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RESEARCH ARTICLE

Therapeutic efficacies of nano carriers in delivering drugs

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Abstract: The drug release rates of poorly soluble medications such as doxorubicin has been investigated in this paper. Since the drug was fixed, different carriers used to deliver it and their release rates compiled from literature were evaluated in this paper. Even though targeting of drugs is very important in drug delivery, it is not within the scope of this paper. However, functionalization of the carrier may provide this benefit, those constructs are included for comparison in terms of hybrid constructs. Dendrimer, micelles and hybrid constructs used in the delivery of doxorubicin compared in this paper with respect to carrier size and drug loading. Assuming that the dissolution follows a slow release, 40-50% of the drug in the phase I representing a sudden or the burst release, followed by a steady release of 50-60% of the drug in phase II, not all the carriers and their sizes exhibited this behavior. Carriers and hybrid constructs 38nm size were more effective where phases I and II observed, however, as the size decreased to 34 nm or increased above 40nm, minimal release occurred meaning the carriers were too big to penetrate the vasculature permeability. Nano-carriers, dendrimers, micelle, hybrid dendrimers and micelles were found to be effective with the carrier manufacturing, generation, polymer, molecular weight of the carrier and other parameters. The release rate of doxorubicin was found to be effective with dendrimers together with hybrid dendrimer exhibiting a bilinear behavior. Micelles 20nm were more effective representing 60% of release in 10 hours followed by additional 25% in 35 hours exhibiting a bilinear behavior. Size greater than 20nm resulted in slow release reaching less than 10 to 40% of drug. Several drugs exhibited multiple slopes in their kinetics when micelle was used. The therapeutic efficacy of hybrid micelle was superior to other nano-carriers.

Keywords: nano-carriers, dendrimers, micelle, dissolution kinetics, therapeutic efficacy

1 Introduction

As the treatment models are individualized, understanding therapeutic efficacies (TE) of various carriers are very important. The TE may be enhanced via new drug development that lowers the side effects at the same time controls the release rate by newer design of carriers. An attempt was made in this paper to fully understand the drug delivery kinetics of nanocarriers (NC) [1] such as dendrimers, micelles, hybrid and other nanoparticles with specific drugs. The TE of NC may be further improved by functionalization. Mono (singular) versus multi-functionalization provide stable constructs with biocompatibility, reduced toxicity with the ability to target ligands and other antibodies. Even though NP may range from 1 to 1000nm, for nanomedicine purposes size within 1-200nm preferred. Hybrid, or a solid-lipid NC may range from 50-1000 nm. The solid-lipid NC surfaces modified with surfactants with hydrophilic polymers such as PEG and poloxamer transform them amphiphilic molecules enhancing biosafety, release rate, drug loading and other benefits. Therefore, in this paper, an attempt was made to evaluate TE of NC – dendrimers, micelles, and hybrid constructs, with the emphasis on size of carriers, drug loading rate and release rates of doxorubicin. Poorly soluble drugs such as doxorubicin were not able to efficiently reach the intended target, such as tumors. Dendrimers, micelles and hybrid constructs have raised drug solubility at the same time enabled targeting though not discussed in this paper. Therefore, there is a need to understand the carriers themselves, how they are made with polymers, coatings, drug loads and other variables and keeping some of the parameters fixed compare their drug release efficacies. In the sections below the NC development discussed (section 1.1), structure (section 1.2), release rates of; dendrimers (section 3), hybrid NC (section 4), micelle (section 5), hybrid micelle (section 6), and NC (section 7). We compiled data from the literature with the normalization matrix presented in each section in representative tables, and readers are directed to those tables to access the data and inclusion criteria for this research.

1.1 Historical timeline of NP carriers

Dendrimers have proven to improve water solubility in specific drugs [2]. Fritz Vogtle [3] discovered dendrimers in 1978 and later by Donald Tomalia [4] and co-workers at Dow Chemical in the 1980's [5]. The design of the PAMAM "starburst polymer" dendrimer was first developed by Tomalia's research group which would eventually become a drug delivery method [5]. In 1989, the convergently synthesized dendrimers were presented to the world by Craig Hawker and Athena Phillipides [5, 6]. Due to the small size of the dendrimers and micelles used in drug delivery, it can be used for drug delivery for specific drugs that do not dissolve which alters the effectiveness of drug release rate. The evolution of dendrimers is presented in Figure 1.

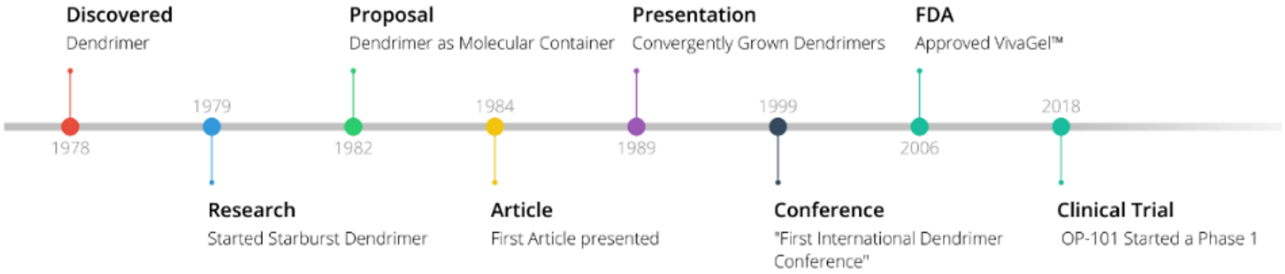

Figure 1 Milestones for the application of dendrimers from 1978-2018 [2, 7–9]

The term "micella" or "micelle" was first coined in 1877 by Nageli and Schwendener [10] to describe molecular aggregates or crystalline particles in cellulose. Nageli theorized that micelles are the first stage in the evolutionary process, starting from non-living molecules to living cellular constructs with cytoplasm, mitochondria, and other cellular components [11]. In 1884, this process became known as "The Micellar Theory of Life" but was later updated by Strick [12] in 2000 [11].

Although, the modern application of using micelle for drug delivery was discovered in 1913 by J. W. McBain [13], it was applied to both therapeutics and drug delivery in the 1960's and 70's [11]. In 1924, d'Herelle describe micella as the smallest particle in a living substance. Micelles may be the answer to deliver poor solubility drugs, due to its size, function and ability to be an effective drug carrier [14]. Figure 2 is a time-line of the history of micelles from 1877 to 2014.

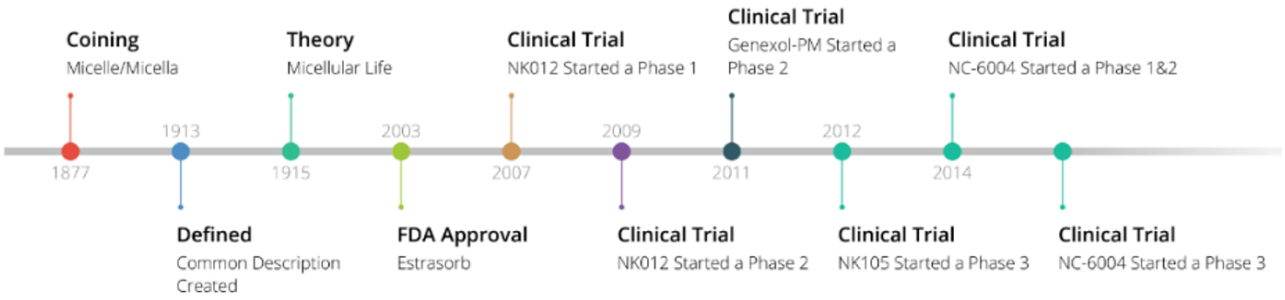

Figure 2 Timeline of milestones for the application of micelles from 1877-2014 [11, 15–21]

Characteristics of dendrimer, micelle, and hybrid NP are summarized in Figure 3. A variety of particles that fall within the range of 1-100 nm [22] considered NP and have a diverse application ranging from drug delivery to imaging. A dendrimer is a sub-particle of a nanoparticle whose size ranges between 1-10 nm. These molecules consist of a multi branched particles that are named based on their generation, which can be seen as a globular structure. A micelle size is defined between 10-100 nm, with a unique characteristic called critical micelle concentration (CMC). CMC is the concentration at which other objects will be allowed to form micelles. At the optimal size the structure is perturbed and protects drugs from possible inactivation. A hybrid nanoparticle is a larger particle size that ranges from 175-225 nm, consisting of a minimum of two compounds that are either organic or inorganic [23, 24]. Hybrid particles are separated by classes, with applications in both commercial and healthcare [23, 24].

