kDa 0.2 dl/g	-	sphere	248.48 ± 11.71, 261.45 ± 12.86, 331.27 ± 19.31 [DLS]	[32]
27	Netilmicin	PLGA	D, L	(50:50)	17 kDa	-	sphere	140.83 ± 2.4 [DLS]	[33]
28	Perphenazine	PLGA (0.8%w/v)	D, L	(50:50)	54–69 kDa	-	sphere	340.5 ± 17.8 [DLS]	[34]
29	Perphenazine	PLGA (1.3%w/v)	D, L	(50:50)	54–69 kDa	-	sphere	382.5 ± 36.5 [DLS]	[34]

(*continued on next page*)

Table 1 (*continued*)

NO. of data set	Drug	Polymer	Lactide stereo-isomeric form	(Lactide: Glycolide ratio)/[PLGA: second polymer ratio]	PLGA MW or inherent viscosity	Surface modification	NP shape	NP size (nm) [analytical method]	Reference
30	Perphenazine	PLGA (1.6%w/v)	D, L	(50:50)	54–69 kDa	-	sphere	376.6 ± 28.6 [DLS]	[34]
31	Curcumin	PLGA-PEG	D, L	NM	NM	-	sphere	70-300 [SEM]	[35]
32	Cisplatin	PLGA	D,L	(50:50)	35–40 kDa	-	sphere	197 ± 16 [TEM] 195.35 ± 2 [DLS]	[36]
33	Topotecan (co-encapsulated with Tamoxifen)	PLGA	D,L	(50:50)	45 kDa 0.4 dl/g	-	sphere	151.2 ± 14.6 [DLS]	[37]
34	Tamoxifen (co-encapsulated with Topotecan)	PLGA	D,L	(50:50)	0.4 dl/g	-	sphere	151.2 ± 14.6 [DLS]	[37]
35	Evodiamine	PLGA	NM	(50:50)	30–60 kDa	-	sphere	157.36 ± 1.7 [DLS]	[38]
36	Thienorphine	PLGA	D,L	(50:50)	15 kDa	-	sphere	118.5 ± 13 [DLS]	[39]
37	Thienorphine	PLGA	D,L	(50:50)	15 kDa	Chitosan coat (MW > 250 kDa)	sphere	121.1 ± 10 [DLS]	[39]
38	Flavopiridol	PLGA	NM	(50:50)	NM	-	NM	NM	[40]
39	Gemcitabine	PLGA	D,L	(50,50)	0.2 dl/g	-	sphere	100-150 [DLS]	[41]
40	ASC-J9	PLGA	NM	(50:50)	45–60 kDa 0.59 dl/g	-	sphere	145.6 ± 22 [DLS]	[42]
41	Trans-resveratrol	PLGA	NM	(50:50)	14.5 kDa 0.53 dl/g	-	sphere	90.35 ± 1.2–366.47 ± 2.6 [DLS]	[43]
42	Felodipine	PLGA	D,L	(50:50)	NM	-	sphere	161.3 ± 2.231 [DLS]	[44]
43	Emtricitabine	PLGA	D,L	(50:50)	14.5 kDa 0.53 dl/g	-	NM	180 [DLS]	[45]
44	Zidovudine	PLGA	NM	(50:50)	7–17 kDa	Tween80	sphere	56-93 [PCM]****	[46]
45	Rapamycin	PLGA	D,L	(50,50)	40–75 kDa	PVA (average 95 kDa)	NM	265 [DLS]	[47]
46	Temazolamide	PLGA	D	(50:50)	NM	-	NM	150-160 [DLS]	[48]
47	Sildenafil	PLGA	D,L	(50:50)	24–38 kDa	-	sphere	240-316 [DSL]	[49]
48	*Caryota mitis* Profilin	PLGA	NM	(50:50)	24–38 kDa	-	NM	180 [DLS]	[50]
49	Paclitaxel	PLGA	D, L	(50:50)	10.5 kDa		sphere	150 ± 6.2 [DLS]	[51]
50	Methotrexate	PLGA	NM	(50:50)	12 kDa 0.16–0.24 dl/g	-	sphere	258 ± 10 [DLS]	[52]
51	Methotrexate	PLGA-PEG	NM	(50:50)	12 kDa 0.16–0.24 dl/g	-	sphere	182 ± 14 [DLS]	[52]
52	Docetaxel	PLGA	D, L	(50:50)	24–38 kDa	-	sphere	130-150 [DLS]	[53]
53	Anastrozole	PLGA	D, L	(50:50)	0.2 dl/g	-	sphere	<200 [DLS]	[54]
54	Ibuprofen	PLGA	D, L	(50:50)	30 kDa	-	NM	NM	[55]
55	Cytarabine	PLGA	D, L	(50:50)	0.22 dl/g	-	NM	125 ± 2.5 [DLS]	[56]
56	Levofloxacin	PLGA	D, L	(50,50)	7–17 kDa	-	sphere	268 ± 18 [DLS]	[57]
57	Curcumin	PLGA	D, L	(50:50)	NM	-	sphere	129.7 ± 9.6 [DLS]	[58]
58	Curcumin	PLGA	D, L	(75:25)	NM	-	sphere	191.1 ± 9.8 [DLS]	[58]
59	Camptothecin	PLGA	NM	(50:50)	0.58 dl/g	-	sphere	158 ± 62 [SEM]	[59]
60	Carvacrol	PLGA	D, L	(50:50)	0.15–0.25 dl/g	-	sphere	209.8 ± 7.2 [DLS]	[60]

