



Poly(lactic acid)-PLA: An Analysis Based on Literature Text Mining

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Abstract: The most researched and used biodegradable aliphatic polyester worldwide is poly (lactic acid) - PLA. Due to its inherent properties, PLA is a leading biomaterial for several and numerous applications and the most promising biopolymer capable of replacing conventional petroleum-derived polymers. Besides, PLA is also one of the most promising candidates for new developments in the traditional sectors such as packaging and the automotive industry, in the electronics industry, and the biomedical area. To verify the importance of drug release in the various applications of PLA, a text mining of the last ten years was carried out. The text-mining tool was used to identify this polymer's main applications in the last ten years, allowing us to draw a map year by year based on correlation analysis. Firstly, an analysis was made of the main applications of PLA in scientific research, by searching for "PLA", in the ScienceDirect scientific base (<https://www.sciencedirect.com/>) and using the online tool Voyant Tools. Some words related to drug release were selected, checking how many times they were mentioned over the years. In this way, it was possible to see which years were the most and least used PLA in drug release. It was not possible to observe a gradual increase or decrease in this polymer's use, for this purpose, over time. The text mining presented here proved to be an efficient and fast way to observe the desired theme.

Keywords: Text mining; PLA; Drug delivery; Biodegradable; Biocompatible, Data mining.

Adherence to the BJEDIS' scope: The article is in agreement with the scope since it is a literature review using the data mining tool.

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1. INTRODUCTION

The most researched and utilized biodegradable aliphatic polyester worldwide is poly(lactic acid) (PLA). PLA is a leading biomaterial for diverse and numerous applications due to its inherent properties, and the most promising biopolymer can replace conventional petrochemical-based polymers(1, 2). Because of its crucial position in the market of biopolymers, PLA is also one of the most promising candidates for further developments, not only in the traditional sectors such as packaging but also in transportation, in the automotive, electronics industry, and biomedical field(3–8). The impressive physical properties of poly(lactic acid), combined with biodegradability and biocompatibility, make this material very versatile with a wide range of potential industrial applications(9). With new technologies and increased utilization of renewable resources and sustainable products, all this advancement could lead to the biopolymers market boom(3). PLA is also quickly processed into the desired configuration using standard plastics equipment to produce molded parts, fibers, or films(10).

Initially, due to the production costs, low availability, and limited molecular weight, the main applications of PLA have been limited to high-value products, focused mainly on medical applications such as implant devices, tissue scaffolds, internal sutures, drug delivery, and others(11–14). However, new techniques developed in the last years allowed the production of high molecular weight PLA (starting with DuPont patent in 1954 and continued with many national and international companies) and decisively contributed to the more extensive utilization of this polymer. This PLA has gained enormous attention as an alternative to well-known synthetic polymers such as PET, PS, PE, etc., in the packaging and/or textile sectors(3, 7, 15, 16). Due to its transparency, low toxicity, and environmentally benign characteristics, PLA is a potential polymer for consumer products such as packaging. However, its low gas barrier properties, high brittleness, and poor crystallization behavior limit its use(9, 17).

As can be seen, the use of PLA has been growing a lot in different areas. However, its use in biomedical research still stands out because of its long history of safety in humans and an extensive range of biomedicine applications(18). As previously mentioned, PLA is applied in the biomedical field in sutures, bone plates (implants), abdominal mesh (scaffolds), and drug delivery(19–21).

Among the various biomedical applications of PLA, drug delivery has gained prominence and is being increasingly studied. PLA is very used for this purpose due to its biocompatibility, controlled biodegradability, relative ease of synthesis, and preparation of a variety of nano- to macro-scale forms and sizes such as polymeric micelles, nanoparticles, and polymersomes (22).

To verify the importance of the release of drugs within the various applications of PLA, a text mining of the last ten years was carried out. It was not possible to observe a gradual increase or decrease in this polymer's use, for this purpose over time, but it was possible to see that the years 2012 and 2018 were the years that most used PLA in drug release and 2013 and 2014 the years that least used.