1.2 Structure

Micelles are self-assembled surfactants with varying levels of branching. Dendrimers are symmetric macromolecules with monodisperse structure called branches or linear polymer core

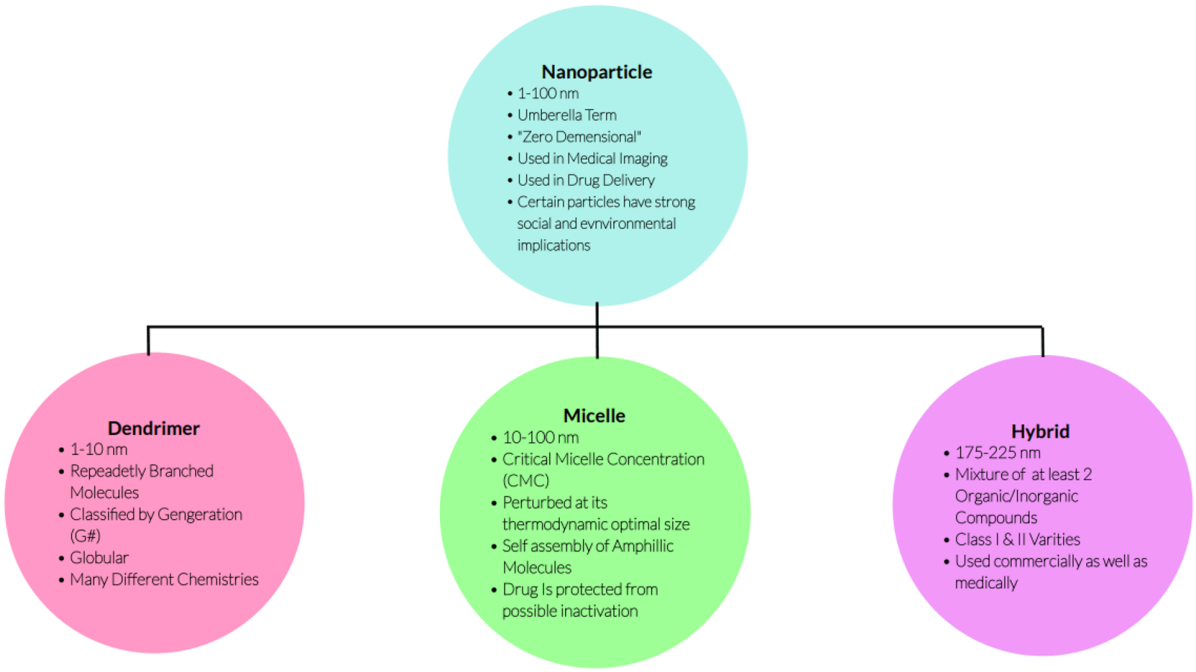

Figure 3 Classification of NP in terms of dendrimer, micelle, and hybrid [22–30].

discovered as stated earlier in Figure 1 and 2, respectively. The American Chemical Society does not have an official definition on what size defines the polymeric particles. Figure 4 to 7 depict a schematic of NP, micelle, dendrimer, and a hybrid construct, respectively.

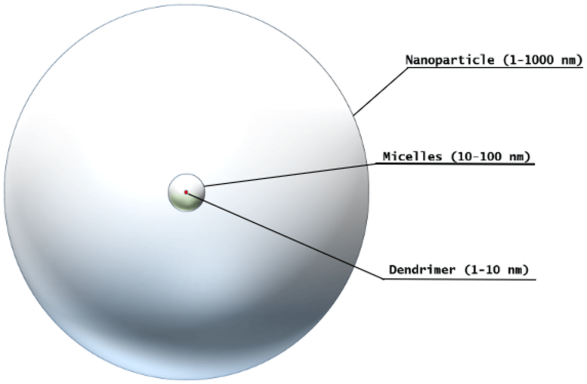

Figure 4 A schematic representation comparing the size of nanoparticles, micelles, and dendrimers.

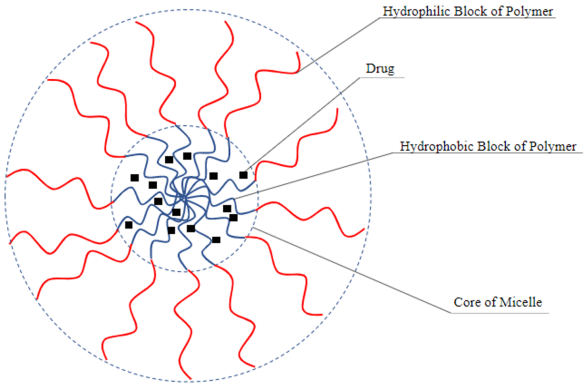

Figure 5 The components that make up a micelle [31]

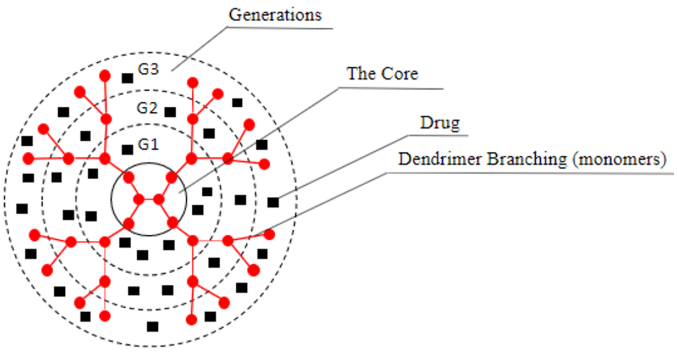

Figure 6 The construct of the G3 PAMAM Dendrimer [32]

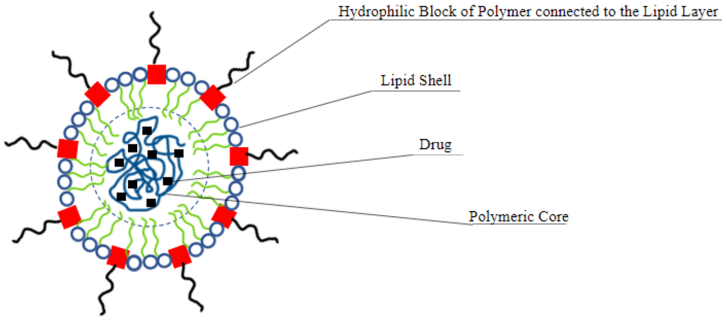

Figure 7 The construct of the of the Hybrid Lipid-Polymer Nanoparticle [33]

Figure 5 is a representation of a copolymer micelle that is separated into a hydrophobic and hydrophilic polymer, used in a micelle. The drug distribution is located in the core area in close proximity of the hydrophobic polymer. Each of these can play a vital role in the distribution of the drug both structurally and in the contents that creates it.

Although the branch structures alter slightly by the type of dendrimer and the branch formation, the microstructure closely resembles the PAMAM structure. Both materials distribute the drug throughout each generation. The branching monomers function to increase the structural integrity. Each of these structures, can alter the rate of drug distribution.

The Hybrid Lipid-Polymer Nanoparticle contains a hybrid structure of both hydrophobic and hydrophilic polymer chains and a lipid shell. The similarity to the micelle is that the drug is contained in a polymeric core, with a similar drug release. The Hybrid Lipid-Polymer Nanoparticle also protects against digestive conditions. In this paper the drugs, carriers, loading details, physical characteristics analyzed [34-74] are tabulated in Table 1.

2 Experimental design

Data was compiled from literature (Table 1) [34-74]. Our inclusion criteria included: (1) dendrimer size, (2) dendrimer drug loading, (3) polymer used in the dendrimer, (4) polymer molecular weight used in the dendrimer, (5) type of hybrid dendrimer, (6) micelle size, (7) drug loading into the micelle, (8) polymer used in the micelle, (9) molecular weight of polymers used in the micelle, (10) the component distribution in the hybrid micelle, (11) comparison of the nanoparticles, (12) a release percentage between 0-40% and particle size, (13) a release percentage of 40-100% and size, and (14) burst release comparisons between carriers.

PlotDigitizer software was utilized to extract graphical data from the literature that met the above inclusion criteria. Table 1 summarizes the citations and characteristics of the data used. The digitized data was exported into Microsoft Excel for necessary plotting. For the purposes of visual comparisons, burst release behavior was represented inside an oval showing the region with specific NC. Beyond these ovals, the sudden burst (BR) transform into a more steady state (SS) dissolution showing the kinetics obtain a plateau for each of the data set. The observed behavior was a result of several iteration steps in which the data conversion and plotting was carried out and represent an approximate empirical behavior.

In the lack of data under similar testing conditions, and the need to establish the TE trends, we included for this study published data and included them for comparisons. The data comprised inherent differences with carriers, size, drugs, loads and by the way the experiments were conducted. The experimental conditions were considered normalized and assumed to contain

differences in the following:

(1) Nanoparticles size;
(2) Polymers and combination;
(3) Additions of other chemicals/polymers added in the fabrication;
(4) Different fabrication methods;
(5) Coating durations;
(6) Drug load into the nanoparticle;
(7) The polymers in each evaluated material.