* NM = Not mentioned in the source.
** "-" = Not applicable.
*** EM = Electrophoretic mobility.
**** Phase contrast microscope/PLGA = Poly lactide-co-glycolic acid; PCL = Poly (ε-caprolactone); PEI = Polyethylenimin.

Table 2. Release media, regression and statistical analysis for referenced formulations.

NO. of data set	Release medium	Time range (days)	Weiball SS residual	Weiball SS total	Weiball MS residual	Weibull AIC	Weiball slope	Weiball intercept	Weiball R2	Weiball E	Kors-meyer-Peppas m	Reference
1	PBS	2	0.02	3.23	3.23	-30.16	0.48	-0.37	0.99	1.67	0.20	[14]
2	PBS	15	0.03	4.53	0.00	-71.71	0.44	-1.75	0.99	1.86	0.26	[15]
3	PBS	1.25	0.16	5.44	0.04	-19.25	1.19	-2.86	0.97	8.64	0.66	[16]
4	PBS	1.25	1.03	7.49	0.20	-12.75	1.13	-3.18	0.86	18.27	0.67	[16]
5	PBS	1	0.19	9.05	0.03	-27.28	0.86	-2.19	0.98	9.5	0.71	[17]
6	PBS	3	0.42	3.88	0.08	-15.69	0.57	1.06	0.89	11.08	0.26	[18]
7	PBS	3	0.12	0.92	0.02	-25.90	0.27	-0.29	0.87	3.35	0.11	[18]
8	Not mentioned	16	0.29	15.84	0.02	-58.08	0.81	-4.21	0.98	7.85	0.63	[19]
9	Not mentioned	16	0.49	16.31	0.04	-46.25	0.82	-4.19	0.97	9.97	0.63	[19]
10	DPBS	6	0.12	10.74	0.01	-40.70	0.66	-2.51	0.99	6.53	0.50	[20]
11	PBS+ 20% ethanol	1	0.15	10.11	0.01	-47.67	0.80	-1.51	0.98	5.37	0.56	[21]
12	PBS	30	0.10	2.53	0.01	-51.49	0.36	-1.05	0.98	5.37	0.26	[22]
13	PBS	7	0.17	4.57	0.03	-20.87	0.72	-2.96	0.96	8.18	0.52	[23]
14	PBS	1	0.36	5.71	0.04	-36.31	0.37	-0.54	0.94	9.45	0.24	[24]
15	PBS	3	0.06	4.21	0.01	-27.98	0.70	-2.69	0.99	4.79	0.50	[25]
16	PBS	3	0.14	6.83	0.03	-24.81	0.89	-3.52	0.98	10.1	0.68	[25]
17	PBS	3	0.01	3.47	0.00	-34.52	0.76	-2.56	1.00	1.8	0.51	[25]
18	PBS	3	0.04	3.79	0.01	-24.65	0.79	-2.80	0.99	3.98	0.56	[25]
19	PBS	3	0.13	12.26	0.00	-105.79	0.57	-1.50	0.99	2.6	0.33	[26]
20	PBS	5	1.33	24.62	0.17	-22.80	1.06	-4.55	0.95	23.36	0.86	[27]
21	PBS	6	0.07	2.40	0.00	-77.49	0.26	-1.30	0.97	3.91	0.20	[28]
22	PBS	3	0.03	0.28	0.01	-19.80	0.25	-0.91	0.89	4.42	0.16	[29]
23	PBS (SDS + sodium azide as preservative)	14	0.04	1.94	0.01	-35.47	0.21	-0.72	0.98	4.13	0.13	[30]
24	PBS	7	0.12	7.08	0.02	-30.61	1.08	-4.45	0.98	6.78	0.67	[31]
25	PBS	10	0.13	5.91	0.02	-36.29	1.09	-5.38	0.98	6.05	0.80	[32]
26	PBS	10	0.18	6.72	0.02	-34.94	1.16	-5.74	0.97	7.52	0.86	[32]
27	PBS	10	0.16	16.74	0.01	-70.00	0.49	-2.60	0.99	5.85	0.41	[33]
28	PBS	4	0.68	6.80	0.07	-22.94	0.45	-0.94	0.90	11.1	0.28	[34]
29	PBS	4	0.17	11.41	0.02	-38.35	0.61	-1.74	0.98	5.36	0.42	[34]
30	PBS	4	0.16	11.89	0.02	-40.40	0.62	-1.97	0.99	6.96	0.46	[34]
31	Phosphate-buffered solution	10	0.44	12.75	0.04	-32.23	0.71	-3.47	0.96	2.02	0.55	[35]
32	PBS	14	0.20	2.71	0.02	-43.86	0.18	-0.65	0.93	5.54	0.11	[36]
33	Phosphate buffer	3	0.02	3.16	0.00	-41.21	0.40	-1.18	0.99	2.98	0.28	[37]
34	Phosphate buffer	3	0.03	3.01	0.00	-40.73	0.39	-1.43	0.99	4	0.30	[37]
35	PBS	7.5	0.42	9.37	0.04	-37.26	0.60	-2.83	0.95	12.19	0.49	[38]
36	PBS	0.5	0.01	2.55	0.00	-48.08	0.53	-0.85	1.00	1.57	0.36	[39]
37	PBS	0.5	0.02	5.14	0.00	-44.31	0.76	-1.49	1.00	3.57	0.57	[39]
38	PBS	3	0.21	12.72	0.03	-26.17	1.08	-3.80	0.98	9.41	0.82	[40]
39	PBS	5	0.25	9.53	0.03	-38.66	0.59	-2.01	0.97	8.33	0.41	[41]
40	PBS	10	0.13	6.24	0.02	-30.23	0.53	-1.14	0.98	5.24	0.32	[42]
41	PBS	12	0.09	6.00	0.01	-53.69	0.97	-4.62	0.98	2.74	0.60	[43]