2. METHODOLOGY

Scientific articles containing the word "PLA" were collected using the ScienceDirect database (<https://www.sciencedirect.com/>) on June 2nd, 2020. One hundred and nine thousand one hundred fifty-seven results were retrieved from this database, allowing the observation of increase and decrease in the number of publications during studied years, as shown in Figure 1. Based on this search, the time was limited between 2009 and 2019, since the year 2020 was not completed, presenting a smaller number of papers.

The first 100 most relevant papers (filter option selected on ScienceDirect) from 2009 to 2019 were selected and collected, totaling 1100 articles. According to each year, these articles were separated into two topics: (i) title and (ii) abstract to facilitate analyzing the main words listed in the documents. The used tools were LibreOffice Calc and LibreOffice Writer (both version: 6.2.3.2 Build ID: aecc05fe267cc68dde00352a451aa867b3b546ac). The online tool used for Text Mining was Voyant Tools (<https://voyant-tools.org/>)50–56. The set conditions were Fixed-term: "PLA" and Minimum coverage: 5%.



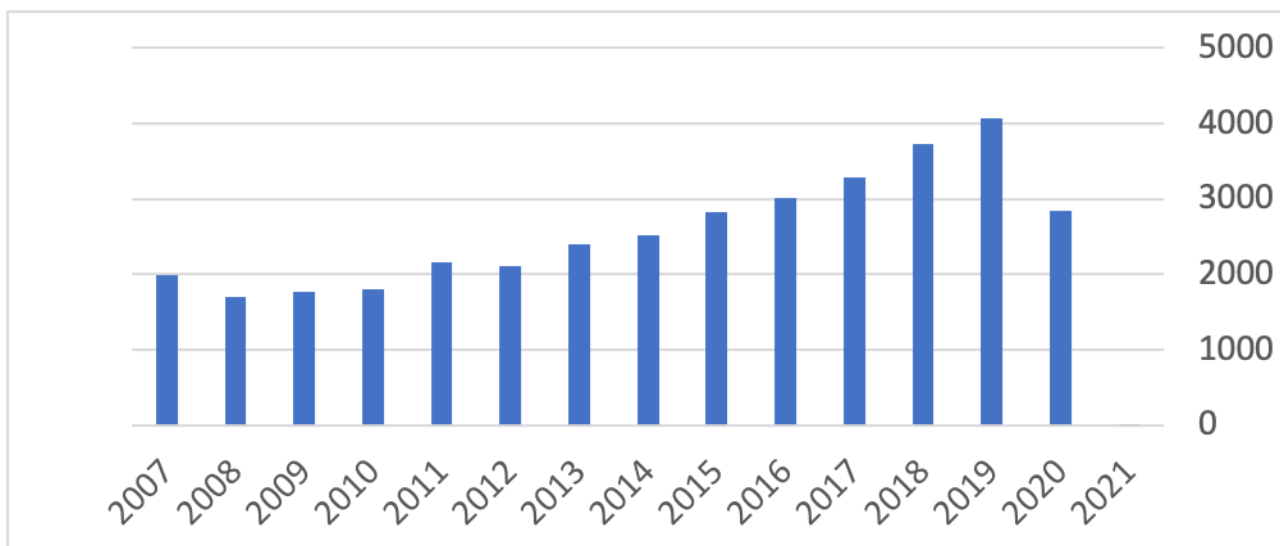


Figure 1. ScienceDirect search sorted by year

For the analysis, the data of the titles were placed on the Voyant, year by year. The correlation tool was used, and the term fixed was "PLA". The correlation and significance data were copied to an Excel spreadsheet from LibreOffice. The same procedure was followed for abstracts. The purpose of this analysis was to present a broad idea of what each year studied most. Besides, with the arrangement of words organized in more excellent correlation, it was possible to verify which years the drug delivery polymers were most used. LibreOffice Calc search tool was used for this purpose. The names of the polymers were searched and marked year by year. The titles' correlations were used to identify the polymers' names and knowledge since they had fewer words (around 100 words) than the abstracts.