Table 1 Properties of dendrimers and micelles

Molecular Weight	Pore Size	Nanoparticle Drug Ratio	Drug Loading	Loading Efficiency	Hydrophilic/Hydrophobic (Drug)	Hybrid	Reference
14 kDa	–	3	Ibuprofen	–	Hydrophobic	No	[34]
–	–	8.77 +/- 0.44	MTX/ATRA	79.74 +/- 1.11%	Hydrophobic	No	[35]
–	–	–	Camptothecine	–	Hydrophobic	No	[36]
–	–	5	Chlorambucil	–	Hydrophobic	No	[37]
550-2000 Da	–	–	5-aminosalicylic acid	13 MTX mol./ G3	Hydrophobic	No	[38]
6-8 kDa	0.45 μm	–	DOX	73.2%	Hydrophobic	No	[39]
–	–	30	DOX	11.9%	Hydrophobic	No	[40]
–	–	1	Ciprofloxacin	–	Hydrophobic	No	[41]
0.5-1 kDa	–	1	Camptothecin	–	Hydrophobic	No	[42]
22.6-61.1 kDa	–	–	DOX	50%	Hydrophobic	No	[43]
6-8 kDa	–	1:320	DOX	38 $\pm$ 9.9	Hydrophobic	No	[44]
7 kDa	–	–	Nimodipine	42.4-74.1%	Hydrophobic	No	[45]
<3.5 kDa	–	–	Vancomycin	–	Hydrophobic	No	[46]
<10 kDa	–	1.2-10	Vancomycin	70-100%	Hydrophobic	No	[47]
8-14 kDa	–	2	Vancomycin	–	Hydrophobic	Yes	[48]
<3.5 kDa	–	–	DOX	–	Hydrophobic	No	[49]
12 kDa	–	–	DOX	–	Hydrophobic	No	[50]
2-8 kDa	–	–	DOX	–	Hydrophobic	No	[51]
5 kDa	–	–	DOX	48.75%	Hydrophobic	No	[52]
12 kDa	–	–	DOX	–	Hydrophobic	No	[53]
10 kDa	–	–	DOX	–	Hydrophobic	No	[54]
1 kDa	–	–	Vancomycin	–	Hydrophobic	No	[55]
5 kDa	0.8 um	0-150	Indomethacin	16.33-42.03%	Hydrophobic	No	[56]
1 kDa	–	–	DOX	58.4-66.6%	Hydrophobic	No	[57]
~2 kDa	–	–	DOX	–	Hydrophobic	No	[58]
3.5 kDa	–	1:0.8	DOX & paclitaxel	58.-64%	Hydrophobic	No	[59]
3.5 kDa	–	1:10	Paclitaxel	8.36%	Hydrophobic	No	[60]
<10 kDa	–	–	Lidocaine	–	Hydrophobic	No	[61]
12.266 kDa	–	–	DOX	–	Hydrophobic	No	[62]
29.5 kDa	–	–	DOX	39.3-49.8%	Hydrophobic	Yes	[63]
12-14 kDa	–	–	DOX	54.5-66.8%	Hydrophobic	No	[64]
12 kDa	–	–	DOX	46-90%	Hydrophobic	No	[65]
2-3.5 kDa	–	–	Vancomycin	35%	Hydrophobic	No	[66]
14 kDa	–	–	Vancomycin	40.96-43.71%	Hydrophobic	No	[67]
PLA = 158.4 kDa	–	–	Vancomycin	–	Hydrophobic	No	[68]
–	–	–	Vancomycin	87.46-94.49%	Hydrophobic	No	[69]
3.5 kDa	–	–	DOX	10.12%	Hydrophobic	No	[70]
Chitosan = 450 kDa	–	–	DOX	50.92-56.21%	Hydrophobic	No	[71]
5 kDa	–	–	DOX & Triptolide	72.3-82.1%	Hydrophobic	No	[72]
12 kDa	–	–	DOX	60-70%	Hydrophobic	No	[73]
6-8 kDa	–	–	DOX	42.73%	Hydrophobic	No	[74]

3 Results

The drug release percentage over time data was compiled from literature as tabulated in Table 1. Several methods of distributing drug involved NP carriers. Dissolution kinetics were compared with one another to evaluate TE. Since the data was from around the world, experimental testing parameters varied as a result. However, drug type, the solution and pH at 37°C, and specific NP carrier used were similar. The cell cultures, polymers, and conditions differed. For the purposes of comparisons among N C and TE, 40% of drug release time was considered Phase I where a sudden burst release (BR) occurred and Phase II where a steady release (SS) occurred for the remainder 60% of the time of release. The overall drug release determines the TE and the prolonging portions of the drug release life cycle will help determine controlled release. The ovals were positioned in the charts to schematically show the regions where sudden burst occurred in the 40% of the life followed by a plateau.

3.1 Dendrimer

Dendrimers (Figure 6) developed into nano size, multifunctional surfaces with high branching making them a class of drug and gene delivery careers. In this effort an attempt made to the drug release strategies to enhance the TE in terms of size, polymers used and other characteristic features describing the surfaces and resulting dissolution. The dissolution kinetics was considered in terms of two phases; 1) BR and 2) transitioning to SS behavior characterized by a linear or plateau for remainder of the release and time. Usually, dendrimers exhibit a pronounced burst release for up to 80% of drug, followed by SS release for remainder 20% for an extended period of time, 2-3 times that of the phase 1. These characteristics are discussed below. Table 2 shows the specific properties of dendrimers and drugs included in for the comparisons.

Table 2 Nanoparticles and properties

Nanoparticle Type	Medicine	Cell Culture	Solution	pH	Configuration	Size	Reference
PAMAM Dendrimer (Linkers)	Ibuprofen	-	Dependent of which plot	varies	G4-GFLG-Ibu	4 nm	[34]
Dendrimer Dual Release (pH)	MTX & ATRA	HeLa cell lines	PBS	7.4	MTX and ATRA-G4 PAMAM	-	[35]
Precise Dendrimer Conjugates	Camptothecine	SKOV-3 ovarian cancer cells and MDA-MB-231 breast cancer cells	PBS	Varies	CPT	-	[36]
Dendrimer Derivatives (w/Poly Shell)	Chlorambucil	-	-	Varies	G3-PDMA	Listed	[37]
Dendrimer Drug interactions	5-aminosalicylic acid	Human colon adenocarcinoma cell line (Caco-2)	-	-	PAMAM-PABA-SA/ PAMAM-PAH-SA	comparison	[38]
Low Toxicity Dendrimer	Doxorubicin (DOX)	HeLa cancer cells & Standard fibroblast cell line NIH3T3	PBS	7.4	DOX-G4.0-PAMAM	Listed	[39]
Duxorubicon PAMAM Dendrimers	Doxorubicin (DOX)	Cancer cells	PBS	Varied	G5.NHAc-DOX	5.4 nm	[40]
Triazine Dendrimer	Ciprofloxacin (CIP)	Staphylococcus aureus and others	-	-	-	2-10 nm	[41]
Dendrimer Hydrogel	Camptothecine (CPT)	HN12 Cancerous Cells	PBS	7.4	G3-CPT	-	[42]
Dendrimer Chain Length Changing	Doxorubicin (DOX)	Multiple types of cancer cells	-	-	G4/G5 PEG	-	[43]
Radiation Based Dendrimer	Doxorubicin (DOX)	Cancer Cells	Varied	Varied	G4.5 dendrimer (GC/DOX)	Table	[44]
Molecules with dendrimer core	Nimodipine	-	Tris/HCl buffer	7.2	Chart	Chart	[45]
Precise Dendrimer Enhanced Atni-	Vancomycin	Gram Positive bacterias	PBS	7.4	G5 PAMAM	-	[46]
Dendrimer Based Multivalent Vancomycin	Vancomycin	Gram Positive bacterial cells	PBS	7.4	(G5) poly(amidoamine) (PAMAM)	Table	[47]
Ultra small Lipid dendrimer hybrid	Vancomycin	S. aureus and MRSA	PBS	7.4	Chart	$<$100 nm	[48]
IONPs + Dendrimer Conjugates	Doxorubicin (DOX)	B16 melanoma F0 cancer cells	PBS	7.4	mPEG-G2.5-DOX and IONP	13 nm	[49]
Dendrimer-grafted nanocrystalline Cellulose	Doxorubicin (DOX)	-	PBS	7.4	NCC-G4A	$<$10 nm	[50]
Enzyme-responsive release from dendrimer NPs	Doxorubicin (DOX)	CT26 colon carcinoma cells	PBS	7.4	DendDP and DendGDP	50-100 nm	[51]
Gold-DOX Np Coupled With Dendrimer (questionable)	Doxorubicin (DOX)	A549 cells	PBS	7.4	Au-PEG-PAMAM-DOX	20-25	[52]
Dendrimer Grafted gold nanoparticles	Doxorubicin (DOX)	lung cancer cells	PBS	7.4	AuNPs and Au-NH2	$<$30 nm	[53]
Surface Functional Groups from Dendrimer carriers	Doxorubicin (DOX)	human epithelial carcinoma cell line	PBS	7.4	G5.NHAc/DOX	N/A	[54]

3.1.1 Dendrimer size

The size of the dendrimer has directly linked with the TE. Literature data compiled included dendrimer size from less than 10 to 63 nm. Figure 8 presents the dendrimer size data loaded with doxorubicin. It was shown that 34.0 nm and 38.0 nm size may release the most doxorubicin over the time-period extending to $\sim$100 hours. The 13 nm NP demonstrates a shortest duration with a complete dissolution at $\sim$35 hours. Although the benefits of higher surface area with smaller NP completes with the drug loading resulting in quick dissolution, at the same time an optimal efficacy obtained with 34-38 nm NP. The 63 nm appears to have the least effective drug release because it fully dissolved below 15 h time. Since only 15% of the drug was released, the TE was compromised. Therefore, dendrimer NP carrier for doxorubicin was effective at a range of 30-40 nm while size between 34 and 38 nm may be very sensitive dictated by vascular permeability.