(*continued on next page*)

Table 2 (*continued*)

NO. of data set	Release medium	Time range (days)	Weiball SS residual	Weiball SS total	Weiball MS residual	Weiball AIC	Weiball slope	Weiball intercept	Weiball R2	Weiball E	Kors-meyer-Peppas m	Reference
42	PBS (1% SLS)	6	0.29	4.53	0.04	-26.50	0.91	-3.55	0.94	7.89	0.50	[44]
43	PBS	15	0.54	6.99	0.04	-39.81	0.87	-4.64	0.92	9.72	0.59	[45]
44	PBS + poloxamer 407	0.5	0.14	8.91	0.02	-48.29	0.74	-1.22	0.98	6.41	0.56	[46]
45	PBS (tween 80)	30	0.77	5.16	0.05	-37.80	0.52	-2.83	0.85	11.42	0.33	[47]
46	Sodium acetate buffer (pH = 5)	5	0.09	2.45	0.01	-34.06	0.36	-1.30	0.96	4.42	0.23	[48]
47	PBS	0.5	0.45	4.45	0.09	-16.73	0.67	-1.45	0.90	16.92	0.52	[49]
48	PBS	14	0.07	6.56	0.00	-75.68	0.47	-2.53	0.99	4.31	0.36	[50]
49	PBS	4	0.54	5.01	0.13	-13.52	0.52	-1.76	0.89	20.57	0.40	[51]
50	PBS	0.5	0.40	7.10	0.07	-22.29	0.85	-0.97	0.94	8.6	0.49	[52]
51	PBS	0.5	0.15	7.61	0.02	-28.86	0.90	-1.51	0.98	7.68	0.64	[52]
52	PBS (1% tween 80)	7	0.43	10.75	0.04	-30.06	0.60	-1.86	0.96	9.48	0.39	[53]
53	PBS	11	0.57	7.59	0.04	-41.62	0.32	-1.83	0.92	12.99	0.25	[54]
54	Distilled water	0.1	0.17	1.28	0.06	-16.24	0.83	0.49	0.86	4.38	0.26	[55]
55	PBS	1	0.03	5.31	0.01	-33.40	0.69	-0.92	0.99	4.12	0.40	[56]
56	PBS	5	0.10	1.08	0.02	-23.10	0.38	-1.76	0.91	6.36	0.26	[57]
57	PBS	7	0.96	11.00	0.10	-25.82	0.72	-2.60	0.91	14.58	0.47	[58]
58	PBS	7	0.17	5.02	0.02	-44.97	0.50	-2.06	0.97	6.66	0.35	[58]
59	PBS	21	0.62	3.21	0.15	-8.57	0.61	-2.69	0.81	16.93	0.21	[59]
60	PBS	1	0.21	6.48	0.04	-25.72	0.77	-0.95	0.96	6.66	0.44	[60]