3. DISCUSSION

One way to extract text data more naturally is by using the Text Mining technique. Text Mining has invaluable commercial value since it is a simplified and faster way to collect data, being applied in different areas (23–41).

A closer observation of each year in the studied period was relevant to understanding the subject's roadmap along these eleven years. Aiming to perform this complicated assignment, the Voyant's Correlation tool(42–45) was used, and the most relevant, irrelevant, and non-related terms were listed year by year. Figures 2 and 3 show a word cloud obtained using Voyant tool from the 2009 and 2019 titles files.

Table 1 - Correlations between polymer and 2nd terms in 2009-2019 Titles & Abstracts

Fixed term	Titles			Abstracts		
	2 nd term	r	p	2 nd term	r	p
PLA	mechanical*	0.6803	0.03039	effects*	0.8798	0.00079
	2009 composites	3.34E-08	1.00000	components	5.13E-08	---
	copolymers	-0.5643	0.08924	diffusion*	-0.9188	0.00017
	flame*	0.7193	0.01905	create*	0.8361	0.00258
	2010 based	-3.28E-08	1.00000	antioxidant	0.0022	---
	nanocomposite	-0.3845	0.27266	phospholipase*	-0.7631	0.01024
	pcl*	0.6678	0.03485	challenge*	0.9026	0.00035
	2011 lactide	0.0000	1.00000	increasing	0.0055	---
	nanocomposites	-0.3317	0.34904	increase*	-0.6527	0.04077
	behavior*	0.8133	0.00422	accumulated*	0.8845	0.00068
	2012 clay	0.0119	0.97396	indicated	0.0068	---
	lactide	-0.4677	0.17285	based*	-0.7459	0.01324
	electrical*	0.7454	0.01335	analyzed*	0.8759	0.00089
	2013 mechanical	0	1.00000	phosphatase	0.0039	---
	biodegradation	-0.3371	0.34083	composite*	-0.8784	0.00082
	nanoparticles	0.6050	0.06385	better*	0.7827	0.00743
	2014 nanocomposites	-0.0375	0.91808	controlled	-0.0055	---
	amphiphilic*	-0.7876	0.00683	developed*	-0.8674	0.00115
	assembled*	0.6939	0.02603	addition*	0.7029	0.02338
	2015 evaluation	-0.0398	0.91297	core	-0.0061	---
	iri*	-0.6575	0.03882	models*	-0.9369	0.00006
	compatibilization	0.6068	0.06287	line*	0.8604	0.00140
	2016 biodegradable	-4.67E-08	1.00000	performance	-0.0050	---
	based*	-0.8147	0.00410	biocompatible*	-0.8446	0.00210
	effects*	0.7882	0.00676	implantation*	0.8165	0.00395
	2017 controlled	-0.0273	0.94031	materials	-0.0066	---
	phase*	-0.8602	0.00141	improved*	-0.8165	0.00395
	block*	0.6708	0.03373	known*	0.7923	0.00628
	2018 drug	-0.0667	0.85481	block	-0.0011	---
	melt*	-0.6831	0.02945	efficient*	-0.7717	0.00892
abs*	0.8457	0.00205	behavior*	0.8441	0.00213	
2019 heat	-0.0292	0.93627	developed	-1.20E-08	---	
iri*	-0.8217	0.00354	model*	-0.8637	0.00128	