3.1.2 Polymer of dendrimer

A large initial release of free doxorubicin, within the first few hours was reported in the literature. The limited data shows that the dendrimers favored the fourth generation of polymer allowing for more accuracy since total amount of drug that is present in the dendrimer (drug loading) dissolved. The conditions used to extrapolate the data used in Figure 9 were consistent among all variables. The PAMAM dendrimer demonstrates superior drug release over the course of $\sim$100 hours. The MPEG, a mixture variation of the PEG polymer, has the least drug release over the course of time at $\sim$45 hours between release and the initial release of the drug. Thus, PAMAM dendrimers have been attributed to their high solubility, stability, oral bioavailability

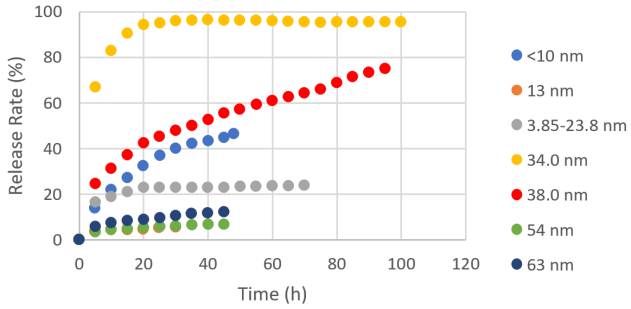

Figure 8 Analysis of the behavior of dendrimer size affects the release rate of doxorubicin over time [35, 43, 44, 49, 51, 53, 54, 60]

of various drugs. Both drug entrapment and release are controlled by dendrimer surfaces which increase with new generations. Even though the drug entrapment and release are a function of structural features, and drug interaction with PAMAM surfaces made with hydroxyl, carboxylate and others, for each drug to be formulated or nano-construct built.

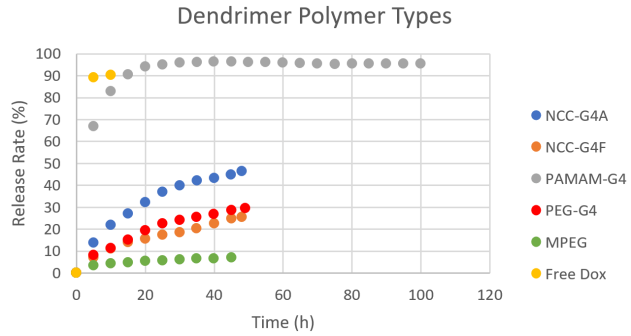

Figure 9 Polymers of dendrimers affect the release rate over time [39, 43, 45, 49, 60, 63–65]

3.1.3 Dendrimer polymer

Several generations of polyethylene glycol (PEG) evolved rendering higher TE. PEG tested here contain a molar mass from 570 to 1100 g/mol and considered to be a low molecular weight and hydrophilic NP. Figure 10 illustrates a large initial drug release, which is immediately followed by a plateau for the free doxorubicin data set. The G5 may allow a greater concentration of drug to be loaded. The G stands for generation which applies layers that contain mostly the specific drug but also other components like polymer coatings. The nanoscopic characteristics of individual PAMAM dendrimers from G5 to G10 associate an increase in mean diameter from 4.3nm to 14.7nm, respectively. G6 and above are highly expensive and toxic. Therefore, beyond G5 are hardly used. The values of 570 and 1100 in Figure 10 illustrate the molecular weight of PEG polymer concentration that was used. The behavior shown in Figure 10 demonstrates that when the polymer concentration increased drug release % over time dedcreased. The similar behavior between the ∼5 hours and ∼20 hours can be observed between G4 PEG1100 and G5 PEG570, indicating differences in physical properties affecting drug release rate.

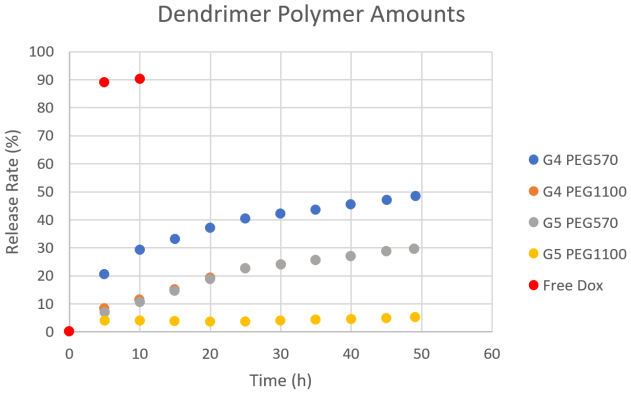

Figure 10 Types of polymers on dendrimers and their release rate over time [43]

3.1.4 Dendrimer drug type

The percent of drug release is affected by the type of the drug loaded, as seen in Figure 11. Ibuprofen appears to have the least effective drug release percent at below 5% over the course of time. Vancomycin has a low initial burst release compared to camptothecine but resulted in being around the same transitioning to steady state phase II which means that the duration of the drug distribution is approximately the same. The additional drugs showed large initial release rates, but the doxorubicin presented a balance of a large initial release and a prolonged release in phase II,

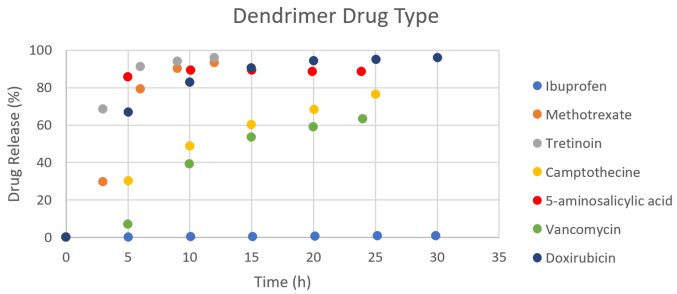

Figure 11 Drug release rate of dendrimers with different drugs [35,38,39,42,44,45]

3.1.5 Burst release of polymers

According to the trend line seen in Figure 11, free doxorubicin has the highest burst release. This value may be skewed due to having fewer data points compared to the other data sets. The initial burst for every polymer type was low compared to the PAMAM dendrimers which had large drug release by 100% of the loaded amount throughout the experiment. The plateau of each, PEG and MPEG, shows small initial burst period in Figure 12.

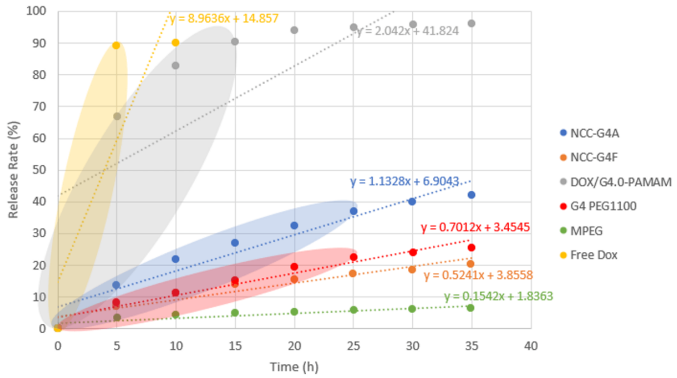

Figure 12 Initial burst release based on six polymer types [39,43,49,55,60,63–65]

3.1.6 Burst release of G4 and G5 polymer

The initial burst release, the amount of drug that was released within the first few hours after the release process begins, is depicted in Figure 13 with ovals, in which the initial burst begins at start and ends prior to plateauing over time. The ovals and the boundaries that contain them show potential ranges the data could be within during those phases of the release process. The data set in Figure 10 was also used in Figure 13. The equation of the line for G4 PEG1100 and G5 PEG570 have similar slopes affirming the results seen in Figure 10. The G4 PEG570 shows a small initial burst and has a continued release unlike the G5 PEG1100. The overlapping of the ovals represents areas in which the data would be similar. Even though up to G10 generations exist, however, only through G5 were considered in this paper due to their higher TE.

3.1.7 Burst release of dendrimer loaded with drugs

The burst release for each drug shows similar results also seen in Figure 11. Ibuprofen, shown there, does not dissolve for 30 h carried in dendrimers. The Vancomycin and camptothecine were comparable to each other regarding the slope of the data sets but the y-intercept of the equation is due to the initial data point being lower for the Vancomycin which may have been the reason that the data sets were not nearly the same as each other. The remaining drugs appear to release 85% of the loaded drugs by sudden burst (Figure 14).

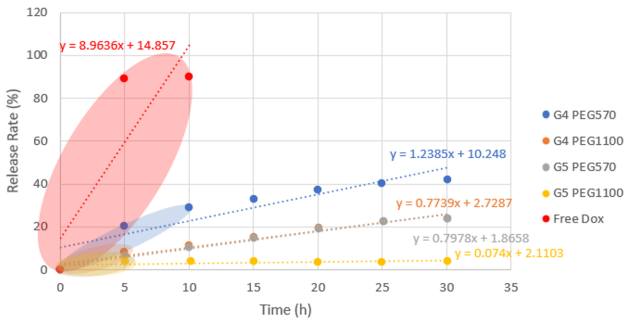

Figure 13 A comparison of G4 and G5 polymer in releasing drug [43]

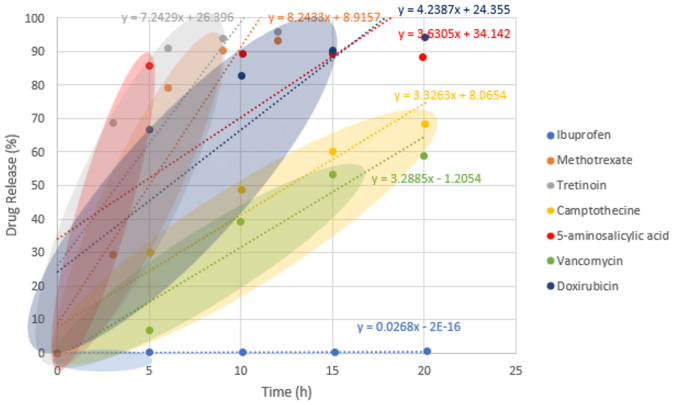

Figure 14 Initial burst release based on the drug that was loaded into the dendrimer [35, 38, 39, 42, 44, 45]

4 Hybrid nanocarriers

Combining organic and inorganic NP in a single hybrid drug delivery system imparts multi-functional characteristics that also enhance the TE. Such a combination of organic and inorganic hybrid nano carrier has been found to be effective in some cancer scenarios. PAMAM dendrimers form a model system and stabilize the inorganic nanocrystals. Hybrid particles forming nanoclusters in individual dendrimer molecules.