the remaining drug concentration. The Higuchi model implies that the amount of drug liberated form the dosage form is a function of the square root of time. The Hixson–Crowell model describes a system that the cube root of the released amount of the incorporated drug is linearly related to the time, which is specifically a system that its surface alters over time. The Square root of mass and the Three second root of mass models are also derived from the Hixson–Crowell model, implying the linear relationship between the time and the square root or the three second root of the remained drug concentration, respectively. In the Weibull model the logarithm of the released drug and logarithm of the time would have a linear relationship. Korsmeyer-Peppas is another comprehensive semi-empirical model, that could generally describe the distinct release phenomena involving either of diffusion or swelling [13, 62, 63].

This study provides valuable evidence for the practical use of the Weibull model in drug release phenomena from PLGA nanoparticles. Among the studied models, Weibull is regarded as a favorable model which includes parameters that are sensitive to ranges of release profile. In Weibull equation, t_d is a location parameter denoting the lag time before the onset of the drug release procedure, while β, a shape parameter, characterises the shape of the release curve and it can be further linked to the physiological effects. In fact, for equations with $\beta = 1$ the shape of the curve is an exponential profile, $\beta > 1$ demonstrates a sigmoidal form and $\beta < 1$ delineates a parabolic graph. In one hand, this implies that Weibull is a flexible model with great potential to be fitted on a variety of release patterns. Release graphs of the 60 mentioned data sets (brought in the supplementaryfile) also endorse this point, as they show very different patterns PLGA nanoparticles generate including almost monophasic, biphasic, triphasic and complex multiphasic release profiles. However, we should ask where this flexibility comes from? The answer is in the mathematical equation of the Weibull model, where changes in the rate of drug concentration are tempered by calculating its natural logarithm. In other words, although Weibull does not neglect alteration in the rate of release between consecutive phases of a single release pattern, it neutralises the effect of these changes on the model by calculating their logarithm. On the other hand, β could be utilised to either predict or optimise the release conditions of a DDS in the development process and have a more desirable release profile in vivo [62, 63].

PLGA is a polyester that can be hydrolysed into soluble oligomers and finally, monomers in the physiological condition. In PLGA matrices, whether the mechanism of dissolution would be balk erosion or surface degradation, diffusion of oligomers or solubility of the oligomers can be rate-limiting factors for the kinetics of the phenomenon. Nevertheless, the result of a study by Körber, clearly shows that degradation controls the bulk erosion of PLGA matrices in the dissolution procedure [64]. Here, a parameter that helps to translate the release mathematics to the mechanistic view is the calculated slope for Korsmeyer-Peppas model for each data set. For spherical particles, $m = 0.43$ reveals the Fickian diffusion and $m = 0.85$ denotes the polymer swelling, while any quantity between these two limitations illustrates an anomalous drug release, a combination of Fickian diffusion and swelling [11]. Accordingly, the average of Korsmeyer-Peppas model slope for 60 datasets is 0.437 that confirms swelling is negligible about all these PLGA-based nanoparticles and thus, is in agreement with the previous studies emphasizing on the role of diffusion in the dissolution procedure of PLGA-based systems [64].

One of the study's challenges was the precision of data gathering, as they were extracted from referenced articles' release graphs. The other issue of concern with such retrospective studies is the reliability of reported data because it is not plausible for a single research team to investigate such a data mass in one lab under the same circumstance and hence must trust reliable sources.