* Statistically relevant terms

Table 2 – Weblinks to Voyant Tools' corpus

Year	Titles
2009	https://voyant-tools.org/?corpus=e72c734f1653e7a88b9ab6b08fd73eff
2010	https://voyant-tools.org/?corpus=02dfabe9ac566638a2c526980b8ee461
2011	https://voyant-tools.org/?corpus=02f9c3faf0f59f77e774d761978d596b
2012	https://voyant-tools.org/?corpus=f379f19f8eface08966f4be741454cd8
2013	https://voyant-tools.org/?corpus=5b2ff454e3e8de285a2018a3bab07fbc
2014	https://voyant-tools.org/?corpus=c28e7fdcf8106a542c6f4a9fbe9b7d23
2015	https://voyant-tools.org/?corpus=953c40b62c57ca8e6cd32227dd38fae
2016	https://voyant-tools.org/?corpus=62d285f7d8e78e203c4eca3ed568128a
2017	https://voyant-tools.org/?corpus=d6a12fcd67963997cc56d1408cc99fb
2018	https://voyant-tools.org/?corpus=52a227dcba66116be00c099325dc0a84
2019	https://voyant-tools.org/?corpus=fc05699d2babfa30a4263b106c6b55a5

Year	Abstracts
2009	https://voyant-tools.org/?corpus=38ea5c3dcd96e2055539e5b104c935ea
2010	https://voyant-tools.org/?corpus=4e8f3c4b9305d8860df2638d91a00955
2011	https://voyant-tools.org/?corpus=2bad42b82fc73a8ffdbefbcdbb84188a
2012	https://voyant-tools.org/?corpus=e98af75068c66862ce7ad2af81700bd6
2013	https://voyant-tools.org/?corpus=d4c8a4f8c1cf5337ea3c38167167b669
2014	https://voyant-tools.org/?corpus=a71190092b7d70a7da75f6dd0ca0e6e5
2015	https://voyant-tools.org/?corpus=1f46ef09f8d85ef1cc30cb43c3e134a8
2016	https://voyant-tools.org/?corpus=a9bee849b35676ee75de3a7ef5c9bce2
2017	https://voyant-tools.org/?corpus=e29e0477346b8ab4f7b595b2b251c0c5
2018	https://voyant-tools.org/?corpus=f05f77e0666785fc2e5da4cbd838ff21
2019	https://voyant-tools.org/?corpus=fd69b2e188e6acad792bb7bbb73e033c

After separating the words that appeared with major, minor and unrelated to PLA, we built a theory of what was most researched each year based on the two words, with the highest correlations in titles and abstracts, and on the authors' prior knowledge. Also, some words correlated with the controlled release of drugs (drug; controlled and delivery) were searched with the calc search tool to investigate whether or not this application was highlighted in that year.

In 2009, the two words most associated with PLA, in the titles, were mechanical and cellulose and, in the abstracts, were effects and exhibit. In 2009, the research focused on the mechanical properties of PLA and its mixtures, mainly with cellulose. The words like degrade, blend, and biodegradation were also positively correlated, which reinforces this theory. In 2009, the words drug, delivery, and controlled did not appear at the top correlations in titles or abstracts, but the word "burst" related to drug explosion release appears in the abstract's top 10 of correlations.

During 2010, the two words most associated with PLA, in the titles, were flame and fillers and, in the abstract, were created and linear. The theory proposed was that the research that year was more related to incorporating charges in the PLA matrices, mainly intending to create or increase its flame potential. The words like blend, filler, and nanocomposites were also highly correlated, which reinforces this reasoning. Cellulose is no longer with such a high correlation. In 2010, the words drug, delivery, and controlled did not appear at the top correlations in titles or abstracts. However, the word Ibuprofen, which is directly linked to drug release, appears in the top 10. We highlight that in 2010 there was a giant leap concerning the release of drugs due to Ibuprofen.

The two words most associated with PLA in the title in 2011, were PCL and agglutinin, and in the abstract were a challenge and clear. Analyzing these words, we saw that the studies shifted the focus from 2009 cellulose mixtures to the PCL and that studies in the biomedical area gained even more strength, with the agglutinin

antibody's appearance at the very top of the correlations. Along with the main words, we also found the words like blended and cellulose, reinforcing this reasoning. In 2011, the words drug, delivery, and controlled did not appear at the top correlations in titles or abstracts.