4.1 Hybrid dendrimer – Drug release

The PAMAM's initial burst release behavior is shown to be under 20%, while the LPCL-PGAMA is under 50% based on the data. The burst release in Figure 15 shows the effectiveness of the PAMAM to have a slower release rate compared to LPCL-PGAMA.

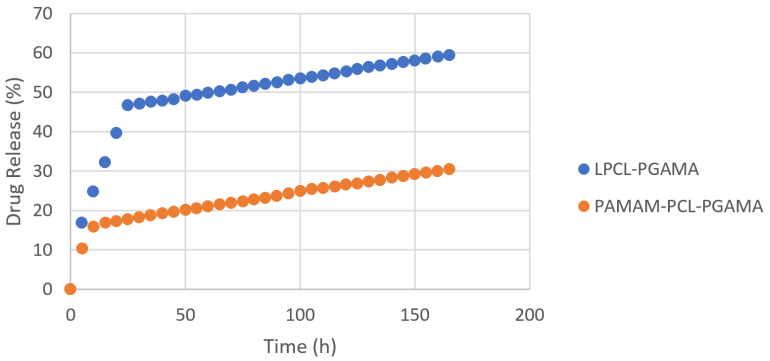

Figure 15 The drug release of the hybrid dendrimer LPCL-PGAMA AND PAMAM-PCL-PGAMA [45]

4.2 Burst release of LPCL-PAMMA and PAMMAM-PCL-PGAMA

The initial burst release trend line shows that the increase for the LCPL is over a longer time period but shows a similar slope within the ovals as the PAMAM. This shows that the PAMAM plateau ending earlier has a major impact on how much of the drug was released because when the plateau occurs it usually is capped at or around that value unless as seen in Figure 16, there

may be multiple plateaus. The prolonged release for each showed similarities between the two however, the kinetics of initial burst release different.

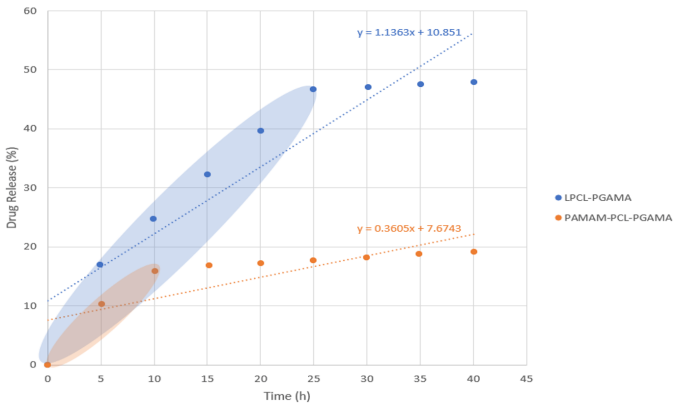

Figure 16 Burst release of LPCL-PAMMA and PAMMAM-PCL-PGAMA [45]

5 Micelles

Micelles were used to deliver genes, proteins, and complex drugs that were low molecular weight and hydrophobic. Micelles are self-assembled microstructures usually <50nm diameters and referred in this paper as such. Polymeric micelles can reach twice as big. Since their size is consistent with the pore sizes in vasculature micelles penetrate blood/tissue and cellular uptake. As a result, the size, polymeric construct, and drugs become important parameters to evaluate the TE. A summary of micelles used for comparison is presented in Table 3.

Table 3 Micelle Data Sources [55–74]

Nanoparticle Type	Medicine	Cell Culture	Solution	pH	Configuration	Size	Reference
Micelle (mPEG-PLCPPA hydrogel)	Vancomycin	C2C12 cells	PBS	7.4	mPEG-PLCPPA	21.73 +/- 0.66	[55]
Micelle	Indomethacin	Cells of the reticuloendothelial system (RES)	PBS	7.4	MePEG/˝-CL	<200 nm	[56]
Degradable Micelle	Doxorubicin (DOX)	HeLa cells	PBS	7.4	PEG-SS-PTMBPEC	450 nm?	[57]
Reduction-Sensitive Micelles	Doxorubicin (DOX)	T24 human bladder cancer cells	PBS	7.4	PEO45-b-PMABC19/ PEO45-bPBEMAGG21	97-126 nm	[58]
Biodegradeable Micelle	DOX and Paclitaxel	–	PBS& Acetate	varied	–	120 nm	[59]
Polymeric Micelle	Paclitaxel (PTX)	MCF-7 cells	PBS	6.5 or 7.4	mPEG-PCL-PLLA	22-51 nm	[60]
Unimolecular Polymeric Micelles	Lidocaine	–	Water	–	Core(laur)PEG5	ca. 50 nm	[61]
Block Copolymer Micelles	Doxorubicin (DOX)	cancer cells - tumor	PBS & Acetate	5 or 7.4	PEG-p(Asp-Abz-Hyd-DOX)	<50 nm	[62]
Hybrid Micelles Containing Triblock Copolymer Micelles	Doxorubicin Hydrochloride (DOX-HCl)	–	Unknown	Varied	PLGA-b-PPO-b-PLGA/ PEG-b-PPO	ca. 90 nm	[63]
Bioresponsive Biodegradeable Micelles	Doxorubicin (DOX)	HeLa and RAW 264.7 cells	Varied	Varied	PEG-P(TMBPEC-co-PDSC)	Varied	[64]
Precise Micellular Drugs	Doxorubicon (DOX)	Cancer Cells	PBS	7.4	PEG-SS-PCL	59.6-110.4 nm	[65]
Antibacterial Micelles	Vancomycin	Luria-Bertani (LB) bacteria	PBS	7.4 or 6	Van-hyd-PECL	Changes	[66]
Alendronate decorated biodegradable polymeric micelles	Vancomycin	LB liquid media bacteria	PBS and citrate-Na2HPO4 buffer solution	7.4 or 5	PLGA-PEG-ALN/ PLGA-PEG-COOH	2 different avg	[67]
LbL coating of chlorhexidine-loaded micelles	Vancomycin	mouse fibroblast cells L-929	PBS	7.4	PLA	–	[68]
Thiolated Pluronic Based Nanomicelles	Vancomycin	S. aureus	PBS	7.4	–	<250nm	[69]
Loaded pH-Responsive Micelles	Doxorubicon (DOX)	HeLa cells	PBS	7.4	PDPA-b-PAMA micelles	136-151 nm	[70]
chitosan-based polymeric micelles	Doxorubicon (DOX)	Ttumor cells	PBS	7.4	DOX-loaded CSO-SA micelles	20.4	[71]
redox-sensitive drug-release polymer micelles	DOX and Triptolide	prostate cancer PC-3 cells	PBS	7.4	DA-ss-DT and other variants	∼100 nm	[72]
Biodegradable micelles with sheddable poly- shells	Doxorubicon (DOX)	Monocyte macrophage cell line (RAW 264.7)	PBS	7.4	PEG-SS-PCL / PEG-PCL	56.3 / 37.7	[73]
Core Cross linked Plymeric Micelles	Doxorubicon (DOX)	HeLa cells	PBS	7.4	DOX@NCMs and DOX@CCM	Dh values (188.13 and 168.14)	[74]

5.1 Micelle size

The 20.4 nm micelles demonstrated the largest initial burst release of the doxorubicin at 80%. The < 50 nm size showed a small initial burst below 10%, followed by a larger, prolonged increase after 5 hours until ∼45% release of doxorubicin at ∼20 hours. The 120 nm had a larger initial release value of 25% but plateauing earlier at around 10 hours. Micelles of 56.3, 136-151, 97-126, 37.7, and 20.4 nm size all exhibit a plateau around the same time (Figure 17).

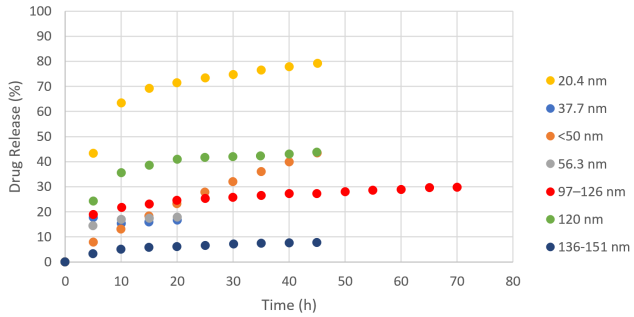

Figure 17 Analysis of how types of polymers on micelles affect the release rate over time [58, 62, 70, 71, 73]

5.2 Micelle polymers

Many of the copolymer builds showed similar data results that coalesced with a range between a 0% release rate and ∼30%. The DA-ss-DT appears to an outlier at ∼80% release rate. The majority of the polymers showed slow rise to over 30% of the total amount of doxorubicin released. There were some similarities based on the "b" that was joining the polymers where the plateaus occurred at similar times but different percentage values of about 5-10%. The similarity was the trajectory and the specific time that the plateau occurred in 10 hours. It will become more visible in Figure 18.