On the other side, the present study attempts to suggest the best conventional mathematical model, describing drug release from PLGA nanoparticles mentioning different surface modifications or various incorporated drugs to investigate their likely overall effect on the

Table 3. Mathematical models, equations and precision determinants [13, 62].

No.	Model name	Equation	Mean AIC	Mean OE	NE< 5%	NE< 10%	NE< 15%	NE< 20%
1	Zero order	$f = K.t$	-22.25	23.40	3.33	16.67	33.33	56.67
2	First order	$\ln(1-f) = -K.t$	-26.58	22.80	1.67	26.67	53.33	60
3	Higuchi	$f = K.t^{\frac{1}{2}}$	-30.35	14.66	8.33	50	65	76.67
4	Hixson-Crowell	$1-(1-f)^{\frac{1}{3}} = -K.t$	-25.47	21.86	5	23.33	51.67	56.67
5	Square root of mass	$1-(1-f)^{\frac{1}{2}} = -K.t$	-24.56	22.25	3.33	16.67	48.33	58.33
6	Three second- root of mass	$1-(1-f)^{\frac{2}{3}} = -K.t$	-23.72	23.02	5	16.67	40	55
7	Weibull	$\ln[-\ln(1-f)] = \beta.\ln(t_d) + \beta.\ln(t)$	-36.37	7.24	33.33	80	91.67	96.67
8	Korsmeyer- Peppas	$\ln(f) = \ln(K) + n.\ln(t)$	-30.24	10.28	18.33	50	85	95
9	Second degree polynomial	$f = a.t^2 + b.t + c$	-29.09	14.50	38.07	60.80	75.27	83.90

Table 4. Comparing all of the models with the Weibull model (% of data sets).

Comparing the models	Possible conditions	R^2	OE	AIC
Weibull vs. Zero order	Weibull is better	85%	91.67%	83.33%
	Both models are equal	0%	0%	0%
	Zero order is better	15%	8.33%	16.67%
Weibull vs. First order	Weibull is better	70%	96.67%	83.33%
	Both models are equal	5%	0%	0%
	First order is better	25%	3.33%	16.67%
Weibull vs. Higuch	Weibull is better	68.33%	85%	73.33%
	Both models are equal	8.33%	0%	0%
	Higuchi is better	23.33%	15%	26.67%
Weibull vs. Hixson-Crowell	Weibull is better	66.67%	88.33%	76.67%
	Both models are equal	13.33%	0%	0%
	Hixson-Crowell is better	20%	11.67%	23.33%
Weibull vs. Square root of mass	Weibull is better	75%	91.67%	81.67%
	Both models are equal	10%	0%	0%
	Square root of mass is better	15%	8.33%	18.33%
Weibull vs. Three-second root of mass	Weibull is better	81.67%	93.33%	85%
	Both models are equal	3.33%	0%	0%
	Three-second root of mass is better	15%	6.67%	15%
Weibull vs. Korsmeyer-Peppas	Weibull is better	70%	78.33%	68.33%
	Both models are equal	11.67%	0%	0%
	Korsmeyer-Peppas is better	18.33%	21.67%	31.67%
Weibull vs. 2^{nd} degree polynomial	Weibull is better	63.33%	90%	75%
	Both models are equal	16.67%	0%	0%
	2^{nd} degree polynomial is better	20%	10%	25%

mathematical model of release. Nevertheless, it has been mentioned in the literature that the loaded drug can affect the rate and mechanism of the release phenomenon for PLGA-based matrices by shifting the degradation between bulk erosion and surface degradation [65]. Finally, it is necessary to keep in mind that kinetic analysis of drug release is crucial to make release phenomenon from novel DDSs predictable, especially for further pharmacokinetic-pharmacodynamic and *in vitro-in vivo* correlation studies.

Since the study of drug release kinetics provides essential data for better realising and optimising nanoparticulate DDSs, there are different methods for the determination of release kinetics from such formulations. In this study, the best fitted mathematical model (among the nine equations evaluated) illustrating drug release pattern from PLGA nanoparticles is figured out that is the Weibull model. It can also be inferred that drug release phenomenon for nanoparticles is dominantly polymer dependent rather than drug dependent; although more investigations might be necessary to evaluate release patterns of different drugs from PLGA matrices different in weight and modifications at the same condition to make a better judgment.

Declarations

Author contribution statement

Leila Pourtalebi Jahromi: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Mohammad Ghazali: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Hajar Ashrafi, Amir Azadi: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.

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