During 2012, the two words most associated with PLA in the titles were behavior and evidence, and in the abstracts were accumulated and hours. The authors were unable to correlate these alone words with any specific topic. However, joining with other top words like PEG, copolymer, and drug (which makes a giant leap going to top correlations), it was possible to conclude that at this year, the polymer most associated with PLA was PEG, different from other years, and the drug controlled delivery took a leap.

In the next year, 2013, the two words most associated with PLA in the titles were electrical and physical, and in the abstracts were analyzed and energy. Thus, the research focus was the electrical properties of the PLA due to the incorporation of a possible charge. Coupled with other words from the highest correlations, like nanocomposites nanoparticles, particles made this hypothesis gain strength. In 2013, the words drug, delivery, and controlled did not appear at the top correlations in titles or abstracts. The most correlated polymer that year was chitosan, standing in front of cellulose in the titles.

In 2014, the two words most associated with PLA in the titles were nanoparticles and pH and in the abstracts were better and decreased. So, the authors were doing much research on incorporating nanoparticles in the PLA matrix. Other words at the top correlations were PCL, PEG showing that PLA was being associated with other biopolymers. In 2014, the words drug, delivery, and controlled did not appear at the top correlations in titles or abstracts.

In the researches of 2015, the two words most associated with PLA in the titles were assembled and branched and in the abstracts were micellar and morphology. Analyzing these words alone, it is possible to assume that the self-assembling PLA systems can occur when linked with other polymers with a more polar character and form micelles. This theory has gained more strength by combining other top correlations words like copolymer, PCL, and cellulose. In 2015, the words drug and delivery can be found at positive correlations in the titles, but the word controlled does not appear in titles or abstracts, showing that the research on the drug controlled delivery has gained some strength.

During 2016, the two words most associated with PLA in the titles were compatibilization and manufacture and in the abstracts were frequency and pd. Analyzing these words alone, it was possible to understand that they could be adding charges to the PLA matrix and need compatibility. Combined with other words from the top like composites and additives, this hypothesis gained more strength. In 2016, the word drug had a positive correlation in titles, and delivery positively correlates with abstracts. The word controlled does not appear at the top correlations in titles or abstracts. The most correlated polymers in that year were PHB and chitosan (top of the titles).

In the next year, 2017, the two words most associated with PLA in the titles were effects and crystallization, and in the abstract were nodules and ester. Analyzing these words alone, it is possible to think that nodules were associated with cancer treatment. Combining with other top correlation words like cancer, breast, and cell, this hypothesis gained more strength. In 2017, in the titles, the word delivery had a positive correlation, drugs and controlled have a positive correlation in abstracts. The most correlated polymer in that year with PLA was PCL.

In 2018, the two words most associated with PLA in the titles were block and combined, and in the abstracts were known and calorimetry. Analyzing these words alone, it was possible to think that the most popular combination, in that year, of PLA with other polymers was the formation of blocks, and the study of the thermal properties of these copolymers stood out. In 2018, only the word drugs is at the top correlation of titles and abstracts, the words controlled and delivery showed a positive correlation only in abstracts. The most correlated polymer with PLA that year was PEG.

In the last year of the study, 2019, the two words most associated with PLA in the titles were abs and fused and in the abstracts were behavior and modification. Analyzing these words together with another word from the topic, composite, it was possible to think about the preparation of PLA / ABS composites. In 2019, only the words controlled and the drug appears in the titles with a positive correlation. In the abstracts, only the word drug has a positive correlation. The most correlated polymer that year was lignin, followed by cellulose.

As a conclusion of this hypothesis analysis, based on the top positive correlations extracted from Voyant tools, in the years 2010 and 2012, the controlled release of drugs was highlighted using the PLA as a matrix. In 2015, 2017, and 2018, this purpose gained strength again, and in 2017 the research of drug delivery using PLA was focused on cancer treatment.