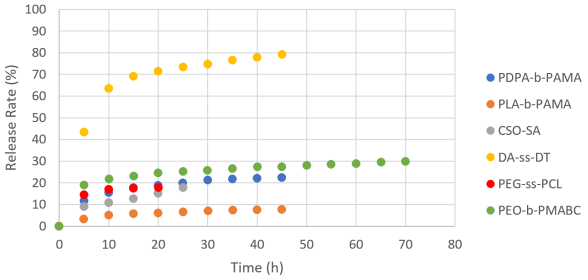

Figure 18 A comparison of doxorubicin release rate based on varying polymers [58, 70–73]

5.3 Micelle drug release based on drug

The data for indomethacin and vancomycin have several data points of interest, in which multiple linear slopes seen, Figure 19. This will allow the possibility that the release rate will continue over an extended period of time compared to the other nanoparticles. Although, the initial burst release values were not equivalent to the doxorubicin and the paclitaxel. The data was cut off in each of these cases so a potential step like structure could still be a possibility with the other drugs. Lidocaine had a large initial release rate of nearly 90% followed by a plateau for 25 hours.

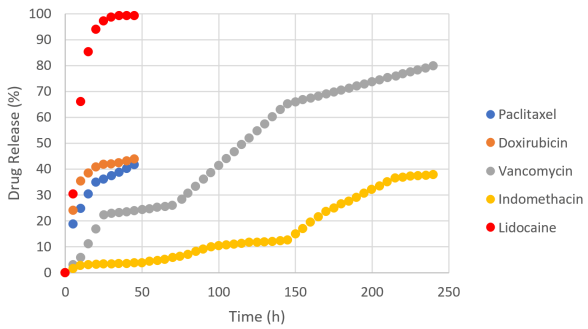

Figure 19 Analysis of five drugs loaded on micelles and there drug release rate [55, 56, 58, 61, 72]

5.4 Drug release of Indomethancin in micelle

The available data obtained from a literature for free indomethacin is limited, as a result an early time period which alters the outcome in Figure 20. DIP 25 has a slow initial release but has a steady prolonged release rate which eventually releases more drug than the other polymers.

The DIP 50 is the exact opposite with one of the highest initial burst releases but plateaus much earlier than the other polymers. The DIP 75 and 100 are similar and show an almost identical final drug release value.

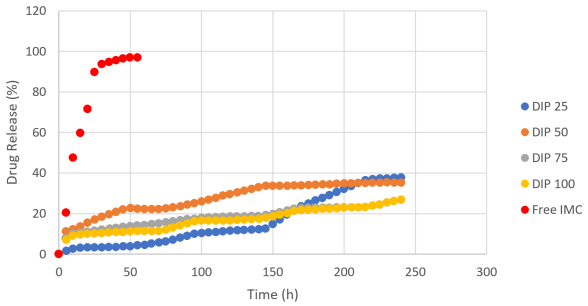

Figure 20 The release rate of based on polymer used [56]

5.5 Burst release based on size

The size of the micelles was considered to affect the TE and dissolution kinetics. Time to percent drug release data plotted below, Figure 21, showing the initial release rate values. The initial release of the 20.4, <50, and the 120 nm micelles showed a delayed burst and transitioning to steady state dissolution where the plateau in the drug release occurred. The 136-151, 37.7, 97-126, and 56.3 nm micelles showed a short initial release transitioning to steady release at smaller release rates. Only 20.4nm size micelle was able to dissolve over 70% of the drugs meaning effective in delivering the drugs. The remainder of the micelles were only releasing less than 50% of the drugs, thus ineffective. The overlapping ovals show early release processes through 10 hours.

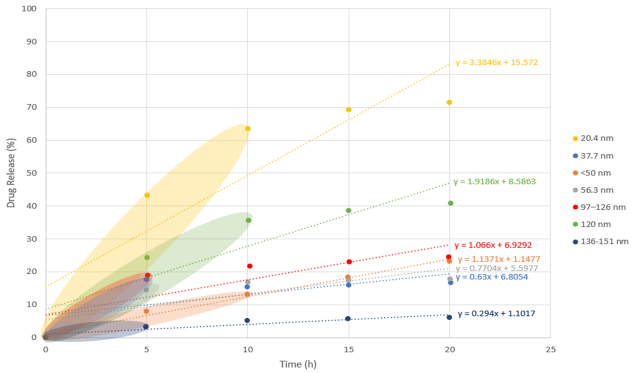

Figure 21 The burst release of micelles based on size [58, 62, 70, 71, 73]

5.6 Micelle bust release

Lidocaine showed a large increase in the initial burst over an extended amount of time showing both gradual and initial release of the drug. Paclitaxel and doxorubicin seemed to show a lot of similarities with the initial burst release (ovals), the slope of the equation, and the time frame in which each started plateauing, Figure 22. Indomethacin seems to have small overall drug release with close to immediate plateauing. Vancomycin showed a gradual incline and then plateaued later than the other drugs being released pointing to less of a burst and more of a slow release over an extended period of time, thus higher TE.

5.7 Burst Release of doxorubicin

Figure 23 analysis used the same data set of Figure 17. The similarities of both graphs can be seen by the ovals and around the time range of between 5-10 hours. The slopes of all of the polymer are quite similar, except for DA-ss-DT which is nearly three times the amount and has a large initial burst release at ∼70%.

5.8 Burst release of indomethacin (IMC)

The free IMC shows the longest burst release (Figure 24) which explains the overall drug release difference. The burst releases show consistency with one another with the duration before the plateau occurs, but the amount of the release is slightly different which is shown when comparing the ovals and the equation values.

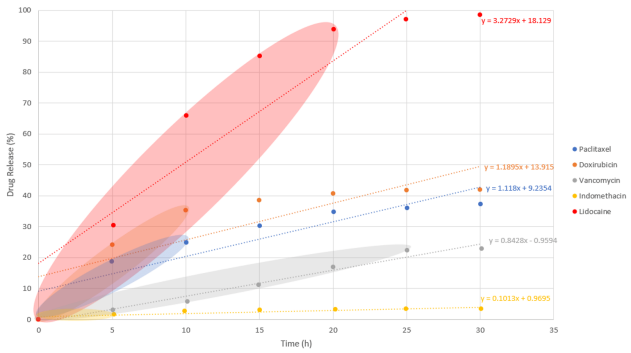

Figure 22 The burst release of six different medications loaded on micelles [55, 56, 59, 61, 72]

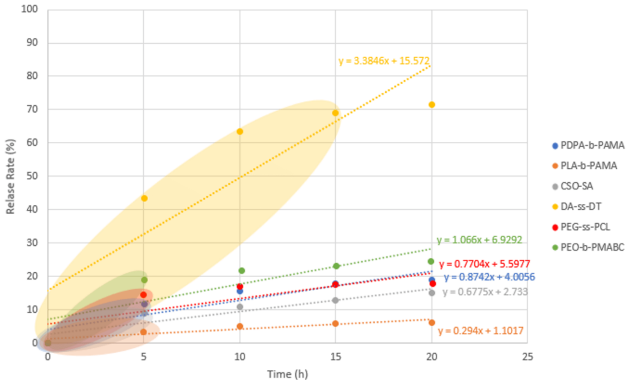

Figure 23 The burst release of doxorubicin to six different types of polymers [55, 70–73]

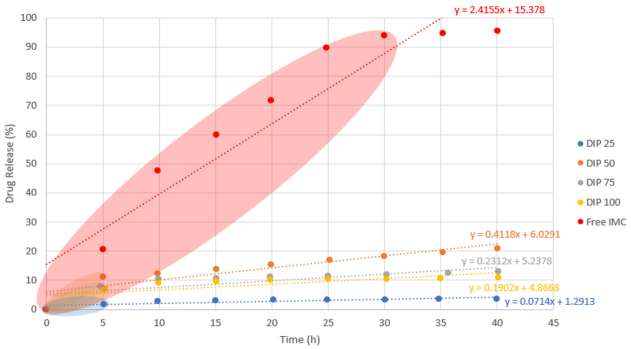

Figure 24 The burst release of the varying polymers with indomethacin (IMC) [56]

The Free IMC has an initial data point at 5 hours that is only 10% above, showing the initial burst is not as significant the initial value of free doxorubicin in a dendrimer. It is more prolonged than that of the dendrimer. Although, this could be due to the drug type.

5.9 Hybrid Micelle

There is a slowdown and a trend toward a plateau at an early time period with the 10/0 distribution which is the distribution of each portion of the hybrid. The 8/2 exhibited the largest overall drug release. Since the behavior of the different variations of nanoparticles are similar, implies that the distribution of the polymers in the hybrid micelle plays a minimal role in drug release within 10% of one another as shown in Figure 25.

5.10 Burst release hybrid micelle

As shown in the Figure 26, the drug release kinetics showing a bilinear behavior where initial release was proportional to time of the release for first 15 to 20 hours, followed by a transition. However, transitioned behavior was also expressed linearly. Ovals were consistent with one another in the initial release phase. It is interesting to note that hybrid micelles do not exhibit sudden burst release as seen in the case of other carriers, dendrimer, Figure 8 and 9, 11, where nearly 90% of drug released during the first 20 hours or earlier. Therefore, the TE of the hybrid micelle is superior to other carriers. The 8/2 and the 2/8 distributions show a slightly

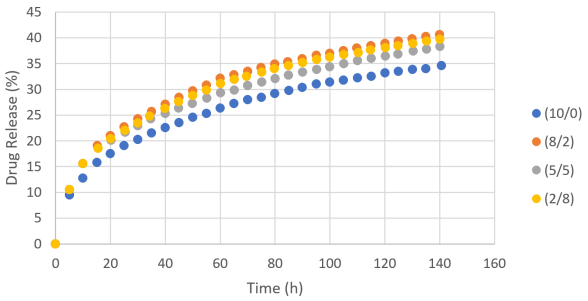

Figure 25 The effects of varying distributions of hybrid micelle breakdown on the drug release [63]

larger release of drug so those consistencies might be the best combination for releasing a larger amount of drug. The 10/0 shows reduced drug release in that composition which could mean that a specific variation could be the most efficient method when delivering drugs with the use of hybrid micelles.

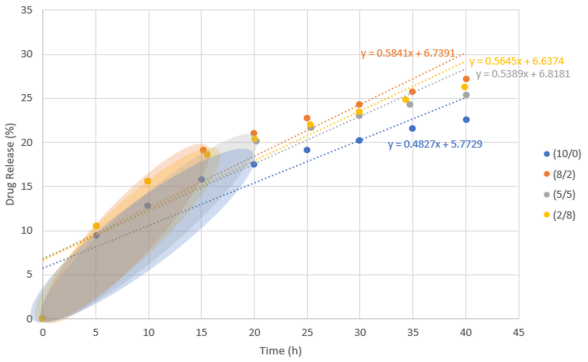

Figure 26 The burst release based on the distribution of hybrid micelle contents [63]

6 Nanoparticles

Nanoparticles provide the needed physical properties at the same time their size enables them to pass through the blood pathways or tissue cellular structures. As a result, their applications have grown in the recent years.

The liposomes had a similar burst release to the dendrimers but does not show similar overall drug release amounts where the difference was around 40%. The mesoporous bioactive glass (MBG) shows large initial jump but as seen in Figure 27 that the duration before the plateau occurs earlier than the rest [75]. The alginate has a slightly earlier transition from initial release to steady state release at a higher rate compared to the rest of the data (Table 4).

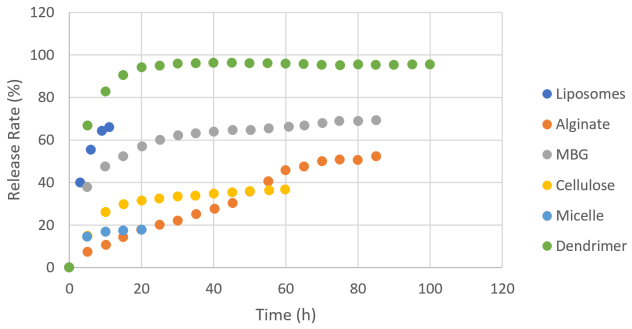

Figure 27 The release rate of nanoparticles [76–79]

Table 4 Other Nanoparticle Data Information [76–79]

Nanoparticle Type	Medicine	Cell Culture	Solution	pH	Configuration	Size	Reference
Liposomal	Doxorubicin (DOX)	BALB/c mice	PBS	7.4	PLGA-PEG-PLGA	75 nm	[76]
Cellulosal	Doxorubicin (DOX)	Balb-c/nude mice	PBS	7.4	CMC-ME 2 MO-DOX	53-65 nm	[77]
Alginate	Doxorubicin (DOX)	Human cancer liver cell	PBS	7.4	Fe3O4-SA-PVA-BSA	240-460 nm	[78]
Mesoporous Bioactive Glass	Doxorubicin (DOX)	human bone cancer cell	PBS	7.4	Ag2O-MBG NPs	60 nm	[79]

6.1 Bust Release of nanoparticles

The initial burst release for the dendrimer was similar to that of the alginate for a given time. Dendrimer releases nearly 80% of the drug quickly, within first 5 to 10 hours, followed by a plateau for the time 3 times longer. The remaining ovals are presented in Figure 28 for 5-10 hours showing the burst and for the remainder of 15-20 hours releasing only 15-20% of the drugs. The burst release % of the liposomes is consistent with the dendrimer, for example, sudden burst, followed by plateau for 20% release in 15-20 hours. The linear equations are consistent with each data set except for the liposomes since the available data was limited.

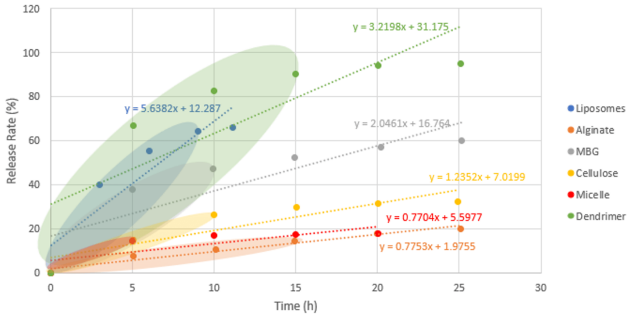

Figure 28 Burst release of six nanoparticles [76–79]

7 Discussion

Nanocarriers (NC) provide in vivo stability, bioavailability, solubility, absorbability, together with targeting. As stated earlier, size of the nanocarriers has to be such that it can penetrate though the vasculature pores and get to the blood stream. As a result, below 30nm carriers are preferred. NC thus comprise of atomic size shapes, may be spheres or tubes [81]. The nanotubes and particles are shown to possess high mechanical strength together with magnetic, electrical, and biological properties. In drug delivery they are encapsulated with drugs and delivered at the site via targeting mechanisms or via gastrointestinal pathways. New branched structures are synthesized for application to determine their TE based on their kinetics. As the BR increases, and time during which the release occurs decreases, results in side effects and drug resistance. Therefore, there is a need to tailor the right carrier for effective TE. In this section it will be prudent to discuss the drug release kinetics for dendrimers and micelles for Phase 1 first.

7.1 Dendrimer *vs* micelles effect of size in phase 1

Two phases of drug release was separated, ideally, into 1) burst release (initial 40% of release) and 2) the SS release (remainder 60% of the release). Many of the carriers presented in this research do not present this ideal behavior, instead as identified Figure 8, 9 and 11, where nearly 80% of the release occurred within 5-15 hours (in phase 1) and only 5-15% of release occurred in phase 2, Figure 29.

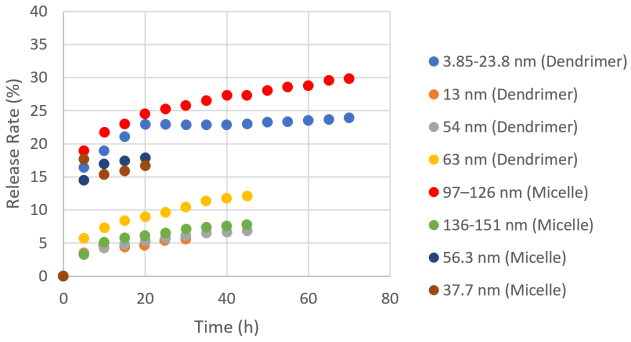

Figure 29 The comparison of total drug release between 0-40% based on drug size [35,43,44, 49,51,53,54,58,60,62,70,71,73]

Within these ranges, Figure 29, of the release, there were similarities between the 97-126 nm micelle and the 3.85-23.8 nm dendrimer exhibiting initial burst release, however, dendrimer transitions to a SS plateau while the micelle begins ending phase 1 releasing 25-27.5% of the drug in 20-30h. Extended SS plateau resulting for micelle and drug release of about 5%. The consistencies with the 56.3 and the 37.7nm micelles show that micelles tend to be more

consistent within the 0-40% drug release range. Dendrimers also result in lower total drug release percentage than the micelle group.

7.2 Dendrimer Bust Release 0-40%

The burst release shows that the smallest dendrimer has the second largest initial burst release but is similar time periods as the 97-126 nm micelle before the SS plateau occurs. The 56.3 and 37.7 nm micelles have a very early plateau which slows the total amount of drug that was released. The remaining dendrimers and the 136-151 nm micelle all start transitioning within 10 hours but the percentage released, Figure 30, during that time was slightly different, 5%.