As previously mentioned, some words related to the controlled drug delivery were found in the correlations, and for better visualization, they were separated and ordered by year according to the correlation, as can be seen in tables 3, 4, and 5, allowing to see more clearly which years related this theme to PLA the most and the least.

Table 3. The word “drug” found using the search tool of Calc LibreOffice

Word “drug” in titles			Word “drug” in abstracts		
YEAR	CORRELATION	P	YEAR	CORRELATION	P
2012	0.54527855	0.103065826	2018	0.4936735	0.14702567
2015	0.3237337	0.36150044	2012	0.49192172	-----
2018	0.2236068	0.53459215	2017	0.21252558	-----
2016	0.15169707	0.67569405	2011	0.14492138	-----
2019	0.11664234	0.74828815	2009	0.13737613	-----
2014	-0.049102835	0.89284617	2010	0.10820776	-----
2010	-0.12169109	0.7377079	2019	0.10730194	-----
2009	-0.2310364	0.5207316	2016	-0.00904066	-----
2017	-0.76871556	0.009368108	2015	-0.12196685	-----
2011	-----	-----	2014	-0.1905310	-----
2013	-----	-----	2013	-0.3345822	-----

Table 4. The word “delivery” found using the search tool of Calc LibreOffice

Word “delivery” in titles			Word “delivery” in abstracts		
YEAR	CORRELATION	P	YEAR	CORRELATION	P
2015	0.3316656	0.34916052	2016	0.41819888	-----
2010	0.21271786	0.5551694	2018	0.16183779	-----
2017	0.16384634	0.65105397	2012	0.08236892	-----
2009	0.05940183	0.87051606	2019	-0.05690302	-----
2011	0.016382439	0.964173	2011	-0.17814936	-----
2016	-0.14002807	0.69962436	2013	-0.23378594	-----
2014	-0.1804154	0.6179384	2010	-0.27832374	-----
2012	-0.1909407	0.59721506	2009	-0.3006589	-----
2019	-0.31180477	0.380461	2017	-0.33445004	-----
2018	-0.4472136	0.19501553	2015	-0.45875293	-----
2013	-----	-----	2014	-0.48644093	0.15396658

Table 5. The word “controlled” found using the search tool of Calc LibreOffice

Word “controlled” in titles			Word “controlled” in abstracts		
YEAR	CORRELATION	P	YEAR	CORRELATION	P
2019	0.20044598	0.5787211	2012	0.58052770	0.07847373
2011	0.03686049	0.91947716	2018	0.31214115	-----
2017	-0.027307672	0.940309	2017	0.22222222	-----
2012	-0.08183173	0.822187	2015	0.14593379	-----
2015	-0.25901760	0.4699066	2014	-0.0054622837	-----
2013	-0.27950850	0.43414527	2019	-0.04883274	-----
2009	-----	-----	2013	-0.05201419	-----
2010	-----	-----	2011	-0.25794417	-----
2014	-----	-----	2016	-0.43690765	0.20675768
2016	-----	-----	2010	-0.45069158	-----
2018	-----	-----	2009	-0.54811907	0.10092427

As can be seen by looking at the Tables 3, 4 and 5 the drug controlled delivery was very prominent in 2012 and 2018. At these years, all the words searched had positive correlations either in the titles or in the abstracts. In the years 2013 and 2014, the searched words presented only negative correlations in the titles or the abstracts. These results showed that at these years, the controlled release of drugs was not highlighted.

CONCLUSION

As shown here, the proposed text mining using the Science Direct and Voyant tools was successfully performed. Hypotheses were made about the subject using the principal words found in the analysis. It was not possible to observe a gradual increase or decrease in this polymer's use for drug delivery over time, but it was possible to see that the years 2012 and 2018 were the years that most used PLA in drug release and 2013 and 2014 the years that least used. This study showed that this approach could be used when it is desired to have a fast way to follow a topic's evolution over time.

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