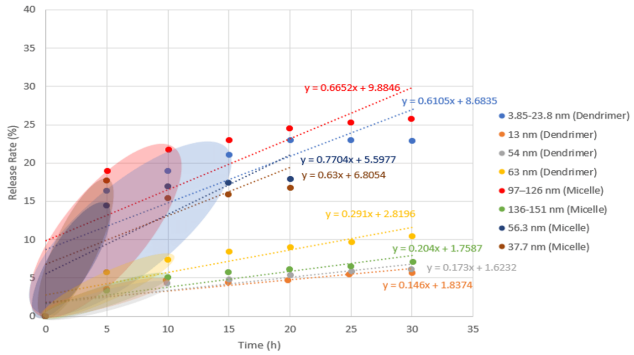

Figure 30 The burst releases of the various sizes between 0-40% release amounts [35, 43, 44, 49, 51, 53, 54, 58, 60, 62, 70, 71, 73]

7.3 Release rate of dendrimer and micelles 0-100%

The overall release shows that the smallest micelle and the 34 nm dendrimer release the most amount of drug with largest initial release by at least 20%. The 38 nm dendrimer and the 50 nm micelle do not show SS behavior like the others but instead show a steady, prolonged release of the drug seen in Figure 31. There is a need to generate the data controlling parameters so that more can be learnt about these behaviors.

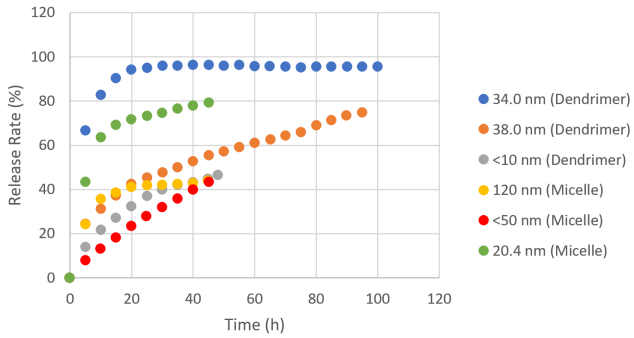

Figure 31 The comparison of total drug release between 0-100% based on drug size [35, 43, 44, 49, 51, 53, 54, 58, 60, 62, 70, 71, 73]

7.4 Burst Release dendrimer and micelle

The initial burst release time of the 34/38 nm dendrimers and the <50 nm micelle are similar based on the initial release but the amount of drug that was released shows a major difference of around 20%, resulting in larger amounts of total drug released throughout each experiment. The burst release is consistent between dendrimers and micelles between the data in Figure 12 to 14 and 21 to 23 with a balanced distribution of data. This could be due to the overall differences in each experiment. The hybrid dendrimer and micelles show their burst behavior in Figures Figure 26 to 28 that is comparable with nano-particles (Figure 32).

Drug release of doxorubicin using multitude of carriers indicates that the TE is a function of carrier size, polymers of construction of dendrimers and micelles, hybrids, and drugs that encapsulated. Each drug-carrier pair was compared with other combination based on drug distribution in this case, doxorubicin. Understanding of the kinetics may develop new strategies in drug delivery methods either via formulation or construct to improve healthcare. The kinetics of dendrimers were a function of size where in 20h 90% of the drug was released by 34nm and 40% of the drug was released by 38nm dendrimers. 20.4 and 37.7nm size micelles released 60% and 35% drug, respectively, in 10 hours. The remainder 20% in 35h and 10% in 35h, by 20.4

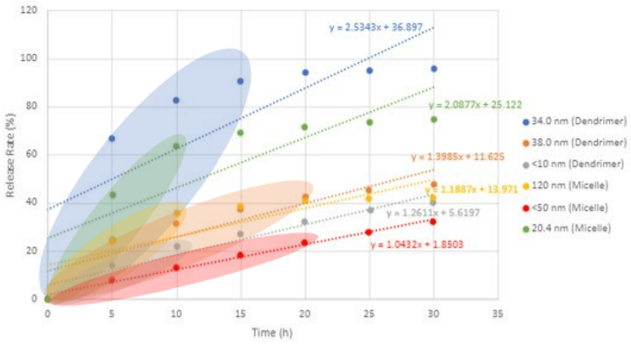

Figure 32 Burst Release dendrimer and micelle according to size [35, 43, 44, 49, 51, 53, 54, 58, 60, 62, 70, 71, 73]

and 120nm micelles, respectively. The larger micelle only releases 40% of the drugs whereas 20.4 nm micelle released 80% of the drugs. The 38nm dendrimer released 60% of the drugs in 80h in phase 2. It exhibited 2/5 time of release in phase 1 and 3/5 in phase 2. This behavior, comprising of a significant phase 1 and 2 was described by a bilinear relationship where the phase 2 had a higher slope than the phase 1. Since micelles were only releasing 40 to 80% of the drugs via inverse proportion to the micelle size, (120nm/20.4nm), the latter size is desirable in controlled release raising the TE. The BR phase was controlled in micelles. However, the released drug was only ½ to 1/3 of the loaded drug. Even though Figure 15 shows micelle size of 37.7nm, the release rates of this carrier was only exhibiting 15% of the release and not comparable. Therefore, in the absence of a smaller micelle carrier (38nm) between 20.4 and 120nm, it is not possible to comment whether dendrimer performed well or micelle matched the dendrimer. Limited data analyzed here tend to indicate that the 38nm dendrimer performed well and will have higher TE. However, larger diameter micelle, 120nm, was big enough to be blocked by the vasculature pores resulting in lack of release. NC made with lipids, metals and polymers are used to increase the penetration of drugs in skins in transdermal drug delivery. Such carriers are used in patches, ointments and cream. Even though the transdermal patches have their limitations with respect to the duration that the adhesives may stick to the skin and patch integrity in the presence of sweat and body temperature cause the spalling these modes need to investigated for targeted release of the advance drugs [82].

One of the limitations of this study was unavailability of dendrimer mechanical properties that control the carrier dissolution kinetics. These properties were correlated with TE else-where [83], where as the polymer strength increased, the melting point increased, elastic modulus increased however, it degraded sooner, releasing the drugs. In this study the data showed significantly reduced drug release using different polymers for micelles and dendrimers. Kinetics show a BR and an SS phase, only for 1/3 to ½ (50%) of the drug release, therefore will not be discussed further. Interested readers are pointed to Figure 9 to 10 and 16 for dendrimers and micelles, respectively.

8 Conclusions

In this study an attempt was made to compile the drug release characteristics of several drugs though mainly focusing on the doxorubicin. Various carriers used were compared to derive trends in drug release kinetics. Size of the nano-carriers plays an important role in drug delivery. Both dendrimers, micelles, their hybrid constructs, and NC presented higher TE if the size was less than 35nm. Even though there is not a critical size of the NC, the permeability of vasculature plays an important role. Larger size does not show a defined burst release and steady state, phases. In those cases, only a limited amount of drug was released ½ to 1/3 of the load. Most sizes included in this research point to too small a size, too fast dissolution, critical size, though not standardized, appears to be 25-35 nm would only be selected for optimum release was also a function of functionalization, polymer coating, hybrid constructs and other combinations of drug loading and molecular weight of polymers used. Therefore, future research will focus on those parameters, sizes, and specific drugs.

Abbreviations

TE	Therapeutic Efficacies
NC	nanocarriers
DOX	Doxorubicin
MTX	Methotrexate

ATRA	all-trans Retinoic acid
Da	Dalton
PAMAM	Poly(amidoamine)
NP	nanoparticle
G#	generation #
CMC	Critical Micelle Concentration
BR	Burst Release
SS	Steady Release
MRSA	Methicillin-resistant Staphylococcus aureus
Ibu	Ibuprofen
GFLG	tetrapeptidic Gly-Phe-Leu-Gly linker
CIP	Ciprofloxacin
CPT	camptothecin
PDMA(EMA)	poly(2-dimethylaminoethyl methacrylate)
PABA	p-Aminobenzoic Acid
SA	salicylic acid
NHAc	A molecule that underwent a acetylation modification
PHA	polyhydroxyalkanoate
PEG	Poly(ethylene glycol)
MPEG	methoxy poly(ethylene glycol)
GC	l-cysteine modified G4.5 dendrimer
IONP	Iron oxide nanoparticle
NCC	nanocrystalline cellulose
DendDP	Dendrimer-MPEG-DOX conjugates without Gly-Phe-Leu-Gly peptide linkage was also synthesized for comparison
DendGDP	Gly-Phe-Leu-Gly peptide was conjugated with the carboxylic acid end groups of a dendrimer, which was then conjugated with MPEG amine and doxorubicin by aid of carbodiimide chemistry
Au	Gold
PCL	Polycaprolactone
LPCL	Thermal and crystallization properties of linear PCL
PGAMA	poly(d-gluconamidoethyl methacrylate)
mPEG-PLCPPA	methoxy polyethylene glycol-co-poly (lactic acid-co-aromatic anhydride)
PEG-ss-PTMBC	poly(ethylene glycol)-SS-poly(2,4,6-trimethoxybenzylidene-pentaerythritol carbonate)
PEO-b-PMABC	poly(ethylene oxide)-b-poly(N-methacryloyl-N'-(t-butyloxycarbonyl)cystamine)
PLLA	poly(l-lactide acid)
Hyd	hydrazone bond
Asp	aspartate
Abz	aminobenzoate
Van	Vancomycin
PECL	poly(ethylene glycol)-b-poly(ε-caprolactone)
CSO	chitosan oligosaccharide
IMC	indomethacin
Ag	silver
MBG	Mesoporous Bioactive glass
PBS	Phosphate buffered saline
LB	Luria Bertani
DIP	A designation that references the ratio of IMC to Polymer (Drug IMC Polymer)

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